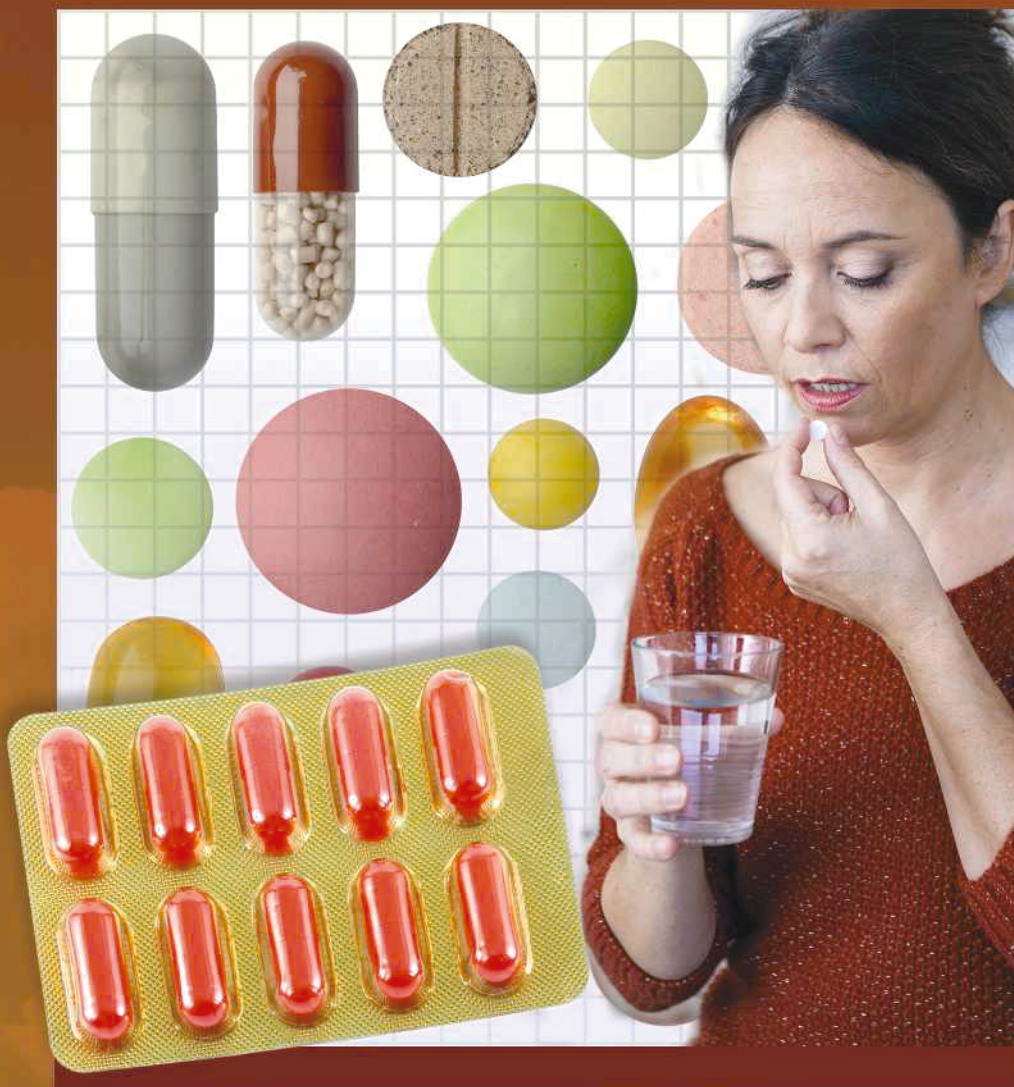


The GALE
ENCYCLOPEDIA
of PRESCRIPTION DRUGS

A Comprehensive Guide to the Most Common Medications



The GALE
ENCYCLOPEDIA *of*
PRESCRIPTION
DRUGS

A COMPREHENSIVE GUIDE TO THE MOST
COMMON MEDICATIONS

**The Gale Encyclopedia of Prescription Drugs:
A Comprehensive Guide to the Most
Common Medications**

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PLEASE READ—IMPORTANT INFORMATION

The Gale Encyclopedia of Prescription Drugs: A Comprehensive Guide to the Most Common Medications is a health reference product designed to inform and educate readers about some of the most commonly prescribed medications. Cengage Learning believes the product to be comprehensive but not necessarily definitive. It is intended to supplement, not replace, consultation with a physician or other healthcare practitioner. While Cengage Learning has made substantial efforts to provide information that is accurate, comprehensive, and up to date, Cengage Learning makes no representations

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FOREWORD

Being told you need to take a prescription drug can sometimes be alarming. A lot happens during the medication process, from when the doctor determines a prescription medication is necessary to when the prescription is picked up at the pharmacy and the first dose is taken. When a doctor determines a prescription medication is necessary, the patient might leave the office with a handwritten or computer-generated prescription, or the doctor could fax, electronically submit, or phone the prescription directly to the pharmacy. For the patient, the entire process can be mysterious, confusing, and maybe even a little frightening. How did my prescription get to the pharmacy? What is the pharmacist doing behind the glass? Why do I need a prescription for some drugs but not others? Why does a generic medication cost so much less, and is it really the same as the brand name product? How will I feel when I take the drug—will it make me feel better or could I feel sicker?

WHAT IS A DRUG?

A medication, or drug, is any product that is intended for use in the diagnosis, treatment, or prevention of an illness or to relieve the symptoms of an illness. Drugs can be divided into two categories: prescription drugs or over-the-counter (OTC) drugs. For example, if you are diagnosed with an ear infection, your doctor may order a prescription antibiotic to treat the infection and instruct you to take an OTC pain reliever/fever reducer to treat the symptoms of the infection.

PRESCRIPTION VS. OTC DRUGS

Prescription drugs are those that require a physician's prescription. These medications are intended for conditions that must be monitored by a physician. OTC medications are those that are sold without a prescription and are regularly available.

OTC medications have been found by the U.S. Food and Drug Administration (FDA) to be suitable for self-administration without a physician's guidance. These

medications are typically not habit-forming and have a low potential of causing harm. The ingredients, strength, expiration date, lot number, directions, and warnings must clearly be printed on the product package.

OTC products may contain more than one active ingredient. This is typically seen in many allergy and cough and cold products. It is crucial to be aware of this, since some ingredients may also be found in prescription medications. Unintentionally ingesting too much of a medication could lead to an overdose or more pronounced side effects, such as sleepiness or dizziness. Acetaminophen, for example, is found in both OTC products and in combination prescription pain medications. Ingesting too much acetaminophen can lead to liver damage.

DRUG APPROVAL

To ensure consumer safety and drug efficacy, the FDA must approve all prescription medications. The medication approval process is a complex one, taking on average 12–15 years to get a new drug from the research laboratory to a pharmacy shelf. The process starts when a sponsor develops or discovers a new drug product. The sponsor may be a drug company, a government agency, a scientific institution, or even an individual.

The sponsor of the new medication first tests the drug on a variety of animals to assess the drug's efficacy and toxicity. Next, the sponsor meets with the FDA and provides them with the animal data. The FDA decides if the new product is suitable to be tested on humans. If so, three phases of clinical trial testing commence.

Phase one is performed on a small group of people, with the goal of observing side effects and seeing how the drug works in the human body. Phase two is performed on a larger group and focuses on how effective the drug is against the condition or disease. Phase three studies the product on a large group of people from a variety of populations and evaluates different dosages.

After all human clinical trials are complete, the sponsor provides the FDA with its findings. The FDA

reviews the data, the drug's labeling, and the manufacturing facilities. If the FDA review team deems the product safe and efficacious, the drug is made available to the public.

BRAND NAME VS. GENERIC DRUGS

During the drug development process, the sponsor obtains a patent to protect the drug formula and the commercial name that will be used in the marketing of the final product. Having a patent means that no other manufacturer can produce, sell, or use the name of the new drug. The patent-protected drug name is referred to as the "brand name." Once the patent for a medication expires, usually 20 years after the patent is obtained, the active ingredient is no longer protected and can be produced and sold by other manufacturers. The name of the active ingredient is called the medication's "generic name."

Generic drug manufacturers require approval from the FDA before they are able to sell their generic product. The manufacturer must prove that they are using the same active ingredient, in the same form, with the same strength, given by the same route of administration as the brand name predecessor. After equivalency is proven and FDA approval is given, a generic medication may be distributed by the manufacturer and substituted for the brand name product in the pharmacy. Generic medications are often less costly than brand name drugs because generic drug manufacturers did not invest billions of dollars in clinical trials, development, and research. However, even though the generic active ingredient must be the same, the inactive ingredients do not need to be. This is why generic drugs often have a different taste, shape, or color.

OTC medications do not require individual FDA approval. Instead, the FDA maintains a database of approved active ingredients. The database, or Federal Register, is made up of active ingredient summaries containing the ingredient, dose, formulation, and labeling rules. As long as a company formulates a new OTC product using approved active ingredients and follows the guidelines for the active ingredients, there is no need for final FDA review.

HERBS AND SUPPLEMENTS

It is important to note that herbal and homeopathic remedies, dietary supplements, and vitamins are not evaluated, approved, or regulated by the FDA. It is important to let your doctor or pharmacist know if you regularly take these types of products so that they can evaluate the safety of combining supplements with a prescription or OTC medication.

DRUG SIDE EFFECTS

All drugs, both prescription and OTC, produce some effect on our bodies. Sometimes, however, these effects may be unwanted. For example, a medication you take for a headache may cause you to have diarrhea. This unwanted effect is known as a "side effect," or an effect of a medication that is not intended. Side effects may not be the same for all who take the same medication. Common side effects include nausea, constipation, and diarrhea, since most medications are taken orally and are absorbed through the digestive tract. Other types of side effects include sleepiness, dizziness, skin flushing, and sensitivity to sunlight.

More severe unwanted effects are categorized as "adverse effects." Adverse effects are those that cause injury to the patient. Some antibiotics, for example, can cause permanent hearing loss or kidney damage if their use is not monitored appropriately. Other types of adverse effects include allergic reactions (swelling, difficulty breathing, hives), irregular heartbeat, an increase or decrease in blood pressure, and bleeding.

Side effects can generally be minimized or avoided if some simple steps are taken:

- Always inform your physician or pharmacist of all medications, vitamins, supplements, and OTC products being taken.
- Read the prescription label and the accompanying drug literature and ask your physician or pharmacist questions.
- Do not combine alcohol or other medications with the drug unless approved by a physician or pharmacist.
- If a medication causes dizziness or sleepiness it can be taken at bedtime; likewise, if a medication causes insomnia or hyperactivity, it can be taken in the morning.

Some side effects may subside after a medication is taken for a few weeks. It is common for nausea, loss of appetite, and dizziness to subside once the body is accustomed to the medication.

DRUG INTERACTIONS

A drug interaction is a response that occurs when a drug effect is altered by another drug or substance (alcohol, tobacco, illegal drugs, dietary supplements). Drug interactions can cause an increase or decrease in the effect of one or more of the combined drugs or substances. Warfarin (Coumadin), for example, is a blood-thinning agent. If this drug is taken with amiodarone (Cordarone), an agent to control an irregular heartbeat, serious bleeding can occur.

Some foods and beverages can also interact with medications. Warfarin interacts with vitamin K, rendering the medication useless. Vitamin K is typically found in green, leafy vegetables and green tea. This interaction can also be used in a patient's favor if they accidentally overdose and their blood becomes too thin. In this case, vitamin K can be used as an antidote. Grapefruit juice also interacts with many medications by preventing them from breaking down in the body. This can lead to toxic levels of the medication.

SAFE MEDICATION PRACTICES

The medication process need not be mysterious, confusing, or frightening. Ask your medical provider or pharmacist questions. Ask if you do not understand how or when to take a medication, what to expect in terms of symptom relief and side effects, and what to do if you

have an adverse reaction. Read the literature that comes with your prescription and save it so that you can refer back to it periodically. Following the simple steps listed to mitigate side effects will help prevent you from having to stop the medication due to discomfort. Make sure to read and understand OTC medication packaging, and ask your pharmacist if you have questions. Pharmacists are experts on prescription and OTC medications and will answer any type of medication question you may have. Finally, be assured that although inexpensive generic medications may look different from pricey brand name medications, generic equivalents are safe and effective.

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INTRODUCTION

The Gale Encyclopedia of Prescription Drugs: A Comprehensive Guide to the Most Common Medications is a new title in the well-known *Gale Encyclopedia of ...* series. It features entries on 300 top prescription medications. The *Encyclopedia* provides in-depth coverage of each drug, including an image. Unlike other sources that feature highly technical drug monographs, the *Encyclopedia* presents medical concepts and terminology in language that general readers can understand, while still providing thorough coverage.

SCOPE

Entries follow a standardized format to help users find information quickly. Rubrics include the following headings (as applicable):

- Definition
- Purpose
- Description
- Recommended dosage
- Precautions
- Side effects
- Interactions
- Resources

The Definition section provides information on the drug's class, and the Description section includes subheadings for U.S., Canadian, and international brand names.

The Recommended dosage and Precautions sections both include subheadings that cover pediatric and geriatric populations, as well as necessary modifications for pregnancy and other conditions or allergies.

The Precautions section also specifies a drug's pregnancy category, as applicable. Pregnancy categories were assigned by the U.S. Food and Drug Administration (FDA) to assess whether or not a drug adversely affected a pregnancy and to rate its level of impact (i.e., sometimes the benefits of a drug outweighed its potential risks). However, while this *Encyclopedia* was being

developed, the FDA decided to redefine its program and eliminate the pregnancy categories. The categories are still provided here to give readers a general idea of a drug's effects during pregnancy, but a pregnant woman should always consult with her physician before starting new or stopping existing medications.

The Interactions section includes not only drug-drug interactions but also drug-food interactions and interactions with other substances.

INCLUSION CRITERIA

A preliminary list of medications was compiled from a wide variety of sources, including professional and government-sponsored medical guides as well as consumer guides and encyclopedias. The advisory board, made up of medical doctors, pharmacists, and nurse practitioners, evaluated the topics and made suggestions for inclusion. Final selection of topics to include was made by the advisory board in conjunction with the editor.

ABOUT THE CONTRIBUTORS

The essays were compiled by experienced medical writers, including physicians, pharmacists, nurses, and other healthcare professionals. The advisory board reviewed the completed essays to ensure that they are appropriate, up to date, and accurate.

HOW TO USE THIS BOOK

The Gale Encyclopedia of Prescription Drugs has been designed with ready reference in mind.

- Straight **alphabetical arrangement** of topics allows users to locate information quickly. Drugs are listed under their generic name.
- **Bold-faced terms** within entries indicate that full-length articles exist for those topics.
- **Cross-references** placed throughout the encyclopedia direct readers from alternate drug names, including brand names, to their intended entries.

- **Patient profiles** in select entries provide a narrative account of an individual's experience with a certain drug.
- A list of **key terms** is provided in most entries to define unfamiliar or complicated terms or concepts.
- **Resources** sections at the end of entries direct readers to additional sources of information on a topic.
- Valuable **contact information** for organizations is included with most entries.
- A comprehensive **general index** guides readers to all topics mentioned in the text.
- **Author and advisor bylines** provide information on who wrote and reviewed the entries, including their credentials.
- The Institute of Safe Medicine Practices (ISMP) has allowed us to reproduce their **list of commonly confused drug names**. ISMP is a nonprofit agency of healthcare professionals certified as a Patient Safety Organization (PSO) by the federal Agency for Healthcare Research and Quality. The inclusion of the list in this guide is intended to prevent medication errors.
- All of the contact information from the entries is compiled and arranged alphabetically in the **Organizations appendix**.
- A **glossary** contains all of the key terms within the entries, arranged alphabetically.

GRAPHICS

The Gale Encyclopedia of Prescription Drugs is enhanced by 300 color photographs. Please note that the photographs depict one possible formulation of each drug. Drug appearances vary greatly due to differences in dosage, manufacturer, form (e.g., capsule or tablet), and other factors. The image shown may not appear the same as the specific form prescribed.

APPENDICES

The *Encyclopedia's* content is enhanced with four appendices in the back of volume 2:

- **Questions to Ask Your Pharmacist** present conversation points to facilitate discussions with a pharmacist.

ALPHABETICAL LIST OF ENTRIES

A

Acetaminophen/codeine
Acyclovir
Adalimumab
Albendazole
Albuterol
Albuterol/ipratropium
Alendronate
Allopurinol
Almotriptan
Alprazolam
Amitriptyline
Amlodipine
Amlodipine/valsartan
Amoxicillin
Amoxicillin/clavulanic acid
Aripiprazole
Armodafinil
Aspirin
Aspirin/extended-release
dipyridamole
Atenolol
Atomoxetine
Atorvastatin
Azithromycin

B

Baclofen
Benazepril
Benazepril/hydrochlorothiazide
Bendamustine
Benzotropine
Bevacizumab
Budesonide

Budesonide/formoterol
Buprenorphine/naloxone
Bupropion
Buspirone
Butalbital/acetaminophen/caffeine

C

Calcitriol
Candesartan
Captopril
Carbamazepine
Carbidopa/levodopa
Carisoprodol
Carvedilol
Cefaclor
Cefdinir
Cefixime
Cefprozil
Celecoxib
Cephalexin
Cetirizine
Cetuximab
Chlordiazepoxide
Chlorhexidine
Ciprofloxacin
Ciprofloxacin/dexamethasone
Citalopram
Clarithromycin
Clindamycin
Clindamycin/benzoyl peroxide
Clomiphene
Clonazepam
Clonidine
Clopidogrel
Clotrimazole/betamethasone

Clozapine
Colchicine
Colesevelam
Conjugated estrogens
Cyclobenzaprine
Cyclosporine
Cyproheptadine

D

Dabigatran
Definition
Desipramine
Dexlansoprazole
Dexmethylphenidate
Dextroamphetamine
Diazepam
Diclofenac
Digoxin
Diltiazem
Diphenhydramine
Donepezil
Dorzolamide/timolol
Doxepin
Doxycycline
Duloxetine
Dutasteride

E

Efavirenz/emtricitabine/tenofovir
Enalapril
Enoxaparin
Epinephrine
Epoetin alfa
Erythromycin

Escitalopram
Esomeprazole
Estradiol, micronized
Eszopiclone
Etanercept
Ethambutol
Etodolac
Etonogestrel/ethinyl estradiol
Ezetimibe

F

Famciclovir
Famotidine
Fenofibrate
Fentanyl
Fexofenadine
Finasteride
Fluconazole
Fluorouracil
Fluoxetine
Fluticasone
Fluticasone/salmeterol
Fluvoxamine
Fosinopril
Furosemide

G

Gabapentin
Galantamine
Gemfibrozil
Glatiramer
Glimepiride
Glipizide
Glyburide
Griseofulvin
Guanfacine

H

Haloperidol
Hydrochlorothiazide
Hydrocodone/acetaminophen
Hydrocodone/ibuprofen
Hydromorphone
Hydroxychloroquine

Hydroxyzine
Hyoscyamine sulfate

I

Ibandronate
Ibuprofen
Imatinib
Imipramine
Imiquimod
Indomethacin
Infliximab
Insulin aspart
Insulin detemir
Insulin glargine
Insulin lispro
Interferon beta 1a
Ipratropium
Irbesartan
Isosorbide
Isotretinoin

K

Ketoconazole
Ketoprofen
Ketorolac

L

Lamivudine/zidovudine
Lamotrigine
Lansoprazole
Levalbuterol
Levetiracetam
Levofloxacin
Levonorgestrel
Levothyroxine
Lidocaine patch
Linezolid
Liraglutide
Lisdexamfetamine
Lisinopril
Lithium
Loperamide
Lorazepam
Losartan

Losartan/hydrochlorothiazide
Lovastatin

M

Mebendazole
Meclizine
Medroxyprogesterone
Megestrol
Meloxicam
Memantine
Mesalamine
Metaxalone
Metformin
Methadone
Methocarbamol
Methotrexate
Methylphenidate
Methylprednisolone
Metoclopramide
Metoprolol
Metronidazole
Milnacipran
Minocycline
Mirtazapine
Modafinil
Mometasone
Montelukast
Morphine
Moxifloxacin
Mupirocin

N

Nabumetone
Nebivolol
Nifedipine
Nitrofurantoin
Nitroglycerin
Norelgestromin/ethinyl estradiol
Nortriptyline
Nystatin

O

Octreotide
Olanzapine
Olmesartan

Olopatadine
Omeprazole
Ondansetron
Oral contraceptives
Oseltamivir
Oxcarbazepine
Oxybutynin
Oxycodone
Oxycodone/acetaminophen

P

Paliperidone
Pantoprazole
Paroxetine
Pegfilgrastim
Phentermine
Phenytoin
Pimecrolimus
Pioglitazone
Potassium chloride
Pramipexole
Prasugrel
Pravastatin
Prednisone
Pregabalin
Promethazine
Propranolol

Q

Quetiapine
Quinapril

R

Rabeprazole
Raloxifene
Ramelteon
Ramipril

Ranibizumab
Ranitidine
Rifampin
Risedronate
Risperidone
Rituximab
Rivaroxaban
Rivastigmine
Rizatriptan
Ropinirole
Rosuvastatin

S

Salmeterol
Sertraline
Sildenafil
Simvastatin
Sitagliptin
Sitagliptin/metformin
Sofosbuvir
Solifenacin
Sotalol
Spironolactone
Sulfamethoxazole/trimethoprim
Sulfasalazine
Sumatriptan

T

Tacrolimus
Tadalafil
Tamoxifen
Tamsulosin
Telmisartan
Temazepam
Terazosin
Terbinafine
Tetracycline
Timolol

Tiotropium
Tizanidine
Tobramycin/dexamethasone
Tolterodine
Topiramate
Torsemide
Tramadol
Tramadol/acetaminophen
Tranexamic acid
Trazodone
Tretinoin (topical)
Triamcinolone
Triazolam

U

Ursodiol

V

Vaccinations
Valacyclovir
Valproic acid
Valsartan/hydrochlorothiazide
Vardenafil
Varenicline
Venlafaxine
Verapamil SR

W

Warfarin

Z

Ziprasidone
Zoledronic acid
Zolmitriptan
Zolpidem

LIST OF ENTRIES BY DRUG CLASS

ACETYLCHOLINESTERASE INHIBITORS

Galantamine

ALPHA-ADRENERGIC BLOCKERS

Tamsulosin

Terazosin

ANALGESICS

Acetaminophen/codeine

Aspirin

Buprenorphine/naloxone

Butalbital/acetaminophen/caffeine

Celecoxib

Diclofenac

Etodolac

Fentanyl

Hydrocodone/acetaminophen

Hydrocodone/ibuprofen

Hydromorphone

Ibuprofen

Indomethacin

Ketoprofen

Ketorolac

Meloxicam

Methadone

Morphine

Nabumetone

Oxycodone

Oxycodone/acetaminophen

Tramadol

Tramadol/acetaminophen

ANDROGEN INHIBITORS

Finasteride

ANESTHETICS

Lidocaine patch

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

Benazepril

Benazepril/hydrochlorothiazide

Captopril

Enalapril

Fosinopril

Lisinopril

Quinapril

Ramipril

ANGIOTENSIN RECEPTOR BLOCKERS

Amlodpine/valsartan

Irbesartan

Losartan

Losartan/hydrochlorothiazide

ANGIOTENSIN II RECEPTOR ANTAGONISTS

Losartan

Losartan/hydrochlorothiazide

Candesartan

Irbesartan

ANGIOTENSIN II RECEPTOR BLOCKERS

Olmesartan

Telmisartan

Valsartan/hydrochlorothiazide

ANTHELMINTIC DRUGS

Albendazole

ANTIACNE DRUGS

Clindamycin/benzoyl peroxide

Isotretinoin

Tretinoin (topical)

ANTIANKXIETY DRUGS

Buspirone

Chlordiazepoxide

ANTIARRHYTHMIC DRUGS

Sotalol

Verapamil SR

ANTIBACTERIAL DRUGS

Clindamycin/benzoyl peroxide

ANTIBIOTICS

Amoxicillin

Amoxicillin/clavulonic acid

Azithromycin

Cefaclor

Cefdinir

Cefixime

Cefprozil

Cephalexin

Ciprofloxacin

Ciprofloxacin/dexamethasone

Clarithromycin

Clindamycin

Doxycycline

Erythromycin

Levofloxacin

Linezolid

Metronidazole

Minocycline

Moxifloxacin

Mupirocin
Nitrofurantoin
Sulfamethoxazole/ trimethoprim
Tetracycline
Tobramycin/dexamethasone

ANTICANCER DRUGS

Adalimumab
Cetuximab
Fluorouracil
Imatinib
Infliximab
Ranibizumab
Rituximab

ANTICHOLINERGICS

Benztropine
Hyoscyamine
Ipratropium
Oxybutynin
Solifenacin
Tolterodine

ANTICOAGULANTS

Clopidogrel
Dabigatran
Enoxaparin
Rivaroxaban
Warfarin

ANTICONVULSANTS

Carbamazepine
Gabapentin
Lamotrigine
Oxcarbazepine
Phenytoin
Pregabalin
Topiramate
Valproic acid

ANTIDEPRESSANTS

Amitriptyline
Bupropion
Citalopram
Desipramine
Desvenlafaxine
Doxepin
Duloxetine

Escitalopram
Fluoxetine
Fluvoxamine
Imipramine
Mirtazapine
Nortriptyline
Paroxetine
Sertraline
Trazodone
Venlafaxine

ANTIDIABETIC DRUGS

Glimepiride
Glipizide
Glyburide
Liraglutide
Pioglitazone

ANTIDIARRHEAL DRUGS

Loperamide

ANTIDYSKINETICS

Carbidopa/levodopa

ANTIEPILEPTIC DRUGS

Levetiracetam

ANTIESTROGENS

Tamoxifen

ANTIFIBRINOLYTICS

Tranexamic acid

ANTIFUNGALS

Clotrimazole/betamethasone
Fluconazole
Griseofulvin
Ketoconazole
Nystatin
Terbinafine

ANTHELMINTIC DRUGS

Mebendazole

ANTIHISTAMINES

Cetirizine
Cyproheptadine
Diphenhydramine

Fexofenadine
Hydroxyzine
Meclizine
Olopatadine

ANTIHYPERGLYCEMIC DRUGS

Metformin
Sitagliptin/metformin

ANTIHYPERTENSIVES

Amlodipine
Amlodipine/valsartan
Benazepril
Benazepril/hydrochlorothiazide
Candesartan
Captopril
Carvedilol
Clonidine
Enalapril
Fosinopril
Guanfacine
Irbesartan
Lisinopril
Losartan
Losartan/hydrochlorothiazide
Nebivolol
Olmesartan
Quinapril
Ramipril
Telmisartan
Valsartan/hydrochlorothiazide

ANTIGOUT DRUGS

Allopurinol

ANTI-INFECTIVES

Chlorhexidine gluconate

ANTI-INFLAMMATORY DRUGS

Colchicine
Mesalamine
Tobramycin/dexamethasone

ANTILIPIDEMIC DRUGS

Atorvastatin
Gemfibrozil

Lovastatin
Pravastatin
Simvastatin

ANTIMANIC DRUGS

Lithium

ANTIMETABOLITES

Methotrexate

ANTIMIGRAINE DRUGS

Almotriptan
Rizatriptan
Sumatriptan
Zolmitriptan

ANTIMUSCARINIC DRUGS

Solifenacin

ANTIMYCOBACTERIALS

Ethambutol
Rifampin

ANTINEOPLASTICS

Bendamustine
Bevacizumab

ANTIPARKINSONIAN DRUGS

Benzotropine

ANTIPLATELET DRUGS

Aspirin/extended-release
dipyridamole
Prasugrel

ANTIPROTOZOALS

Hydroxychloroquine

ANTIPSYCHOTICS

Aripiprazole
Clozapine
Risperidone

ANTIPSYCHOTICS, ATYPICAL

Olanzapine
Paliperidone
Quetiapine
Ziprasidone

ANTIRETROVIRALS

Efavirenz/emtricitabine/tenofovir
Lamivudine/zidovudine

ANTIRHEUMATICS

Adalimumab

ANTISPASMODICS

Baclofen
Hyoscyamine
Oxybutynin

ANTIVIRALS

Acyclovir
Famciclovir
Oseltamivir
Sofosbuvir
Valacyclovir

BARBITURATES

Butalbital/acetaminophen/caffeine

BENZODIAZEPINES

Alprazolam
Clonazepam
Diazepam
Lorazepam
Temazepam
Triazolam

BETA ADRENERGIC BLOCKER

Dorzolamide/timolol

BETA AGONISTS

Levalbuterol
Salmeterol

BETA-BLOCKERS

Atenolol
Carvedilol
Metoprolol
Nebivolol
Propranolol
Timolol
Sotalol

BILE ACID

Ursodiol

BILE ACID SEQUESTRANTS

Colesevelam

BIOLOGICAL-RESPONSE MODIFIERS

Imiquimod

BIOLOGICS

Etanercept

BIPHOSPHONATES

Alendronate
Ibandronate
Risedronate
Zoledronic acid

BRONCHODILATORS

Albuterol
Albuterol/ipratropium
Budesonide/formoterol
Fluticasone/salmeterol
Ipratropium
Tiotropium

CALCIUM CHANNEL BLOCKERS

Amlodipine
Amlodipine/valsartan
Diltiazem
Nifedipine
Verapamil SR

CARBONIC ANHYDRASE INHIBITORS

Dorzolamide/timolol

CEPHALOSPORINS

Cefaclor
Cephalexin
Cefprozil
Cefdinir
Cefixime

CENTRAL ALPHA-2 AGONISTS

Guanfacine

CENTRAL ALPHA-ADRENERGIC AGONISTS

Clonidine

**CENTRAL NERVOUS SYSTEM
STIMULANTS**

Armodafinil
Dexmethylphenidate
Dextroamphetamine
Lisdexamfetamine
Methylphenidate
Modafanil
Phentermine

**CHOLESTEROL ABSORPTION
INHIBITORS**

Ezetimibe

CHOLINESTERASE INHIBITORS

Donepezil

COLONY-STIMULATING FACTORS

Pegfilgrastim

CONTRACEPTIVES (COMBINATION)

Etonogestrel/ethinyl estradiol
Norelgestromin/ethinyl estradiol

CORTICOSTEROIDS

Budesonide
Budesonide/formoterol
Ciprofloxacin/dexamethasone
Clotrimazole/betamethasone
Fluticasone
Fluticasone/salmeterol
Methylprednisone
Mometasone
Prednisone
Triamcinolone

CYCLOOXYDASE 2 INHIBITOR

Celecoxib

CYTOKINES

Interferon beta 1a

DIGITALIS GLYCOSIDES

Digoxin

DIPEPTIDYL PEPTIDASE-4 INHIBITORS

Sitagliptin
Sitagliptin/metformin

DIURETICS

Benazepril/hydrochlorothiazide
Furosemide
Hydrochlorothiazide
Losartan/hydrochlorothiazide
Spironolactone
Torsemide
Valsartan/hydrochlorothiazide

DOPAMINE AGONISTS

Pramipexole
Ropinirole

ELECTROLYTE SUPPLEMENTS

Potassium hydrochloride

ENZYME INHIBITORS

Imatinib

**ERYTHROPOIESIS-STIMULATING
AGENTS**

Epoetin alfa

ESTROGENS

Conjugated estrogens
Estradiol, micronized
Oral contraceptives

FIBRATES

Fenofibrate
Gemfibrozil

5 ALPHA-REDUCTASE INHIBITORS

Dutasteride

5-HT3 RECEPTOR ANTAGONISTS

Ondansetron

FLUOROQUINOLONES

Levofloxacin
Moxifloxacin

HISTAMINE 2 ANTAGONISTS

Ranitidine

HISTAMINE 2 BLOCKERS

Famotidine

HMG-COA REDUCTASE INHIBITORS

Atorvastatin
Pravastatin
Rosuvastatin

HORMONES

Epinephrine
Fluticasone
Levothyroxine

HYPNOTICS

Clonazepam
Zolpidem

IMMUNOMODULATORS

Glatiramer
Imiquimod
Pimecrolimus
Tacrolimus

IMMUNOSUPPRESSANTS

Cyclosporine

INSULINS

Insulin aspart
Insulin detemir
Insulin glargine
Insulin lispro

LEUKOTRIENE RECEPTOR AGONISTS

Montelukast

MONOCLONAL ANTIBODIES

Bevacizumab
Rituximab

MUSCLE RELAXANTS

Baclofen
Carisoprodol
Cyclobenzaprine
Metaxalone
Methocarbamol
Tizanidine

NARCOTICS

Fentanyl
Hydrocodone/acetaminophen
Oxycodone

NITRATES

Isosorbide
Nitroglycerin

N-METHYL-D-ASPARTATE RECEPTOR ANTAGONISTS

Memantine

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Aspirin
Celecoxib
Diclofenac
Etodolac
Hydrocodone/ibuprofen
Ibuprofen
Indomethacin
Ketoprofen
Ketorolac
Meloxicam
Nabumetone

OCTAPEPTIDES

Octreotide

OPIATES/OPIOIDS

Acetaminophen/codeine
Buprenorphine/naloxone
Fentanyl
Hydrocodone/ibuprofen
Hydromorphone
Methadone
Morphine
Oxycodone/acetaminophen
Tramadol
Tramadol/acetaminophen

OVULATORY STIMULANTS

Clomiphene

PHENOTHIAZINES

Promethazine

PHOSPHODIESTERASE TYPE 5 INHIBITOR

Sildenafil
Tadalafil
Vardenafil

PROGESTINS

Levonorgestrel
Medroxyprogesterone
Megestrol
Oral contraceptives

PROKINETICS

Metoclopramide

PROTON PUMP INHIBITORS

Dexlansoprazole
Esomeprazole
Lansoprazole
Omeprazole
Pantoprazole
Rabeprazole

RETINOIDS

Isotretinoin
Tretinoin (topical)

REVERSIBLE ACETYLCHOLINESTERASE INHIBITORS

Rivastigmine

SALICYLATES

Aspirin

SALICYLATE-SULFONAMIDE DRUGS

Sulfasalazine

SEDATIVES

Clonazepam
Eszopiclone
Ramelteon

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Raloxifene

SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITOR

Atomoxetine
Duloxetine

SELECTIVE SEROTONIN RECEPTOR AGONISTS

Rizatriptan

Sumatriptan
Zolmitriptan

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Citalopram
Escitalopram
Fluoxetine
Fluvoxamine
Paroxetine
Sertraline

SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS

Desvenlafaxine
Milnacipran
Venlafaxine

SMOKING CESSATION AIDS

Varenicline

STATINS

Atorvastatin
Lovastatin
Pravastatin
Rosuvastatin
Simvastatin

STIMULANTS

Butalbital/acetaminophen/caffeine

SUFONYLUREAS

Glimepiride
Glipizide
Glyburide

TETRACYCLINES

Doxycycline
Minocycline

TRANQUILIZERS

Haloperidol

TRICYCLIC ANTIDEPRESSANTS

Amitriptyline
Desipramine
Doxepin
Imipramine
Nortriptyline

TRIPTAN

Rizatriptan
Sumatriptan
Zolmitriptan

**TUMOR NECROSIS FACTOR
BLOCKER**

Adalimumab

**TUMOR NECROSIS FACTOR-ALPHA
INHIBITOR**

Etanercept
Infliximab

**VASCULAR ENDOTHELIUM GROWTH
FACTOR A ANTAGONIST**

Ranibizumab

VASODILATOR

Isosorbide

VITAMIN D3 ANALOG

Calcitriol

XANTHINE OXIDASE INHIBITORS

Allopurinol

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A

Abilify see **Aripiprazole**

Accupril see **Quinapril**

Accutane see **Isotretinoin**

Acetaminophen/butalbital/caffeine see
Butalbital/acetaminophen/caffeine

Acetaminophen/codeine

Definition

Acetaminophen with codeine is a drug that combines acetaminophen, a nonprescription painkiller (analgesic), with codeine, an opium-based painkiller. It belongs to the family of drugs called opioid analgesics.

Purpose

Acetaminophen with codeine is used to treat mild to moderately severe pain that is not relieved by nonprescription painkillers alone.

Description

Acetaminophen with codeine is a white, disk-shaped tablet 10 millimeters (mm) in diameter. The strength of the tablet (rated 2, 3, or 4) is embossed on one side. The pill is to be taken whole by mouth with or without food. In the United States, acetaminophen with codeine is a Schedule III controlled substance. This means that:

- The drug has the potential for abuse at a lower level than Schedule I or Schedule II drugs.
- The drug has legitimate medical uses.
- Prolonged use of the drug can cause low to moderate physical dependence or high psychological dependence.

KEY TERMS

Analgesic—A drug used to control pain.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Pregnancy category—A system of classifying drugs for their use during pregnancy. Category A: Controlled human studies have identified no fetal risk. Category B: Animal studies indicate no fetal risk but no human studies exist, or adverse effects have been seen in animals but not in well-controlled human studies. Category C: No adequate animal or human data is available, or adverse effects have occurred in animal studies but no human data is available. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk, and risks outweigh any benefits.

Tolerance—The condition that arises when an individual must take more and more of a drug to achieve the same effect.

Acetaminophen with codeine tablets come in three strengths:

- 300 mg acetaminophen with 15 mg codeine (strength 2)
- 300 mg acetaminophen with 30 mg codeine (strength 3)
- 300 mg acetaminophen with 60 mg codeine (strength 4)

Acetaminophen with codeine is sold in the United States by several generic manufacturers and under various brand names, including:

- Capital & Codeine



Acetaminophen/codeine, 300 mg/30 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

- Tylenol (#2, #3, #4)
- Fioricet with codeine
- Phrenilin with caffeine
- codeine containing added caffeine and butalbital

Canadian brand names

In Canada, a formulation containing 325 milligrams (mg) acetaminophen, 8 mg of codeine, and 15 mg caffeine is available without a prescription. It is sold as Tylenol #1 and under other names.

In Canada, acetaminophen with codeine is sold under the names Acet codeine, Procet-30, ratio-Emtec-30, ratio-Lenoltec No. 4, Triacet-30, and Tylenol #4. Many other formulations include acetaminophen, codeine, and caffeine, including Atasol, Exdol, and Tylenol. These brand names are available in varying strengths from 8 mg to 35 mg of codeine.

International brand names

Internationally, acetaminophen is known as paracetamol. There are dozens of brand names for the combination of paracetamol and codeine, depending on the country of origin. For example, in countries such as India, other drugs are added to the paracetamol-codeine combination or another analgesic such as **aspirin** or **ibuprofen** is substituted for paracetamol. Internationally,

the combination of paracetamol and codeine is also available in capsule form.

Recommended dosage

The dosage should always be the lowest dosage needed to control pain and within the acceptable limitations listed in Precautions. Usual adult doses range from 15 to 60 mg codeine and 300 to 1,000 mg acetaminophen. Doses may be repeated every 4 hours, with a maximum 24-hour dosage of 360 mg codeine and 4,000 mg acetaminophen.

This drug is not recommended for use in children under three years old. The usual dosage for children is 0.5 mg per kilogram (kg, or 2.2 lb.) of body weight, repeated every four hours.

Precautions

The U.S. Food and Drug Administration (FDA) requires a boxed warning for this drug indicating that acetaminophen has been associated with cases of acute liver failure, usually at doses greater than 4,000 mg per day. An additional warning indicates that acetaminophen with codeine should not be used in children who have had a tonsillectomy or adenoidectomy.

Other precautions include the warning that codeine can be physically and psychologically addictive if used for a long time and that tolerance can develop. Individuals with a history of substance abuse are at higher risk for addiction. In addition, this drug may not be appropriate or the usual dosage may need to be reduced in individuals who have severe renal (kidney) or hepatic (liver) impairment, head injuries, elevated intracranial pressure, hypothyroidism, Addison's disease, constriction of the urethra, or enlarged prostate.

In the body, codeine is converted into **morphine**. Some individuals have a genetic mutation (CYP2D6 polymorphism) that causes them to convert codeine at an ultra high rate. In these ultra-high metabolizers, the level of codeine in the blood and in the breast milk of nursing mothers can become high enough to depress the respiratory system, with life-threatening consequences. Testing for this genetic mutation is not common practice, so individuals may be unaware of the condition.

Long-term heavy alcohol abusers are at increased risk of liver damage from acetaminophen use beyond the standard dosage.

In January 2014, the FDA recommended that healthcare professionals cease prescribing or dispensing drug products that contained more than 325 mg of acetaminophen per dose. There is no evidence that higher doses of acetaminophen (more than 325 mg) provide

benefits that outweigh the risks to the liver, and limiting the dosage helps reduce the risk of liver injury. Accidental acetaminophen overdose can result in liver failure, the need for liver transplant, and death.

Cases of severe liver damage have occurred in patients who:

- exceeded the prescribed dose of acetaminophen within a 24-hour period
- took more than one product that contained acetaminophen
- consumed alcohol while taking acetaminophen

Pediatric

Acetaminophen with codeine is not recommended for children under age three. Children should not be given acetaminophen with codeine after having tonsils or adenoids removed, especially if this was a treatment for sleep apnea. In addition, children who are ultra-high metabolizers of codeine are at high risk for respiratory depression and death.

Geriatric

All individuals, but especially older individuals who have decreased liver or kidney function may not clear acetaminophen or codeine from the body as rapidly as individuals with fully functioning kidneys and livers. This can allow the drug to build up in the blood, causing more liver damage. Dosage must be adjusted in these individuals.

Pregnant or breastfeeding

Acetaminophen with codeine is a pregnancy category C drug. Codeine crosses the placenta. The newborn may show withdrawal effects if the mother has taken codeine even at low doses as little as ten days before delivery. Acetaminophen with codeine should be given only if benefits outweigh risks.

Codeine crosses into breast milk. Women who are ultra-high metabolizers of codeine may have levels of codeine in breast milk high enough to cause respiratory depression or death in the nursing infant. However, acetaminophen with codeine is considered compatible with breastfeeding by the American Academy of Pediatrics.

Side effects

Rarely acetaminophen may cause a serious skin reaction that can be fatal. At the first sign of any rash or sign of hypersensitivity, individuals should stop taking the drug. Hypersensitivity reactions include swelling of

the face, mouth, or throat; difficulty breathing; rash or skin eruptions; and vomiting.

Common but less serious side effects include dizziness, lightheadedness, drowsiness, nausea, and constipation. Mental abilities and physical responses may be delayed. Other side effects are possible. Individuals should report to their healthcare provider any unusual, unexpected, or troubling side effects.

Laboratory tests for serum amylase and urinary 5-hydroxyindoleacetic acid may be altered by this drug.

Interactions

Drugs

All drugs that depress the central nervous system enhance the effect of codeine. These include other narcotics and sleep medicines. Buprenorphine, naltrexone, and quinidine may decrease the effectiveness of acetaminophen with codeine. This drug may increase the chance of side effects in individuals taking anticoagulants such as **warfarin** (Coumadin). Certain chemotherapy drugs and drugs to treat human immunodeficiency virus (HIV) can increase liver damage. Other drugs not listed here may interact with acetaminophen with codeine. Individuals should review all medications they are taking with their doctor or pharmacist before starting this drug.

Herbs and supplements

As of early 2015, there was no definitive research on which drugs and supplements may interact with acetaminophen with codeine. Individuals should review all herbs and supplements with their doctor or pharmacist before starting this drug.

Food and other substances

Both alcohol and codeine are central nervous system depressants. Taken together, they can cause respiratory depression or death. Acetaminophen is more likely to cause liver damage in individuals who are heavy consumers of alcohol.

Resources

BOOKS

Estren, Mark J. *Prescription Drug Abuse*. Berkeley, CA: Ronin, 2013.

PERIODICALS

Franceschi, F., et al. "Safety and Efficacy of the Combination Acetaminophen-Codeine in the Treatment of Pain of Different Origin." *European Review for Medical and Pharmacological Sciences* 17, no. 16 (August 2013): 2129–35.

WEBSITES

- MedlinePlus. "Acetaminophen and Codeine." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601005.html> (accessed March 30, 2015).
- Physicians' Desk Reference. "Tylenol with Codeine." PDR Health. <http://www.pdrhealth.com/drugs/tylenol-with-codeine> (accessed April 7, 2015).
- U.S. Food and Drug Administration. "Acetaminophen Prescription Combination Drug Products with More Than 325 mg: FDA Statement—Recommendation to Discontinue Prescribing and Dispensing." <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm381650.htm> (accessed December 5, 2014).

ORGANIZATIONS

- American Chronic Pain Association, PO Box 850, Rocklin, CA 95677, (800) 533-3231, APAC@theacpa.org, <http://www.theacpa.org/>.
- National Pain Foundation, 14828 W 6 Avenue, Suite 16-B, Room 1, Golden, CO 80401-5000, (720) 541-6808, (720) 541-6809, <http://www.thenationalpainfoundation.org/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Tish Davidson, AM

REVIEWED BY GREGORY A. PRATT, RPh

Acetaminophen/hydrocodone see
Hydrocodone/acetaminophen

Acetaminophen/oxycodone see
Oxycodone/acetaminophen

Acetaminophen/tramadol see **Tramadol/acetaminophen**

Aciphex see **Rabeprazole**

Actigall see **Ursodiol**

Actiq see **Fentanyl**

Actionel see **Risedronate**

Actos see **Pioglitazone**

Acular see **Ketorolac**



Acyclovir, 800 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

The purpose of acyclovir is to control symptoms that accompany infections with HSV 1, HSV 2, or VZV, and to either provide suppressive therapy or decrease recurrent outbreaks. HSV 1 causes most cold sore symptoms. HSV 2 is a sexually transmitted virus that causes genital herpes. VZV causes chickenpox in children and young adults. VZV can emerge in older individuals who have had chickenpox when young and cause shingles (also called zona). Shingles usually occurs in people over age 60. Once infected, the body never clears any of these three viruses, so recurrent outbreaks of cold sores and genital herpes or re-emergence of VZV as shingles is common. Acyclovir suppresses these viruses and helps to reduce symptoms and outbreaks. It is not a cure for infection with these viruses, but it can control the symptoms they produce.

Description

Acyclovir is available as a tablet, capsule, or suspension to be taken orally. The drug is produced by many manufacturers. There is no standardized shape or color to the tablet, although often the tablet is a white oval. Acyclovir is also available as a cream and an ointment. An intravenous form is available for use in a medical setting. Acyclovir works by interfering with the reproduction of the virus. Three strengths of oral acyclovir are available:

Acyclovir**Definition**

Acyclovir is an antiviral drug used to control infections with herpes simplex type 1 (HSV 1), herpes simplex type 2 (HSV 2), and varicella-zoster virus (VZV).

- 200 mg (tablet or capsule)
- 200 mg/5 mL suspension
- 400 mg (tablet)
- 800 mg (tablet)

U.S. brand names

In the United States and Canada, acyclovir is sold under the brand name Zovirax. Internationally, it is sold under several dozen different brand names.

Recommended dosage

The dosage depends on the reason the drug is being taken. For an initial infection of genital herpes (HSV 2), the usual dosage is 200 milligrams (mg) every four hours, taken five times daily for seven to ten days; or 400 mg three times daily, according to the U.S. Centers for Disease Control and Prevention (CDC). After this dosage, the drug can be given at 400 mg twice daily for up to 12 months to suppress the virus. Alternately, a dosage of 200 mg three to five times daily may be prescribed. When the individual is not taking long-term suppressive doses and a recurrent outbreak occurs, the CDC recommends taking 400 mg three times daily for five days, 800 mg twice daily for five days, or 800 mg three times daily for two days. The drug is most effective if started at the first signs or symptoms of a recurrent outbreak.

In adults with chickenpox or shingles, the usual dosage is 800 mg five times daily for seven to ten days.

Pediatric

For treatment of chickenpox in children over age two, the dose is 20 mg per kilogram (kg, or 2.2 lb.) of body weight per dose four times daily. Treatment is most effective in reducing symptoms when it begins as soon as possible after diagnosis of chickenpox. This drug has not been studied in children younger than two years old.

Precautions

Pregnant or breastfeeding

Acyclovir is a category B pregnancy drug. The drug passes into breast milk and should be used by nursing mothers only when benefits outweigh the risks of use.

Other conditions and allergies

Individuals who are allergic to **valacyclovir** (Valtrex) are likely to be allergic to acyclovir and should not take the drug.

KEY TERMS

Cold sore—A fluid-filled blister usually found on or near the lips caused by the herpes simplex virus type 1 (HSV 1).

Genital herpes—A sexually transmitted infection caused by the herpes simplex virus type 2 (HSV 2), which affects both men and women and can cause pain, itching, and irritation in the genital area.

Pregnancy category—A system of classifying drugs for their use during pregnancy. Category A: Controlled human studies have identified no fetal risk. Category B: Animal studies indicate no fetal risk, but there are no human studies, or adverse effects have been found in animals but not in well-controlled human studies. Category C: No adequate animal or human data is available, or adverse effects have been found in animal studies, but no human data is available. Category D: Evidence of fetal risks exists, but the benefits outweigh the risks. Category X: Evidence of fetal risks exists, and the risks outweigh any benefits.

Shingles—An acute nerve inflammation caused by the reactivation of latent chickenpox virus in the body.

Adults who have impaired kidney function may need to have their dosage of acyclovir reduced because they will not clear the drug from their bodies as rapidly as those with full kidney function. Overdose of the drug can cause kidney failure and death.

Side effects

Any signs of difficulty breathing; swelling of the face, tongue, or throat; or hives indicate a rare but serious allergic reaction and should be treated as an immediate medical emergency.

Serious but uncommon side effects that require prompt medical attention include:

- pain in the lower back
- reduced or no urination
- unusually easy bruising or excessive bleeding
- unusual weakness

More common and generally mild side effects include nausea, diarrhea, headache, dizziness, and swelling of the hands and feet.

Other side effects are possible.

Pediatric

The most common side effect in children treated for chickenpox is diarrhea, although the side effect is not common.

Geriatric

The most common side effect in individuals being treated for shingles is malaise (general discomfort and weakness), although this side effect was observed at almost the same rate (11.5% vs. 11.1%) in individuals given a placebo during clinical trials. In addition, older adults and adults with reduced kidney function are more likely to report nervous system symptoms such as confusion, delirium, dizziness, seizure, and tremors.

Interactions

Drugs

Probenecid (Benemid), which is used to treat gout, may decrease the effectiveness of acyclovir.

Herbs and supplements

Patients should check with their physicians before taking any other drugs or supplements while taking acyclovir, including alcohol.

Food and other substances

There are no known interactions of food with acyclovir, and it may be taken with meals or on an empty stomach.

Resources

BOOKS

Acyclovir versus Valacyclovir for Herpes Virus in Children and Pregnant Women: A Review of the Clinical Evidence and Guidelines. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health, September 5, 2014. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK253720/> (accessed January 22, 2015).

PERIODICALS

- Ganguly, S. "A Randomized, Double-Blind, Placebo-Controlled Study of Efficacy of Oral Acyclovir in the Treatment of Pityriasis Rosea." *Journal of Clinical and Diagnostic Research* 8, no. 5 (2014): YC01–4. <http://dx.doi.org/10.7860/JCDR/2014/8140.4360> (accessed January 22, 2015).
- Le Cleach, L., et al. "Oral Antiviral Therapy for Prevention of Genital Herpes Outbreaks in Immunocompetent and Nonpregnant Patients." *Cochrane Database of Systemic Reviews* 8, art. no. CD009036 (2014). <http://dx.doi.org/10.1002/14651858.CD009036.pub2> (accessed January 22, 2015).

WEBSITES

- "Acyclovir." Drugs.com. <http://www.drugs.com/pro/acyclovir-tablets.html> (accessed December 23, 2014).
- AIDSinfo.gov. "Acyclovir." National Institutes of Health. <http://aidsinfo.nih.gov/drugs/8/acyclovir/0/patient> (accessed December 23, 2014).
- MedlinePlus. "Acyclovir." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a681045.html> (accessed December 23, 2014).

ORGANIZATIONS

- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Tish Davidson

REVIEWED BY GREGORY A. PRATT, RPH

Adalat CC see **Nifedipine**

Adalimumab

Definition

Adalimumab is a tumor necrosis factor (TNF)-alpha inhibitor. It is used to treat various autoimmune disorders by blocking the action of TNF, an immune system protein that produces widespread inflammation. Adalimumab is a type of medication called a biologic. Because it is used to treat rheumatoid arthritis (RA), it is also classified as a disease-modifying antirheumatic drug (DMARD).

Purpose

Autoimmune disorders are conditions in which the immune system attacks the body's own healthy tissues, causing inflammation, swelling, pain, loss of function, and permanent damage. TNF inhibitors such as adalimumab do not cure these disorders, but they can control the symptoms and prevent progressive structural damage. This reduces severe complications, hospitalizations, and surgeries and improves patient quality of life. Adalimumab is used alone or in conjunction with other medications to treat:

- RA
- juvenile idiopathic arthritis (JIA)
- chronic plaque psoriasis, in which red, scaly patches form on the skin
- psoriatic arthritis (PsA), a serious complication of plaque psoriasis



Humira (adalimumab). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

- ankylosing spondylitis, RA of the joints of the spine
- moderate to severe Crohn's disease (CD), in which the immune system attacks the digestive tract lining, causing pain, fever, diarrhea, and weight loss
- ulcerative colitis (UC)

Adalimumab can reduce or eliminate the use of steroids for treating autoimmune conditions. Clinical studies have found adalimumab to be about as effective as the nonbiologic DMARD **methotrexate** (MTX) for decreasing RA symptoms. In combination with MTX, it prevents progressive structural damage and deterioration of function in RA patients who have not responded adequately to MTX alone. Adalimumab improves PsA symptoms, patients' range of activities, and quality of life. It induces and maintains remission in CD patients who have not responded adequately to conventional therapy or who have stopped responding to or are intolerant of the similar TNF inhibitor infliximab. Adalimumab reduces CD fistulas—small tunnels that connect an intestinal loop to another part of the intestine or another organ. Adalimumab is used to manage both newly diagnosed and advanced CD and UC.

Adalimumab may be prescribed for other conditions. For example, one study found that weekly treatments improved symptoms and quality of life in patients with moderate to severe hidradenitis suppurativa (HA), a chronic autoimmune disease of the sweat glands.

Description

Adalimumab and other TNF-alpha inhibitors are among the ten best-selling drugs in the United States. They can effectively treat diverse conditions that are both

common and chronic, and they must generally be used long term. For example, RA affects about 1% of the U.S. population, with a peak onset in patients in their 40s.

Adalimumab is a genetically engineered, fully human monoclonal antibody produced in cell cultures. It specifically binds to and blocks the action of both soluble and membrane-bound TNF-alpha, a cytokine that plays a central role in immune system function but that also promotes inflammation in the joints, spine, skin, and digestive tract in various autoimmune conditions. Because adalimumab is a powerful immune system suppressant that increases the risk of severe infection, it is used only for moderate to severe disease that has not responded well to conventional therapies.

Adalimumab is about 1,000 times larger than chemically synthesized drugs—too large to be well absorbed by the gastrointestinal tract—so it must be injected. It is supplied in prefilled, single-use syringes and dosing pens containing the correct amount of clear, colorless liquid. The usual response time is about four weeks.

U.S. brand names

Adalimumab is marketed under the brand name Humira in most countries worldwide. The name is derived from the acronym for “human monoclonal antibody in rheumatoid arthritis.”

Origins

Since 2002, adalimumab has been approved by the U.S. Food and Drug Administration (FDA), the European Commission, and various other countries for treating a range of autoimmune conditions in children and adults, including RA, JIA, plaque psoriasis, PsA, and ankylosing spondylitis. Most recently, it received FDA approval in 2012 for treatment of moderate to severe UC in adults and, in 2014, for moderate to severe CD in children aged six and older.

Recommended dosage

Recommended adult dosages are:

- arthritis: 40 milligrams (mg) every other week; possibly weekly for RA patients not also taking MTX
- plaque psoriasis: initial dose of 80 mg, followed by 40 mg every other week beginning one week after the initial dose
- CD and UC: 160 mg on day 1 (four 40 mg injections on day 1 or two 40 mg injections on two consecutive days); 80 mg two weeks later (day 15); maintenance doses of 40 mg every two weeks beginning two weeks later (day 29); discontinued if no sign of remission by eight weeks (day 57)

KEY TERMS

Ankylosing spondylitis—Rheumatoid arthritis of the spine.

Autoimmune disorders—Conditions caused by inappropriate immune system activity.

Biologics—Naturally occurring compounds in the human body, usually proteins, that are used to treat disease.

Crohn's disease (CD)—A chronic inflammatory autoimmune disease involving any part of the gastrointestinal tract but commonly involving the large intestine, with scarring and thickening of the bowel wall.

Disease-modifying antirheumatic drug (DMARD)—A drug, such as adalimumab, that suppresses the immune system to decrease inflammation from rheumatoid arthritis.

Fistula—An abnormal passageway between tissues and organs.

Hidradenitis suppurativa (HA)—A chronic, painful, draining, and foul-smelling autoimmune disease of the sweat glands in the armpits, groin, and under the breasts.

Infliximab (Remicade)—A tumor necrosis factor (TNF) inhibitor that is very similar to adalimumab.

Juvenile idiopathic arthritis (JIA)—A type of arthritis that affects children aged 16 and younger and that can delay growth and development.

Methotrexate (MTX)—A drug used to treat severe psoriasis and rheumatoid arthritis.

Monoclonal antibodies—Identical antibodies that recognize and bind to a specific protein; commonly used for targeted drug therapies.

Plaque psoriasis—An autoimmune disorder that causes patches of inflamed skin.

Pregnancy category—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk, but there are no human studies, or adverse effects have been seen in animals but not in well-controlled human studies. Category C: No adequate human or animal studies exist, or adverse fetal effects have been seen in animal studies, but there is no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk and risks outweigh any benefits.

Psoriatic arthritis (PsA)—Joint inflammation that develops in some psoriasis patients.

Rheumatoid arthritis (RA)—A chronic autoimmune disease that causes pain, stiffness, inflammation, swelling, and sometimes destruction of joints.

Tuberculosis (TB)—A highly variable chronic bacterial infection that affects the lungs and can spread to other parts of the body.

Tumor necrosis factor (TNF)-alpha—A protein called a cytokine that mediates inflammation throughout the body and activates immune system cells. Inhibited by adalimumab.

Ulcerative colitis (UC)—A chronic, episodic, inflammatory autoimmune disease of the large intestine and rectum characterized by bloody diarrhea.

After receiving the first dose in a healthcare provider's office, the patient or a family member or friend is instructed on injecting adalimumab under the skin (subcutaneously). It can be injected anywhere on the front of the thigh or the stomach except within 2 in. (5 cm) of the navel. A list of injection sites should be kept so that each injection is at least 1 in. (2.5 cm) from previous sites to reduce the risk of soreness. The syringe or pen should not be reinjected even if there is solution remaining. A missed dose should be injected as soon as possible, with the next dose on the regularly scheduled day. However, if it is almost time for the next dose, the missed dose should be skipped. The syringes or pens should be kept refrigerated, protected from light, and disposed of in a puncture-resistant container.

Pediatric

The recommended dosages for JIA in children aged 4 to 17 are 20 mg every other week for patients weighing 33 lb. (15 kg) to less than 66 lb. (30 kg), and 40 mg every other week for those weighing 66 lb. (30 kg) or more.

Precautions

Patients should discuss the risks of adalimumab with their healthcare provider. Adalimumab carries a boxed warning issued by the FDA:

- Adalimumab can decrease the body's ability to fight infection and increase the risk of severe or life-threatening fungal, bacterial, and viral infections that could spread through the body.

- Healthcare providers should be informed of any infections, including open cuts or sores, intermittent infections such as cold sores, or chronic infections. Patients should be monitored for any signs of infection before, during, and after treatment.
- Healthcare providers should be informed of any current or past conditions or medications that affect the immune system and whether patients have ever lived in areas such as the Ohio or Mississippi River valleys, where fungal infections are common.
- Patients should be tested for inactive tuberculosis (TB) or hepatitis B infection before treatment.
- Healthcare providers should be informed if patients have ever had TB, ever been in a country where TB is common, or been around someone who has ever had TB.
- Healthcare providers should be informed immediately of any of the following symptoms before, during, or shortly after treatment: sweating; sore throat; cough; coughing up bloody mucus; fever; weight loss; weakness; loss of muscle tone; yellowing of the skin or eyes; loss of appetite; nausea or vomiting; muscle aches; dark urine; clay-colored bowel movements; chills; stomach pain; rash; extreme tiredness; diarrhea; stomach pain; warm, red, or painful skin; painful, difficult, or frequent urination; or other signs of infection.

Adalimumab should not be stopped without consulting the prescribing physician. All healthcare providers, including dentists, should be told about adalimumab treatment before any type of surgery. Patients should not receive any **vaccinations** without talking to their doctor.

Adalimumab is very expensive—about \$2,450 per month for two 40 mg injections—and lifelong treatment may be required. It is not clear whether disease remission can be maintained after stopping adalimumab. For example, HA symptoms worsened in some patients when treatment frequency was reduced.

Pediatric

Children should have all of their required vaccinations before beginning treatment with adalimumab. Some children, teens, and young adults treated with adalimumab or similar medications have developed severe or life-threatening cancers, including lymphoma. Some adolescents and young adult males treated with adalimumab or similar medications—usually for CD or UC along with the drugs azathioprine or 6-mercaptopurine—have developed hepatosplenic T-cell lymphoma, which is often quickly fatal.

Pregnant or breastfeeding

Adalimumab is in the FDA low-risk pregnancy category B. Studies have not found any increased risk of birth defects or miscarriage in women treated with adalimumab or other TNF inhibitors during pregnancy. Large amounts of adalimumab are not expected to reach the placenta until the second or third trimester of pregnancy. On average, it takes about ten weeks after the last injection for adalimumab to completely clear the body. Adalimumab is being studied to determine whether it can improve the success of some fertility treatments in certain women. Nevertheless, women who are pregnant or breastfeeding, planning to become pregnant, or become pregnant while taking adalimumab should consult with their healthcare providers.

Because adalimumab is a very large protein, very little will pass into breast milk, and studies have suggested that breast milk levels are very low. Furthermore, adalimumab is not well absorbed by the gut, so any present in breast milk would not be well absorbed by the baby's digestive system. Premature infants with underdeveloped digestive systems may absorb more.

Other conditions and allergies

Patients should inform their healthcare providers if they are allergic to adalimumab, any of its ingredients, or any other medications, and if the patient or person injecting the drug is allergic to latex or rubber. Healthcare providers should be informed if patients have ever had numbness or tingling in any part of the body; any disease that affects the nervous system, such as multiple sclerosis; cancer; or heart disease. Patients with psoriasis should inform their healthcare providers if they have been treated with light therapy.

Side effects

The most common side effects of adalimumab are:

- injection site reactions such as redness, rash, swelling, itching, pain, or bruising
- upper respiratory infections, including sinus infections
- headaches
- rash
- nausea

The most serious potential side effects of adalimumab are TB, sepsis (a life-threatening blood infection), and, rarely, cancer, including lymphoma or skin cancer. In addition to the symptoms in the boxed warning, side effects that are medical emergencies include:

- numbness or tingling
- vision problems

- leg weakness
- chest pain
- shortness of breath
- sunlight-sensitive rash on the cheeks or arms
- new joint pain
- itching or hives
- swelling of the face, feet, ankles, or lower legs
- difficulty breathing or swallowing
- fever, sore throat, chills, or other signs of infection
- unusual bruising or bleeding
- pale skin
- dizziness
- red, scaly patches or pus-filled bumps on the skin

Interactions

Patients should tell their healthcare providers about all of their prescription and nonprescription medications, vitamins, nutritional supplements, and herbal products.

Drugs

Medications that decrease immune system activity and may require changing adalimumab dosages or monitoring for side effects include:

- abatacept
- anakinra
- certolizumab
- **etanercept**
- golimumab
- **infliximab**
- MTX
- **rituximab**
- steroids such as dexamethasone, **methylprednisolone**, **prednisone**, or prednisolone

Resources

BOOKS

Koo, John Y. M., et al, eds. *Moderate to Severe Psoriasis*. Boca Raton, LA: CRC Press, 2014.

PERIODICALS

Curtis, Jeffrey R., et al. "Estimating Effectiveness and Cost of Biologics for Rheumatoid Arthritis: Application of a Validated Algorithm to Commercial Insurance Claims." *Clinical Therapeutics* 36, no. 7 (July 2014): 996–1004.

Kimball, A. B., et al. "Adalimumab for the Treatment of Hidradenitis Suppurativa." *Annals of Internal Medicine* 157, no. 12 (2012): 1–50.

Shader, Richard I. "Rheumatoid Arthritis and More." *Clinical Therapeutics* 36, no. 7 (July 2014): 993–94.

Tanaka, Yoshiya, and Shintaro Hirata. "Is It Possible to Withdraw Biologics from Therapy in Rheumatoid Arthritis?" *Clinical Therapeutics* 35, no. 12 (December 2013): 2028–35.

Tkacz, Joseph, et al. "Utilization and Adherence Patterns of Subcutaneously Administered Anti-Tumor Necrosis Factor Treatment among Rheumatoid Arthritis Patients." *Clinical Therapeutics* 36, no. 5 (May 2014): 737–47.

OTHER

Organization of Teratology Information Specialists. "Adalimumab (Humira) and Pregnancy." http://www.mothertobaby.org/files/Adalimumab_Humira.pdf (accessed January 15, 2015).

U.S. Food and Drug Administration. "Medication Guide Humira (Hu-MARE-ah) (Adalimumab) Injection." AbbVie Inc. <http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088611.pdf> (accessed January 15, 2015).

WEBSITES

Agency for Healthcare Research and Quality. "Medicines for Psoriatic Arthritis: A Review of the Research for Adults." Effective Health Care Program: Helping You Make Better Treatment Choices. <http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1312> (accessed January 15, 2015).

U.S. National Library of Medicine. "Adalimumab Injection." MedlinePlus. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a603010.html> (accessed January 15, 2015).

ORGANIZATIONS

Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, (301) 427-1364, <http://www.ahrq.gov/>.

Crohn's & Colitis Foundation of America, 733 Third Avenue, Suite 510, New York, NY 10017, (800) 932-2423, info@ccfa.org, <http://www.ccfa.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Adderall see **Dextroamphetamine**

Adipex-P see **Phentermine**

Adrenaclick see **Epinephrine**

Advair see **Fluticasone/salmeterol**

Advil see **Ibuprofen**

Aggrenox see **Aspirin/extended-release dipyridamole**

Albendazole

Definition

Albendazole is an anthelmintic drug used to treat infections with parasites such as worms. It is considered a broad-spectrum agent, meaning that it has activity against a wide variety of parasites.

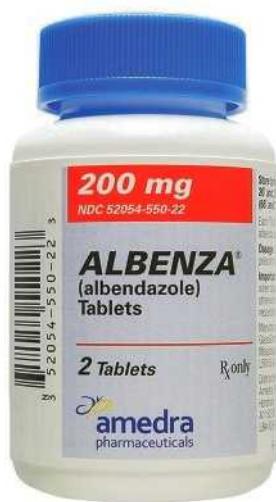
Purpose

Albendazole is used to treat an infection of the brain (neurocysticercosis) by the pork tapeworm called *Taenia solium*, as well as infections of the liver, lung, or lining of the abdominal cavity (peritoneum) known as hydatid disease, caused by the larval form of the dog tapeworm *Echinococcus granulosus*.

Description

Albendazole is a 12-millimeter (mm) round, white tablet imprinted on one side with a pentagon and either ap;550 or SB;5500. Each pill contains 200 milligrams (mg) of active drug. The medication is taken by mouth and must be prescribed by a healthcare provider.

Albendazole is on the World Health Organization's list of essential medicines. It is also frequently used in veterinary medicine.



Albenza (albendazole), 200 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

U.S. brand names

Albendazole is sold in the United States under the name Albenza.

Canadian brand names

Albendazole is not commercially available in Canada.

International brand names

Albendazole is sold in many countries worldwide under a variety of names, including Abentel (China and Thailand), AL (India), Albakil (Kenya), Bruzol (Mexico), Parasin (Brazil), Vermigen (Ecuador). In some countries, Albendazole is only one component of the medication, and there are other medications included in the formulation. In some locations, it is available only for veterinary, not human, use.

Recommended dosage

Children and adults who are treated with albendazole should be prescribed 15 mg per kilogram (kg, or 2.2 lb.) of body weight per day, with a maximum daily dosage of 800 mg, divided into two daily doses. The length of treatment varies, running between 8 and 30 days (for example) for infections caused by the pork tapeworm *Taenia solium*. Infections with the dog tapeworm *Echinococcus granulosus* are treated in three cycles, with each cycle alternating 28 days of treatment with albendazole followed by 14 days without the drug.

Albendazole should be taken by mouth with a high-fat meal for optimal absorption. If swallowing is difficult for children or the elderly, the tablets may be crushed or chewed.

Precautions

The following precautions apply to all individuals:

- Albendazole should be taken for the entire length of the prescription, even if symptoms have ceased. Failure to take a complete course of the medication can result in a return of the infection.
- The drug should not be taken by individuals who are hypersensitive to albendazole or other anthelmintic drugs or to any other ingredient of the preparation.
- During the first week of therapy with albendazole, the patient should also take an anticonvulsant medication (to prevent seizures) and a corticosteroid (to decrease inflammation).
- Albendazole can cause liver damage. Liver function should be monitored every two weeks throughout treatment. If blood tests reveal severe liver problems, treatment may need to be interrupted and restarted when

KEY TERMS

Anthelmintic—A drug that is used to treat an infection with parasitic worms.

Hydatid—A cyst (fluid-filled sac) containing the dog tapeworm *Echinococcus granulosus*.

Larval—Describing the earliest life-form of a worm.

Neurocysticercosis—An infection of the brain by the pork tapeworm called *Taenia solium*, resulting in the establishment of larva-containing cysts throughout the brain substance.

Parasite—A type of organism that survives within another living host and nourishes itself by using that host's energy stores without providing the host with any benefit.

Peritoneum—The smooth membrane that lines the abdominal cavity.

Tapeworm—A type of flatworm that has many segments and lives within the intestine of its hosts (which can include humans and other animals that have backbones [vertebrates]).

levels return to normal. Individuals with a history of liver problems should inform their health provider prior to starting the medication.

- Albendazole can lead to potentially life-threatening bone marrow suppression. Blood counts should be monitored every two weeks throughout treatment. Individuals who have poor liver function are at higher risk of this complication.
- Individuals may notice upset stomach or nausea.

Pregnant or breastfeeding

Albendazole is classified as a pregnancy category C drug, meaning that risk to a developing fetus cannot be ruled out in pregnant women. If at all possible, this drug should be avoided during pregnancy. A negative pregnancy test should be obtained prior to starting treatment. If pregnancy occurs during treatment, the drug should be stopped. Women should wait for at least one month after treatment is over to attempt to become pregnant.

Small amounts of albendazole pass into human milk. Nonetheless, care should be used when it is prescribed to a breastfeeding woman.

Side effects

Common side effects of albendazole treatment include:

- upset stomach or indigestion
- nausea
- headache, especially among those treated for neurocysticercosis
- blood test evidence of liver damage, especially among those treated for hydatid disease

Uncommon side effects of albendazole treatment should be reported to the healthcare provider. These include:

- signs of infection
- bleeding
- yellow skin
- yellow tone to the whites of the eye
- severe headache
- weakness
- vision changes

Rare but serious signs of a significant reaction to albendazole should prompt the individual to seek immediate medical care. These include:

- difficulty breathing
- wheezing
- fever
- cough
- blue skin or lips
- seizures
- swollen face, lips, tongue, or throat

Interactions

Drugs

Drugs that may decrease the amount of albendazole in the bloodstream include antimalarial drugs such as aminoquinolines as well as the drugs **carbamazepine** (Tegretol), phenobarbital, and **phenytoin** (Dilantin).

Food and other substances

Grapefruit and grapefruit juice may increase levels of the drug in the body and should be avoided.

Resources

BOOKS

- Cherry, J., et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Saunders/Elsevier, 2014.
- Drug Information Handbook*. 23rd ed. Hudson: Lexicomp Inc., 2014.
- Magill, Alan J., et al, eds. *Hunter's Tropical Medicine and Emerging Infectious Disease*. Philadelphia: Saunders/Elsevier, 2013.

Mandell, G. L., et al. *Douglas and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. London: Churchill Livingstone, 2015.

Rang, H. P., et al. *Rang & Dale's Pharmacology*. 7th ed. London: Churchill Livingstone, 2012.

PERIODICALS

Shah, C., et al. "Recurrent Acute Hepatitis Caused by Albendazole." *Tropical Gastroenterology* 34, no. 1 (2013): 38–39.

OTHER

World Health Organization (WHO). *WHO Model List of Essential Medicines*. 18th ed., April 2013. Available online at: http://apps.who.int/iris/bitstream/10665/93142/1/EML_18_eng.pdf (accessed January 27, 2015).

WEBSITES

MedlinePlus. "Albendazole." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a610019.html> (accessed January 11, 2015).

Toxnet. *LactMed: Drugs and Lactation Database*. U.S. National Library of Medicine, National Institutes of Health. <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm> (accessed January 11, 2015).

U.S. Food and Drug Administration. "Albendazole." http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Set_Current_Drug&ApplNo=020666&DrugName=ALBENZA&ActiveIngred=ALBENDAZOLE&SponsorApplicant=AMEDRA%20PHARMS&ProductMktStatus=1&goto=Search.DrugDetails (accessed January 11, 2015).

ORGANIZATIONS

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rosalyn S. Carson-Dewitt, MD

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Albenza see **Albendazole**

Albuterol

Definition

Albuterol is a medication that helps prevent or ease symptoms of asthma and chronic obstructive pulmonary disease (COPD). The medicine usually comes in liquid form that is inhaled by mouth through an aerosol dispenser.



Proventil HFA (albuterol) inhaler. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

More than 230 million people around the world have asthma, a chronic lung disease that narrows the airways. Another 200 million have COPD. As a bronchodilator, albuterol helps to dilate, or open, the airways. The medicine may be used as a rescue drug to provide quick relief to a person with asthma who needs help breathing. In other cases, albuterol is used to prevent the airways from closing. People who become short of breath when they exercise may inhale albuterol before beginning exercise to help keep their airways open while they exert themselves. The medicine can also be long acting, helping people who have chronic lung diseases such as COPD keep their chests from tightening, ease coughing, and breathe easier throughout the day. Inhaled bronchodilators such as albuterol are the medicines used most often to help people who have COPD.

Description

Also known as albuterol sulfate, albuterol is a clear, sterile solution in liquid form. Although the generic form of the drug is called albuterol in the United States, the World Health Organization (WHO) refers to the same generic medicine as salbutamol. The drug is contained inside a small aerosol canister. The active ingredient in albuterol is a beta-2 receptor agonist, which also comes in pill form. Using inhaled forms of albuterol and similar medicines is preferred because the drugs act more quickly and because inhaling the medicine before exercise can help prevent

exertion-related asthma attacks. Irritation in the lungs can cause the muscles around the airways to tighten. The beta-2 agonists relax the muscles around airways, helping them open up to allow improved breathing.

Most forms of albuterol are short acting, meaning they provide relief quickly, but the effect of the albuterol wears off after four to six hours. Albuterol may also be inhaled through the use of a nebulizer, a small device that changes medicine from a liquid to a mist so that the patient can more easily inhale. Breathing treatments with a nebulizer take longer, generally about 10–15 minutes. Patients may use albuterol in nebulizers at home or in hospitals and other health settings. There are long-acting forms of the medication as well.

In the past, substances called chlorofluorocarbons (CFCs) were added to the inhalers to help propel the albuterol sulfate out of the container, through a plastic tube called an actuator, and into a patient's mouth. After December 31, 2008, inhalers with CFCs were no longer allowed to be sold in the United States. The CFCs are harmful to the earth's ozone layer and were discontinued in the inhalers because of international agreements. Newer inhalers have hydrofluoroalkanes (HFAs), which exert a slightly softer propulsion of the medicine.

U.S. brand names

Inhaled albuterol is available only with a prescription in the United States and is sold under several brand names, including:

- Proventil HFA
- Ventolin HFA
- ProAir HFA
- Accuneb

Canadian brand names

In Canada, albuterol, or salbutamol, comes in several brands, including:

- Ventolin Inhaler
- Alti-Salbutamol Inhalation Aerosol
- Salbutamol Nebuamp

Recommended dosage

Dosage for albuterol inhalation varies according to the reason for its use. The inhaler meters the dose so that only a specified amount of medicine is released from the canister with each puff. Generally, adults using albuterol inhalers for acute asthma, or asthma attacks, take two puffs every four to six hours as needed. The same dose is recommended for adults with COPD, who may receive

KEY TERMS

Acute—Having a sudden onset and lasting a short time.

Bronchodilator—A drug that dilates, or expands, the air passages, also known as the bronchi. Albuterol is a bronchodilator.

Chronic—A disease or condition that progresses slowly but persists or recurs over time.

Chronic obstructive pulmonary disease (COPD)—A group of respiratory, or lung, diseases that cause blocked airflow and difficulty breathing. The most common are chronic bronchitis and emphysema. COPD usually becomes progressively worse over time, and the lung damage cannot be reversed.

Diuretic—A drug or agent that causes urine to be excreted from the body, often used to prevent fluid retention; also called water pills.

other treatments along with albuterol inhalation to control their symptoms.

Anyone prescribed albuterol inhalation should carefully read and follow instructions for the inhaler's use. Although doses are metered and relatively easy to use, there is a specific technique of breathing that ensures the user receives a full dose of the medicine. For example, when people use an inhaler, they should close their mouths around the dispenser and hold their breath for ten seconds before breathing out. It is recommended that patients demonstrate the proper technique for their doctor or other healthcare provider before leaving with the medication to show that they understand the proper use of the inhaler.

Pediatric

Infants and children up to age four years old with asthma usually receive albuterol through a nebulizer every four to six hours, gradually reducing frequency until the acute episode has improved. Dose is based on the child's age and size. After age four or five, children can use inhalers every four to six hours as necessary.

Precautions

When a doctor prescribes albuterol with an inhaler, it is essential to learn how to use the inhaler appropriately and to follow all dosing directions in the medicine's literature. Following the directions that accompany the albuterol prescription can help reduce the risk of complications. Patients should rinse their mouths after

PATIENT PROFILE

A young man aged 18 with chronic asthma since childhood had been using albuterol inhalation solution to reduce coughing spasms (bronchospasms) and wheezing associated with various allergies and physical exertion. Treatment consisted of breathing albuterol sulfate (Proventil) drug solution delivered by a jet nebulizer. Albuterol is a bronchodilator that opens the inflamed airways characteristic of asthma and bronchitis. Breathing the drug solution relaxes airway muscles, which increases airflow to the lungs and improves breathing. Although asthma had been diagnosed in this patient during childhood and was expected to improve as he matured, he still experienced asthma symptoms when he played baseball, exercised at the gym, or went running. As a child and throughout his teen years, the patient received regular nebulizer treatments using 1.2 mg per 3 mL of albuterol inhalation solution up to four times a day to relieve symptoms. However, when he was a college student playing soccer and baseball, this dosage no longer relieved his symptoms effectively. His doctor then prescribed an adult dose of 2.5 mg albuterol in each 3 mL of solution, as needed, using a hand-held metered-dose inhaler. He was instructed to keep the inhaler with him at all times, since the drug's lack of effectiveness could be a sign that his asthma was worsening or that he might be at risk of having a more serious asthma attack.

Although the increased dose of albuterol reduced his asthma symptoms, the young man had begun to experience dizziness, a feeling of nervousness, and tremors after using the medication, especially after starting a new cannister. In a visit to the doctor, the patient revealed that he had been using the inhaler regularly before practice and during

games to try to prevent asthma attacks before they happened. Although this extra usage did not constitute an overdose, the doctor estimated that it exceeded the amount the young man should be taking based on his weight and overall health status and had resulted in the troublesome symptoms. The doctor confirmed that the symptoms were definitely associated with albuterol use, especially excessive use, and advised the patient that his treatment should be re-evaluated and dosage controlled more carefully.

A new regimen was suggested by the doctor that would combine two treatments to handle both short-term and long-term asthma symptoms. Short-term treatment for immediate relief when needed would still include using an albuterol inhaler, but only in those situations, such as after exercise, when symptoms flared suddenly. For immediate relief, the patient was instructed to take a maximum of three metered aerosol treatments of 2.5 mg 20 minutes apart within one hour. For longer-term effects and maintenance, the patient was given a prescription for a long-acting beta-2 agonist called salmeterol, prepared in powder form in an inhaler. It would be taken daily on schedule (one puff every 12 hours). In addition, his doctor reminded him that the best way to avoid asthma attacks was to avoid what triggered them. Understanding that participating in athletics was important to this young man, the doctor suggested limiting his actual playing time, taking time to cool down and rest after games, and following his treatment regimen precisely. Applying this regimen for three months showed that use of the long-acting drug did not interfere with the effectiveness of the short-acting emergency treatment, and no side effects developed with the combined treatment.

using a metered dose inhaler. If use of albuterol causes wheezing or difficulty breathing, patients should stop using the drug and contact their healthcare provider right away.

Pediatric

Children who have a condition called status asthmaticus, which is characterized by severe asthma attacks that do not respond to bronchodilators, often require a hospital stay. They may require continuous albuterol therapy along with other treatment. Children may need help learning to use their inhalers properly and remembering to take all doses as directed.

Geriatric

COPD occurs most often in people age 64 and older. As people age, their response to bronchodilators may not be

as rapid or effective. Still, use of inhaled albuterol can help relieve symptoms during flare-ups of COPD symptoms.

Pregnant or breastfeeding

Inhaled albuterol is labeled as category C for pregnant women, meaning that the drug has shown some harmful side effects in animal studies and should be used only when its benefits outweigh potential risks. There are limited studies about albuterol's effects in breastfeeding, but it is generally not recommended that women who breastfeed use the drug. Women who rely on albuterol inhalers should contact their healthcare providers when they become pregnant to discuss how they will manage their respiratory diseases during pregnancy.

Side effects

The most common side effects of inhaled albuterol use are trembling and shakiness in the hands, feet, arms,

and legs. Many patients also report feeling their hearts pound, race, or beat irregularly. This could indicate a serious side effect and should be reported to a physician. The drug has other reported side effects, but anyone using the medicine, especially for the first time, should report any unusual symptoms to their doctors. Possible side effects include:

- coughing
- nervousness
- hoarseness
- throat irritation
- pain in the back or other bones and muscles
- slowed or irregular breathing
- hives or rashes
- facial swelling
- wheezing or noisy breathing
- chest pain
- itching
- difficulty breathing
- problems with swallowing
- increased sweating

Pediatric

Many of the reported side effects can occur in children. In addition, some children using inhaled albuterol experience insomnia, nosebleeds, and hyperactivity. There may be an increased risk of conjunctivitis, an eye infection commonly known as pink eye, in young children using albuterol. In general, children can be more sensitive to the drug's effects and may require dose adjustments.

Geriatric

As people age, they can become less tolerant of all drugs and may be more sensitive to albuterol, resulting in more side effects or more severe effects.

Interactions

When prescribed albuterol, patients should inform their doctor or pharmacist of any other drugs they are taking, including herbs and supplements. The doctor may be able to find alternatives for one of the medicines or adjust doses to prevent bothersome or serious side effects. In some cases, drug interactions cause one drug not to work as it should.

Drugs

A drug used to treat depression and anxiety called **duloxetine** (Cymbalta) can increase heart rate, which can also occur with albuterol. Using both drugs together can

cause serious problems, especially for patients who have heart disease or high blood pressure (hypertension). Taking albuterol with the diuretic **furosemide** (Lasix) can put some people at higher risk for severely low potassium levels in their blood and associated complications. Other interactions are likely minor, but patients taking the following medications should be especially sure to mention the drugs to their doctors:

- beta-blockers (such as **propranolol** or metoprolol)
- **epinephrine**
- other bronchodilators or other drugs that relax the air passages, such as metaproterenol
- antidepressants such as **amitriptyline** or clomipramine, as well as others

Resources

PERIODICALS

Kenyon, Chen C., et al. "Safety and Effectiveness of Continuous Aerosolized Albuterol in the Non-Intensive Care Setting." *Pediatrics* 134, no. 4 (2014): e976–82.

OTHER

Forum of International Respiratory Societies. *Respiratory Diseases in the World: Realities of Today—Opportunities for Tomorrow*. <http://www.thoracic.org/global-health/firs-report-respiratory-diseases-in-the-world/resources/firs-report-for-web.pdf> (accessed December 23, 2014).

WEBSITES

"Albuterol Inhalation." Drugs.com. <http://www.drugs.com/albuterol.html> (accessed December 23, 2014).

Asthma Society of Canada. "How to Use Your Inhaler." <http://www.asthma.ca/adults/treatment/meteredDoseInhaler.php> (accessed December 23, 2014).

MedlinePlus. "Albuterol." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a607004.html> (accessed December 23, 2014).

MedlinePlus. "Albuterol Oral Inhalation." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682145.html> (accessed December 23, 2014).

Medscape. "Albuterol RX." <http://reference.medscape.com/drug/proventil-hfa-ventolin-hfa-albuterol-343426#0> (accessed December 23, 2014).

U.S. Food and Drug Administration. "Transition from CFC Propelled Albuterol Inhalers to HFA Propelled Albuterol Inhalers: Questions and Answers." http://www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm077808.htm#How_different (accessed December 23, 2014).

U.S. National Library of Medicine. "Albuterol—Albuterol Aerosol, Metered." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5928> (accessed December 23, 2014).

ORGANIZATIONS

American Lung Association, 55 W. Wacker Drive, Suite 1150,
Chicago, IL 60601, (202) 452-1805, (800) 586-4872,
<http://www.lung.org/>.

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Albuterol/ipratropium

Definition

Albuterol and **ipratropium** bromide are bronchodilators, which are drugs that relax the muscles in the airways. This action opens the airways and increases airflow to the lungs. Individually, albuterol and ipratropium are often used to provide relief of bronchospasm, which is a tightening of the muscles around the airways. The two drugs are also used in combination (albuterol/ipratropium) to treat certain patients who have chronic obstructive pulmonary disease (COPD).

Purpose

The combination of albuterol and ipratropium is prescribed for select patients who have chronic bronchitis, emphysema, or other forms of COPD and are already

using a regular inhaler but are still experiencing bronchospasm and would benefit from additional care. Chronic bronchitis causes swelling of the bronchi, which are two large air tubes that branch off the windpipe (trachea) and lead to the lungs. Emphysema is a disease in which the air sacs, or alveoli, in the lungs are damaged. Both chronic bronchitis and emphysema fall under the classification of COPD, which includes a wide variety of diseases that cause lung and airway problems.

Description

The combination of albuterol and ipratropium is used for the treatment of COPD. The drugs act on bands of muscles around the bronchi and the bronchioles, which are smaller branches of the bronchi. When the lungs are irritated, these muscle bands can tighten and constrict the bronchi and bronchioles, which limits the amount of air that can flow through them.

Both the sympathetic and parasympathetic nervous systems are involved in controlling the muscles of the blood vessels. Albuterol has its effects on the sympathetic system and ipratropium on the parasympathetic system.

Albuterol and the sympathetic system

The sympathetic nervous system is often described as the “fight or flight” system. **Epinephrine** (also known as adrenalin) prepares the body for action by binding to ports called receptors on certain nerves, which go by the name of adrenergic nerves. There are several different adrenergic receptors, including the beta-2 adrenergic receptor. When this receptor binds with epinephrine, it causes the smooth muscles of the airways to relax, which allows the person to take in more air, including the oxygen that fuels cells.

Albuterol works by mimicking epinephrine. Known as a beta-agonist, albuterol binds to the beta-2 adrenergic receptor, and, as occurs with epinephrine, the smooth muscles of the airways relax to let more air through.

Ipratropium and the parasympathetic system

The parasympathetic nervous system is often described as the “rest or digest” system, because it controls body functions associated with those two activities (as well as others). Instead of epinephrine and adrenergic receptors, as seen in the sympathetic system, the counterparts in the parasympathetic system are acetylcholine and cholinergic receptors. When acetylcholine binds to cholinergic receptors, the smooth muscles of the airways contract, making the airways narrower. Ipratropium disrupts the binding of acetylcholine, which allows the airways to relax and open and improves airflow. Because of ipratropium’s relationship to cholinergic receptors, it is known as an anticholinergic drug.



Albuterol/ipratropium, 0.5 mg. (Reprinted with permission.
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Combination albuterol/ipratropium

Although albuterol and ipratropium have different mechanisms and work on distinct nervous systems, their ultimate effect is the same: the smooth muscles of the airways relax, the airways open, and the patient can breathe easier. Combination albuterol/ipratropium is typically administered via aerosol inhalers. The patient inhales the combination drug, and within a matter of three to five minutes, the muscles begin to relax. The drugs typically continue working for four to six hours.

U.S. brand names

Combination albuterol/ipratropium is sold in the United States under the brand names of:

- Combivent Respimat
- DuoNeb

Until 2013, many patients used Combivent Inhalation Aerosol inhalers. These, however, were phased out because the inhalers contained chlorofluorocarbons (CFCs), known to harm the environment. These CFCs, which had been utilized in many aerosols, contribute to the depletion of the atmospheric ozone layer. The ozone layer protects the earth from the sun's ultraviolet (UV) radiation, especially the portion of UV light known as UVB, which can cause skin cancer and cataracts in humans.

Canadian brand names

In Canada, Ratio-Ipra Sal Udv is a brand name for combination albuterol/ipratropium.

International brand names

International brand names for combination albuterol/ipratropium include:

- Almeida
- Atrolin
- Besmate
- Biwind
- Combipramol
- Combipul
- Demoren
- Dospir
- Duavent
- Duoastalin
- Duolin
- Iprasol Naos
- Pulmodual
- Ren Shu
- Salbair-I
- Salipra

KEY TERMS

Acute—Having a sudden onset and lasting a short time.

Alveoli—Small spherical sacs at the ends of the bronchioles in the lungs in which blood gases are exchanged.

Bronchi—Two large air tubes that branch off the windpipe (trachea).

Bronchioles—Very small, thin-walled air passages in the lungs that branch off from the bronchi.

Bronchodilator—A drug that dilates, or expands, the air passages (bronchi).

Bronchospasm—Tightening of the muscles around the airways.

Chronic—Progressing slowly but persisting or recurring over time.

Chronic obstructive pulmonary disease—A collection of respiratory diseases (often abbreviated COPD) that cause breathing difficulties. Two common COPDs are chronic bronchitis and emphysema.

Diuretic—A drug or agent that causes urine to be excreted from the body and is often used to prevent fluid retention; also called water pills.

- Sulprex
- Windel Plus

Recommended dosage

Combination albuterol/ipratropium is typically used in aerosol form and administered with an inhaler. The dosage per pump of the Combivent Respimat inhaler is 20 micrograms (mcg) of ipratropium bromide and 100 mcg of albuterol. This is administered via one inhalation of the inhaler four times a day, not to exceed six doses in a 24-hour period. Some inhalers administer half of these amounts, and dosage is adjusted accordingly. Patients inhale as the dose is administered. Patients should pay careful attention to their healthcare providers' instructions regarding the correct use of the inhaler and should be confident in their ability to use it properly to ensure that they receive the full dose of medication.

Precautions

Healthcare providers should take into account a patient's other health conditions before prescribing combination albuterol/ipratropium. Specific conditions of concern include cardiovascular disease, arrhythmia (abnormal

heartbeat), hypertension (high blood pressure), epilepsy or other seizure disorder, glaucoma, urination difficulties (including those associated with enlarged prostate), liver disease, kidney disease, diabetes, and overactive thyroid.

Pediatric

Children are typically not candidates for this treatment because they are not normally part of the target population (people who have COPD and are already using a regular inhaler but are still experiencing bronchospasm).

Geriatric

Geriatric individuals are more likely to have other health conditions, especially cardiac and certain respiratory disorders. This may lead the healthcare provider to monitor the patient more carefully while the patient is taking combination albuterol/ipratropium, especially initially.

Pregnant or breastfeeding

Although studies have not demonstrated specific side effects in pregnant or nursing women or in the fetus or infant, patients who are pregnant or nursing should consult their doctors about the use of combination albuterol/ipratropium and potential risks. Combination albuterol/ipratropium may interfere with contraction of the uterus during labor and delivery, so this medication should be used with caution in patients for whom the benefits are greater than the risks.

Other conditions and allergies

Persons with allergic reactions to either albuterol or ipratropium should not take this medication.

Side effects

Common side effects include a mild headache and symptoms similar to those of a cold. Some individuals may experience allergic reactions to combination albuterol/ipratropium. Symptoms of a reaction may include hives; swelling of the throat, face, lips, or tongue; and difficulty breathing. Patients who experience any of these allergic reactions should seek emergency medical assistance. Other side effects, which can be serious, include:

- swelling of the extremities
- chest pain, possibly accompanied by a pounding or fluttering heartbeat
- blood pressure that reaches dangerously high levels, possibly accompanied by irregular heartbeat, severe headache, and anxiety
- vision problems, such as blurring or halos around lights
- eye pain and possibly increases in eye pressure, which can exacerbate any existing glaucoma

- urine retention
- difficult or painful urination
- breathing problems, such as bronchospasms, choking, or wheezing, which can be life threatening
- potassium levels that are too low, possibly accompanied by confusion or other symptoms

Patients with these serious side effects should contact their doctor without delay and, when conditions warrant, should seek emergency care.

Geriatric

No additional side effects are noted for geriatric patients, but side effects among older patients may occur more often and with increased severity compared with a younger population.

Interactions

Patients should inform their doctors or pharmacists of any other drugs they are taking, including herbs and supplements, to avoid potential interactions.

Drugs

Interactions may occur between combination albuterol/ipratropium and the following drugs:

- other anticholinergic or beta-adrenergic medications, which may increase the risk for side effects associated with ipratropium (an anticholinergic drug) or albuterol (a beta-adrenergic drug).
- beta-receptor blocking agents
- certain diuretics (often called “water pills”), especially loop or thiazide diuretics
- monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants (Lomont, Norpramin, Noveril, Pamelor, Pertofrane, and others)

Resources

BOOKS

- Namba, Jennifer M., and Michael J. Freudiger. “Pharmacotherapy.” In *Manual of Clinical Problems in Pulmonary Medicine*, edited by Timothy A. Morris, Andrew L. Ries, and Richard A. Bordow. 7th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2014.
- Wells, Barbara, et al. “Chronic Obstructive Pulmonary Disease.” In *Pharmacotherapy Handbook*. 9th ed. New York: McGraw-Hill Education Medical, 2015.

PERIODICALS

- Bollu, V. K., et al. “Comparison of Efficacy and Safety Outcomes in Randomized Trials of Long-Acting and Short-Acting B2-Agonists for Chronic Pulmonary Disease: A Review.” *Pulmonary & Respiratory Medicine* 3, no. 1 (2013): 1–5.

Zanasi, A., et al. "A Randomized, Placebo-Controlled, Double-Blind Trial on the Management of Post-Infective Cough by Inhaled Ipratropium and Salbutamol Administered in Combination." *Pulmonary Pharmacology & Therapeutics* 29, no. 2 (2014): 224–32.

WEBSITES

AHFS Consumer Medication Information. "Albuterol and Ipratropium Oral Inhalation." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601063.html> (accessed February 20, 2015).

American Academy of Allergy, Asthma & Immunology. "Asthma Conditions and Treatments." AAAAI.org. <http://www.aaaai.org/conditions-and-treatments/asthma.aspx> (accessed December 31, 2014).

American Thoracic Society. "What Are Beta-Agonists?" Thoracic.org. <http://www.thoracic.org/clinical/copd-guidelines/for-patients/what-kind-of-medications-are-there-for-copd/what-are-beta-agonists.php> (accessed December 31, 2014).

Asthma Society of Canada. "How to Use Your Inhaler." Thoracic.org. <http://www.asthma.ca/adults/treatment/meteredDoseInhaler.php> (accessed February 20, 2015).

Boehringer Ingelheim Pharmaceuticals, Inc. "Combivent Respimat." Combivent.com. <http://www.combivent.com> (accessed December 31, 2014).

Drugs.com. "Ipratropium Bromide." <http://www.drugs.com/international/ipratropium-bromide.html> (accessed December 31, 2014).

Mayo Clinic staff. "Albuterol (Inhalation Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/albuterol-inhalation-route/description/drg-20073536> (accessed December 31, 2014).

Palo Alto Medical Foundation, Sutter Health. "Rescue Reliever Medications & Short-Acting Beta Agonists." <http://www.pamf.org/asthma/medications/inhaled/shortacting.html> (accessed December 31, 2014).

U.S. Food and Drug Administration. "Transition from CFC Propelled Albuterol Inhalers to HFA Propelled Albuterol Inhalers: Questions and Answers." <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm077808.htm> (accessed February 20, 2015).

ORGANIZATIONS

American Lung Association, 55 W. Wacker Drive, Suite 1150, Chicago, IL 60601, (800) 586-4872, <http://www.lung.org/>.

COPD Foundation, 20 F Street NW, Suite 200-A, Washington, DC 20001, (866) 316-COPD (316-2673), info@copd-foundation.org, <http://www.copdfoundation.org/>.

National Heart, Lung, and Blood Institute (NHLBI) Health Information Center, PO Box 30105, Bethesda, MD 20824, (301) 592-8573, nhlbiinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov/>.

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Aldactone see **Spironolactone**

Aldara see **Imiquimod**

Alendronate

Definition

Alendronate is a drug that regulates the levels of calcium in the blood and slows the breakdown of bone. It is used to treat osteoporosis.

Purpose

Alendronate is used to treat osteoporosis, which is a common medical condition that causes bones to weaken, making them more likely to break. According to the National Osteoporosis Foundation, approximately 54 million Americans have either osteoporosis or low bone mass, which puts them at increased risk for developing the disease. In addition, as many as 50% of women and 25% of men will suffer a bone break due to osteoporosis in their lifetimes. Often, osteoporosis carries no symptoms, so individuals are not aware that they have the disease until they suffer a broken bone. A bone density test can alert patients about their bone health as well as diagnose osteoporosis.

Uses for alendronate include the treatment of osteoporosis in postmenopausal women and glucocorticoid-induced osteoporosis among both men and women who are taking at least 7.5 milligrams (mg) daily of **prednisone** (Cortan, Deltasone), a corticosteroid drug used to treat allergic disorders, ulcerative colitis, psoriasis, and arthritis.



Alendronate, 35 mg. (U.S. National Library of Medicine, Pillbox)

Alendronate is also used to increase bone mass in men with osteoporosis; to treat Paget disease of the bone, which is abnormal bone destruction and regrowth that leads to deformed and weakened bone; and to help prevent postmenopausal osteoporosis in women.

Description

Alendronate is one of the bisphosphonates, which are a class of drugs that have two phosphonate (phosphorus-oxygen-phosphorus) molecular groups. Preparations of alendronate are available in both brand-name and generic forms for the treatment of osteoporosis. Brand names include Fosamax, which was approved by the U.S. Food and Drug Administration (FDA) in 1995, and Binosto, which received FDA approval in 2012. Both work by slowing the resorption of bone. Resorption is the removal of old bone. In osteoporosis, old bone is removed more quickly than new bone can be manufactured to replace it. By slowing resorption, the body has a chance to make sufficient replacement bone, so there is no net loss.

Alendronate typically comes in tablet form, and the tablets are taken by mouth. In some cases, such as Binosto, the tablet is first dissolved in water, where it effervesces. Some preparations are available as a solution.

Origins

Bisphosphonates were originally developed in the late nineteenth century, but it was not until decades later that researchers first began studying their medical applications. In 1960, researchers reported that the compounds could be used as a dental detergent, and in 1968, a bisphosphonate called etidronate disodium was used to treat a child with myositis ossificans progressiva (fibrodysplasia ossificans progressiva), an inherited disorder in which muscle and connective tissue are gradually ossified (replaced by bone). It was successful in controlling the patient's condition and continued to do so for many years.

This spurred studies of bisphosphonates for other medical conditions, including Paget disease of bone. Research also showed that a regimen of etidronate increased the levels of calcium and other minerals in bones and reduced the rate of vertebral fractures in high-risk patients. In the mid-1980s, a research group at Proctor & Gamble began studying the ability of bisphosphonates to treat and possibly prevent postmenopausal osteoporosis. They developed a type of bisphosphonate known as **risedronate** sodium (Actonel), which was useful in both men and women, including postmenopausal women and patients who were taking glucocorticoids.

U.S. brand names

Brand names for alendronate in the United States (as well as Canada) include:

- Fosamax
- Binosto

International brand names

Alendronate is sold under many names internationally. These include:

- Alant
- Alendix
- Bifosa
- Denfos
- Fosavance
- Ossmax
- Osteofos
- Restofos

Recommended dosage

To increase bone mass in men who have osteoporosis and to treat osteoporosis in postmenopausal women, the dosage is one 70 mg tablet or one bottle of 70 mg oral solution taken once a week, or one 10 mg tablet taken once a day.

For prevention of osteoporosis in postmenopausal women, the dosage is either one 35 mg tablet taken weekly or one 5 mg tablet taken once a day. For the treatment of glucocorticoid-induced osteoporosis in postmenopausal women who are not on hormone-replacement therapy, the dosage is one 10 mg tablet taken once a day. For the treatment of others who have glucocorticoid-induced osteoporosis, the recommended dosage is one 5 mg tablet taken once a day.

The recommended dosage for patients with Paget disease is 40 mg once a day for six months. The healthcare provider may consider a new prescription if a patient has a relapse.

Pediatric

The safety and efficacy of alendronate have not been established for pediatric patients. Studies have noted severe side effects in children, including vomiting, fever, and other flulike symptoms.

Precautions

It is recommended that patients take alendronate in the morning, swallowing a whole tablet (not crushed or chewed) with a full glass of six to eight ounces of plain water at least 30 minutes before eating or drinking

anything else—including other medications. Medication should be taken while the patient is in an upright position (sitting or standing), and the patient should remain upright for 30 minutes after taking the drug. This is because lying down after taking the drug has been reported to cause inflammation or other esophageal problems.

Patients should discuss with their healthcare provider whether they should also take a calcium supplement and vitamin D while on alendronate or before beginning alendronate.

Individuals with severe renal impairment should not take alendronate. Those who have Barrett's esophagus, difficulty swallowing (dysphagia), inflammation of the stomach lining or the first section of the intestine (gastritis or duodenitis), ulcers, or other active upper gastrointestinal problems should discuss with their healthcare provider the potential for alendronate to cause irritation of the digestive system. In addition, any patients who experience dysphagia, painful swallowing (odynophagia), pain behind the breastbone (retrosternal pain), or new or worsening heartburn should discontinue the medication and seek medical attention.

Geriatric

Elderly patients, as well those with certain gastrointestinal or other chronic conditions, may be more prone to vitamin D insufficiency and may require supplements.

Side effects

Potential side effects include:

- stomach pain
- constipation or diarrhea
- bloody or tarry stools
- digestive gas
- nausea, possibly accompanied by dark, coffee-ground-like vomit
- bone or joint pain
- muscle pain
- osteonecrosis of the jaw (bone loss due to reduction in blood supply to the bone)

If osteonecrosis of the jaw occurs, it is often associated with an invasive dental procedure, cancer or cancer treatment, poor oral hygiene, or another dental issue. The healthcare provider may recommend that the patient temporarily stop the alendronate regimen if he or she is undergoing an invasive dental procedure.

Some patients, usually postmenopausal women, have reported severe bone, muscle, or joint pain after taking alendronate, but studies have shown that the incidence is similar to that reported in other patients who

are not taking the medication. Similarly, some patients have reported low-energy femoral fractures (fractures of the upper leg bone [femur] that follow a nonsevere impact), which often manifest as hip, thigh, or groin pain, but studies have found a similar incidence of such fractures among patients who are not taking the drug.

Pregnant or breastfeeding

Healthcare providers should be cautious about prescribing alendronate to women who are pregnant or planning to become pregnant. Even if the woman stops the medication, it may remain in her body for a long period of time, and its effects on the fetus or a nursing infant are not known. A 2014 study of case reports, however, noted that the reviewed reports suggested “maternal use of bisphosphonates before or during pregnancy does not have serious fetal or neonatal adverse effects.”

Other conditions and allergies

Serious allergic reactions are rare, but patients who experience an allergic reaction (such as a rash or trouble breathing) should seek medical attention immediately.

Interactions

Patients should discuss possible interactions between alendronate and any other medications they are taking, and they should also ask the healthcare provider about the timing of drug administration.

Drugs

One particularly noted interaction is between alendronate and deferasirox (Exjade), which is used to manage iron overload caused by blood transfusions. The combination may heighten the risk for gastrointestinal ulcers and bleeding. Many other common drugs, such as **aspirin**, ibuprofen, and naproxen, and other less common medications are also known to interact with alendronate, so patients should carefully discuss all drugs they are taking with their doctor so they fully understand the risks.

Herbs and supplements

Patients should discuss all supplements, particularly mineral-containing vitamins, with their healthcare provider before beginning an alendronate regimen. Vitamins that contain calcium, magnesium, iron, or other minerals have the potential to interfere with the absorption of alendronate, impacting its effectiveness. If the treating provider does approve the use of a multivitamin, the patient should still adhere to the administration guidelines and refrain from taking the vitamin until at least 30 minutes after taking alendronate.

KEY TERMS

Bisphosphonate—One of a class of drugs, which has a phosphorus-oxygen-phosphorus structure and is often used to treat osteoporosis.

Dysphagia—Difficulty swallowing.

Ossification—The creation of new bone.

Osteoporosis—A common medical condition that causes bones to weaken, making them more likely to break.

Paget disease of the bone—Abnormal bone destruction and regrowth that leads to deformed and weakened bone.

Foods and other substances

As noted, no food or beverages should be taken until at least 30 minutes following the alendronate dosage.

Resources

BOOKS

Grob, Gerald N. *Aging Bones: A Short History of Osteoporosis*. Baltimore: Johns Hopkins University Press, 2014.

Marx, Robert E. *Oral and Intravenous Bisphosphonate-Induced Osteonecrosis of the Jaws: History, Etiology, Prevention, and Treatment*. 2nd ed. Hanover Park, IL: Quintessence, 2011.

PERIODICALS

Green, Sarah B., and Ashley L. Pappas. "Effects of Maternal Bisphosphonate Use on Fetal and Neonatal Outcomes." *American Journal of Health-System Pharmacy* 71, no. 23 (2014): 2029–36.

Ott, Susan M. "Debating the Duration of Bisphosphonate Therapy." *Journal of the American Academy of Physician Assistants* 26, no. 8 (2013): 64–65.

Shah, S. K., and G. T. Gecys. "Prednisone-Induced Osteoporosis: An Overlooked and Undertreated Adverse Effect." *Journal of the American Osteopathic Association* 106, no. 11 (2006): 653–57.

WEBSITES

"Alendronate Oral Solution." Drugs.com. <http://www.drugs.com/pro/alendronate-oral-solution.html> (accessed January 11, 2015).

Kaiser Permanente staff. "Osteoporosis: Should I Take Bisphosphonate Medicines?" Healthy.KaiserPermanente.org. https://healthy.kaiserpermanente.org/health/care/!ut/p/a0/FYhdCsIwEAbP0gOUD_zBnzfPEESTF1nTtQINN-qEuam9vA_MwM3C4wwl94kgai1Ba2_oiyqLnwJQ09Cx-8aIUHlLhBg3VcM0-wD7Km_K9GuzzjRmgpXSe_KB29OIMuz0bB6-cYBVPuxPGxiWx9Wg5nzcruwuXfcHKpbEBw!!/ (accessed January 11, 2015).

Kennel, Kurt A. "How Serious Are the Risks of Bisphosphonates, Such as Alendronate (Fosamax) and Risedronate (Actonel), When Taken for Osteoporosis? Can They Actually Cause Additional Bone Problems?" MayoClinic.org. <http://www.mayoclinic.org/diseases-conditions/osteoporosis/expert-answers/fosamax/faq-20058121> (accessed January 11, 2015).

Medicines and Healthcare Products Regulatory Agency. "Bisphosphonates." Mhra.gov.uk. [http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice-A-F/Bisphosphonates/](http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice-A-F/Bisphosphonates/) (accessed January 11, 2015).

MedlinePlus. "Osteoporosis." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601063.html> (accessed January 11, 2015).

Merck & Co. "Fosamax: Highlights of Prescribing Information." Merck.com. http://www.merck.com/product/usa/pi_circulars/f/fosamax/fosamax_pi.pdf (accessed January 11, 2015).

Mission Pharmacal Co. "Why Effervescent Alendronate?" Binosto.com. <http://www.binosto.com/why-effervescent-alendronate> (accessed January 11, 2015).

National Osteoporosis Foundation. "What Is Osteoporosis?" <http://nof.org/articles/7> (accessed January 11, 2015).

Physicians' Desk Reference. "Fosamax." PDRhealth.com. <http://www.pdrhealth.com/drugs/fosamax> (accessed January 28, 2015).

U.S. Food and Drug Administration. "Medication Guide: BINOSTO." FDA.gov. <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM318435.pdf> (accessed January 11, 2015).

ORGANIZATIONS

American Osteopathic Association, 142 E. Ontario Street, Chicago, IL 60611-2864, (800) 621-1773, (312) 202-8000, Fax: (312) 202-8200, <http://www.osteopathic.org/>.

National Osteoporosis Foundation, 1150 17th Street NW, Suite 850, Washington, DC 20036, (800) 231-4222, (202) 223-2237, info@nof.org, <http://nof.org/>.

Leslie A Mertz, PhD

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Allegra see **Fexofenadine**

Allopurinol

Definition

Allopurinol is used to lower uric acid levels in the blood and urine. It is in a class of drugs known as xanthine oxidase inhibitors.



Allopurinol, 300 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Allopurinol is prescribed for the treatment and prevention of elevated uric acid levels, which are associated with gout and certain types of kidney stones. Uric acid elevation may also occur in patients undergoing chemotherapy for the treatment of leukemia, lymphoma, or other types of cancer. If left untreated, high uric acid levels in patients receiving cancer chemotherapy can cause kidney stones and kidney failure.

Description

Uric acid is a waste product that is normally removed from the body by the kidneys. If uric acid is not properly excreted and builds up in the blood, it forms small crystals that can lead to gout or the development of kidney stones. Allopurinol decreases uric acid levels in the blood and urine by inhibiting a certain enzyme responsible for production of uric acid. It has been used for over three decades for the prevention of gouty arthritis and kidney stones, as well as to prevent tumor lysis syndrome in cancer patients.

U.S. brand names

In the United States, allopurinol is sold under the brand name Zyloprim.

Recommended dosage

Allopurinol should be taken after meals to avoid stomach upset. Patients should drink plenty of fluids (at least eight glasses of water per day) while taking this

medicine unless otherwise directed by a physician. Drinking a lot of water can help prevent the formation of kidney stones.

Adults

For mild gout, the recommended dose is 200–300 milligrams (mg) per day. For severe gout, 400–600 mg may be taken per day.

To prevent uric acid kidney stones in cancer patients, a daily amount of 600–800 mg is given in divided doses, usually starting one to two days before cancer chemotherapy and stopping two to three days after the chemotherapy is completed for that cycle.

Any total daily dose greater than 300 mg should be given in divided doses.

Pediatric

To prevent chemotherapy-related kidney stones in children younger than 10, the dose is 10 mg per kilogram (kg, or 2.2 lb.) of body weight per day, given in two to three divided doses up to a maximum dose of 800 mg per day. Another alternative is to give 150 mg per day in three divided doses for children up to 6 years of age and 300 mg per day in two to three divided doses for children 6–10 years of age.

Geriatric

Patients older than 65 years of age should be started at 100 mg per day. This dose can be increased until desired uric acid levels in the blood are reached.

Precautions

Allopurinol should be used with caution by the following populations:

- patients who have had an allergic reaction to allopurinol in the past.
- breastfeeding mothers
- children (except those who have high uric acid levels caused by cancer, chemotherapy, or genetic diseases)

Patients should call a doctor immediately if any of these symptoms develop:

- rash, itching, swelling of lips or mouth, trouble breathing (also known as hypersensitivity reaction)
- yellowing of the skin or eyes
- pain when urinating or blood in the urine
- unusual bleeding or bruising

Patients taking allopurinol will need to see a physician before starting therapy and occasionally during

KEY TERMS

ACE inhibitors—A group of drugs used to treat high blood pressure. These drugs work by decreasing production of a certain chemical in the kidneys that causes constriction of blood vessels.

Gout—A disease, especially common in men, in which patients may have high uric acid levels in the blood and sudden attacks of severe joint pain and swelling caused by deposits of uric acid crystals in those joints. These gout attacks most commonly affect the big toe.

Kidney stone—A concretion in the kidney made of various materials, such as uric acid crystals, calcium, or lipids. These concretions, or stones, cause severe pain when they are transported from the kidney into the bladder and out of the body.

Tumor lysis syndrome—A potentially life-threatening condition caused by cancer chemotherapy that is characterized by very high blood levels of uric acid, phosphate, and potassium; low levels of calcium; and acute kidney failure.

Uric acid—White, poorly soluble crystals found in the urine. Sometimes uric acid forms small, solid stones or crystals that are deposited in different organs in the body, such as the kidney. High levels of uric acid can be seen in patients with gout or cancer.

therapy to undergo blood tests for monitoring of kidney and liver function and complete blood count.

Pregnant or breastfeeding

The use of allopurinol in pregnant women should be avoided whenever possible because its effects on the human fetus are not known.

Other conditions and allergies

Patients with kidney problems may need to use lower doses of allopurinol.

Side effects

Allopurinol is usually well tolerated by most patients. The most common side effects are skin rash, hives, and itching. Loss of hair, fever, and feelings of discomfort or uneasiness may occur alone or in combination with a rash. The risk of rash is higher in people with kidney disease or people taking **amoxicillin** or ampicillin. The use of allopurinol should be discontinued at the first sign of a

rash. Other side effects include nausea, vomiting, decreased kidney function, and drowsiness (especially during the first few days of therapy). Because allopurinol can cause drowsiness, caution should be taken when performing tasks requiring alertness, such as cooking or driving.

Interactions

To avoid drug interactions, patients should always inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs and herbal or dietary supplements.

Drugs

Patients who are taking certain medicines for high blood pressure, such as diuretics (water pills) or angiotensin-converting enzyme (ACE) inhibitors (**captopril**, **lisinopril**, **enalapril**), may be at risk of hypersensitivity to allopurinol.

Allopurinol can prolong the effects of blood thinners such as warfarin (Coumadin) and put patients at risk for bleeding. It can also increase the risk of developing low blood glucose levels when taken with chlorpropamide (Diabinese), or of nerve toxicity if taken with vidarabine (Vira-A). Allopurinol can decrease the rate of breakdown of azathioprine (Imuran), mercaptopurine (6-MP), **cyclosporine** (Neoral, Sandimmune) and theophylline (Theo-Dur, Theolair, Theo-24) by the liver, increasing blood levels and side effects. Doses of azathioprine and mercaptopurine need to be reduced when they are used together with allopurinol. Mercaptopurine can be substituted for thioguanine (6-TG) to avoid this interaction altogether.

The use of amoxicillin and ampicillin should be avoided if possible in patients taking allopurinol because of increased risk of rash. Diuretics such as **hydrochlorothiazide** (Diuril) can increase the risk of toxicity and allergic reaction if used with allopurinol.

Food and other substances

Patients should consult their doctor before drinking alcoholic beverages, as alcohol can decrease the effectiveness of allopurinol. People consuming large amounts of vitamin C can be at an increased risk for kidney stones.

Resources

BOOKS

Chu, Edward, and Vincent T. DeVita Jr. *Physicians' Cancer Chemotherapy Drug Manual 2014*. Burlington, MA: Jones & Bartlett Learning, 2014.

PERIODICALS

Lam, M. P., C. K. Yeung, and B. M. Cheung. "Pharmacogenetics of Allopurinol—Making an Old Drug Safer." *Journal of Clinical Pharmacology* 53, no. 7 (2013): 675–79. <http://dx.doi.org/10.1002/jcph.67> (accessed February 11, 2015).

WEBSITES

- American Cancer Society. "Allopurinol." <http://www.cancer.org/treatment/treatmentsandsideeffects/guidetocancer-drugs/allopurinol> (accessed February 11, 2015).
- Healthwise. "Allopurinol for Kidney Stones." HealthLink BC. <http://www.healthlinkbc.ca/medications/content.asp?hwid=hw204203> (accessed February 11, 2015).
- Micromedex. "Allopurinol (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/allopurinol-oral-route/description/drg-20075476> (accessed February 11, 2015).
- U.S. National Library of Medicine, National Institutes of Health. "Allopurinol." LiverTox. <http://livertox.nih.gov/Allopurinol.htm> (accessed February 11, 2015).

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Almotriptan

Definition

Almotriptan is a migraine headache medication. It is in the drug class called selective serotonin receptor agonists (SSRAs) or triptans.

Purpose

Almotriptan is used to treat symptoms of acute migraines—severe headaches that may be accompanied by nausea and sensitivity to light and sound. It is used for migraines with and without aura—the visual symptoms such as flashing lights and wavy lines that sometimes accompany or precede migraines. Almotriptan reduces the symptoms of migraines, but it does not prevent headaches or reduce their frequency. Almotriptan is sometimes used for other conditions, such as cluster headaches.

Description

Migraine headaches are believed to be caused by the widening (dilation) of cranial blood vessels that puts pressure on the brain. Triptans, such as almotriptan, specifically bind to a class of receptors called 5-hydroxytryptamine 1 (5-HT₁) receptors. 5-HT₁ receptors normally bind the neurotransmitter serotonin (5-hydroxytryptamine) in blood vessels. Almotriptan is called a selective serotonin receptor “agonist” because it specifically binds the vascular serotonin 5-HT₁ receptor subtype and exerts the same effects as serotonin binding, acting as a powerful vasoconstrictor that narrows the widened blood vessels in the brain. This reduces pressure on the brain and blocks the transmission of pain signals and the release of the

Almotriptan (Axert). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

inflammatory neuropeptides that cause pain, nausea, and other migraine symptoms. Almotriptan works best when it is taken at the first symptoms of a migraine.

U.S. brand names

Almotriptan malate is marketed under the brand name Axert in the United States and Canada.

International brand names

In most other countries, almotriptan is marketed under the brand name Almogran. In Italy, it is also marketed as Almotrex, and in Luxembourg, it is also marketed as Amignul. In Spain, it is marketed under the names Almogran Gervasi and Amignul.

Origins

Almotriptan was approved by the U.S. Food and Drug Administration (FDA) in 2001 for the treatment of migraine in adults. In 2009, it became the first triptan approved for treatment of migraine in adolescents aged 12–17. It is supplied as 6.25 and 12.5 milligram (mg) oral tablets.

Recommended dosage

The recommended initial dosage of almotriptan for both adults and teens is one 6.25 mg or 12.5 mg tablet. If symptoms improve after the first dose but then return, a second dose can be taken at least two hours after the initial dose, but no more than 25 mg (two 12.5 mg tablets) should be taken in a 24-hour period. If symptoms do not

KEY TERMS

Agonist—A drug, such as almotriptan, that binds to a receptor and mimics the effects of the endogenous receptor-binding substance.

Aura—Visual and other sensory disturbances that can precede the onset of a migraine headache.

Axert—The U.S. and Canadian brand name for almotriptan malate.

Cluster headaches—Severe and recurrent headaches on one side of the head, typically affecting one eye.

5-hydroxytryptamine 1 (5-HT₁)—A serotonin receptor in blood vessels in the brain that binds almotriptan.

Migraine—A common primary headache characterized by debilitating neurological symptoms, especially severe throbbing pain on one or both sides of the head, lasting for several hours or more.

Neurotransmitter—A chemical that carries nerve impulses from one nerve cell to another across a synapse or from a nerve cell to a muscle cell.

Receptor—A molecule, such as a protein, inside or on the surface of a cell, that binds a specific substance.

Selective serotonin receptor agonist (SSRA)—A drug, such as almotriptan, that binds to specific

serotonin receptors, mimicking the effects of serotonin binding.

Selective serotonin reuptake inhibitors (SSRIs)—A class of antidepressants that increase levels of serotonin in the brain by preventing its reuptake by nerve-cell endings.

Serotonin—5-Hydroxytryptamine; a neurotransmitter in the brain and blood. Low levels of serotonin are associated with various disorders, including migraines and depression.

Serotonin-norepinephrine reuptake inhibitors (SNRIs)—A class of antidepressants that increase the levels of the neurotransmitters serotonin and norepinephrine by preventing their reuptake.

Serotonin syndrome—A potentially life-threatening reaction to excess serotonin that can result from drugs that increase serotonin or its effects.

Triptans—A class of drugs that bind to serotonin receptors and mimic the action of serotonin; thought to treat migraine headaches by constricting cranial blood vessels, inhibiting inflammatory neuropeptides, and blocking the transmission of pain signals.

improve with the first dose, a second dose should not be taken without consulting the prescribing physician. Almotriptan should be taken with 8 oz. (240 mL) of water, with or without food. The tablet should be swallowed whole, without breaking, crushing, or chewing.

Other conditions and allergies

For patients with liver dysfunction or decreased kidney function, the recommended dosage is 6.25 mg, with a maximum daily dose of 12.5 mg. A second dose may not be appropriate for patients on kidney dialysis.

Precautions

The first dose of almotriptan may be given in the healthcare provider's office or a medical facility so that the patient can be monitored for serious reactions. The healthcare provider should be consulted if almotriptan does not stop or decrease the severity of a migraine, and almotriptan should not be used to prevent migraines or for headaches that differ from a patient's usual migraines. Almotriptan and other headache medications should not be taken for more than ten days per month, as overuse can worsen headaches. Taking almotriptan more frequently or for longer than the recommended period may

also worsen headaches or increase their frequency. The safety of treating more than four headaches in 30 days with almotriptan has not been established.

Additional precautions include:

- Almotriptan may cause drowsiness or dizziness. Patients should not drive or perform similar tasks until they know how almotriptan affects them.
- Almotriptan can cause potentially fatal serotonin syndrome, especially in combination with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). Symptoms can include agitation, confusion, mental or mood changes, hallucinations, fever, fast or irregular heartbeat, tremor, loss of coordination, excessive sweating, muscle spasms, nausea, vomiting, diarrhea, or coma.
- Rarely, serious or fatal heart problems, such as irregular heartbeat or heart attack, have occurred within a few hours of taking almotriptan. A physician should be consulted immediately in case of fast or irregular heartbeat; tightness, pain, pressure, or heaviness in the chest, throat, jaw, or neck; cold sweat; shortness of breath; numbness or tingling in an arm or leg; severe stomach pain, dizziness, or vomiting; or fainting.

PATIENT PROFILE

A 45-year-old woman sought medical help for migraine headaches that were becoming worse as she aged and for which common pain medications such as aspirin or naproxen sodium (Aleve) no longer provided relief. Her doctor first obtained a complete medical history, which included lifelong allergies to various foods and beverages. She also underwent a thorough physical examination and laboratory tests of her blood and urine. The exam and blood work revealed that she was essentially a healthy adult with no signs of major illness. Although the patient had never undergone allergy testing, she had noticed over the years that certain kinds of fish, especially shellfish, and preserved meats such as ham, luncheon meats, and even hot dogs containing nitrites seemed to provoke migraine attacks. She noticed also that MSG, and perhaps other additives in prepared foods, resulted in heavy migraine headaches. Rather than having the patient undergo allergy testing, the doctor recommended keeping a food diary for one month and recording all food consumed so that they could see which foods were followed by migraines. She was advised to return in four weeks, and they would review her food diary together.

Meanwhile, the doctor advised the patient to discontinue using over-the-counter pain remedies for her headaches and instead prescribed almotriptan malate (Axert), an FDA-approved drug indicated specifically for treating the acute headache phase of migraine attacks with or without aura. Almotriptan works by narrowing blood vessels in the brain, the opposite of the widening of blood vessels and increasing pressure in the head that occur in migraine headaches. An appropriate dose of almotriptan redistributes blood flow in the brain without altering blood pressure or heart rate. The standard adult dose of almotriptan prescribed for this patient was a 12.5 mg tablet to be taken with a full glass of water as soon as she noticed symptoms of a migraine attack. She was

advised that a second dose could be taken if the headache returned after two hours, but that she should call her doctor if the headache was not relieved within two hours or if the headache changed in any way after starting to use the medication.

At her four-week follow-up visit, a review of the food diary confirmed that fish, various meats, certain prepared foods, coffee, and chocolate triggered migraine attacks. The patient also reported that the prescribed medication effectively relieved her migraine headaches but that using the drug also caused dizziness, even when no migraine headache was present. This inspired the physician to ask how often the patient was actually taking almotriptan, to which she replied "only once a day." The doctor explained that this frequent usage was likely responsible for the dizziness, since almotriptan should be taken only to relieve an acute migraine headache. It should never be used to prevent or reduce the number of migraine attacks experienced, and regular daily usage could actually result in having more and heavier migraine attacks. The general rule of thumb is that almotriptan can be taken up to ten times within a four-week period. Reducing migraine attacks must be done by eliminating the triggers, which for this patient were food-related allergic reactions. Going forward, the doctor advised that all shellfish, preserved meats, prepared foods with additives, and caffeine should be avoided, and that almotriptan should be taken only when symptoms of a migraine appeared, not at any other time. Only in this way could the patient avoid migraine triggers and prevent possible side effects of almotriptan, such as dizziness. The patient and her doctor agreed to continue recording foods consumed and the frequency of migraine headaches. Reducing the dosage of almotriptan was also a goal, after first reducing the number of migraine attacks.

- Rarely, serious or fatal blood vessel problems in the brain, including stroke, have occurred with almotriptan. Symptoms include confusion, one-sided weakness, or speech or vision changes.
- Blood pressure should be checked frequently, and lab tests, including heart function tests, may be performed.

Pediatric

The safety and effectiveness of almotriptan for children under 12 has not been confirmed. It should be used with extreme caution in younger children.

Geriatric

Almotriptan should be prescribed with caution for postmenopausal women, women who have had a hysterectomy, and men over age 40. The elderly may be more sensitive to almotriptan effects.

Pregnant or breastfeeding

Almotriptan is in the FDA pregnancy category C, meaning that it is not known whether the drug poses harm to the fetus, but animal studies indicate that it might. Animal studies have found almotriptan in breast

milk several hours after dosing, but it is not known whether it is excreted in human milk. The potential risks of using almotriptan while pregnant or breastfeeding should be weighed against the benefits.

Other conditions and allergies

Almotriptan should not be used by anyone who has:

- allergies to any ingredient in the medication
- a history of angina, heart attack, coronary artery disease, or other moderate to severe heart conditions; a blood vessel disease in the brain, including stroke or transient ischemic attack; or other blood vessel diseases, such as Raynaud's syndrome or ischemic bowel disease
- uncontrolled high blood pressure
- hemiplegic or basilar migraine headaches

Almotriptan should be prescribed with caution for people who are very overweight. The treating physician should be informed of:

- any allergies to medicines, foods, or other substances
- any family members who have had heart disease
- previous severe allergic reactions to any sulfonamide medicines, including acetazolamide, **celecoxib**, certain diuretics such as **hydrochlorothiazide**, **glyburide**, probenecid, sulfamethoxazole, valdecoxib, or zonisamide
- a history of liver or kidney problems, cardiovascular disease, seizures, or other types of headaches, such as cluster headaches
- shortness of breath, chest pain, or a history of high blood pressure, heart attack, stroke, high cholesterol, diabetes, or smoking
- risk factors for coronary artery disease

Side effects

Some side effects may disappear as the body adjusts to almotriptan. The healthcare provider should be notified of the following common side effects if they are persistent or bothersome:

- dizziness
- drowsiness
- dry mouth
- headache
- nausea
- vomiting

Less common side effects include:

- sinus aching, fullness, or tension
- anxiety
- back pain
- belching

- taste changes
- chills
- mucus-producing cough
- decreased touch sensitivity
- feeling of movement or spinning
- feeling of warmth or heat
- increased sense of hearing
- indigestion
- weakness
- muscle aches
- nosebleed
- painful menstrual periods
- quivering or trembling
- restlessness
- runny or stuffy nose
- sore throat
- insomnia

Less common side effects that require immediately notifying the doctor are:

- burning, crawling, itching, numbness, prickling, or tingling feelings
- chest pain
- eye irritation or discharge
- fast, irregular, pounding, or racing heartbeat or pulse
- itching, skin redness, rash, or swelling
- neck pain or rigidity
- shortness of breath
- throat tightness

Rare side effects include:

- abnormal increase in reflexes
- abnormal feelings of mental and physical well-being
- buzzing or ringing in the ears
- changes in dreams or nightmares
- changes in sense of touch or smell
- clumsiness or unsteadiness
- continuous, uncontrolled, back-and-forth or rolling eye movements
- cough
- difficulty concentrating
- double vision
- drooling
- dry eyes
- dry throat
- hoarseness or loss of voice
- increased sensitivity to sunlight
- increased thirst

- depression
- muscle stiffness
- nervousness
- pain, redness, swelling, or warmth in the joints
- sneezing
- stabbing pain

Rare side effects that require immediate medical attention are:

- severe allergic reactions, including rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue
- abdominal or stomach cramping or pain
- black, tarry stools
- blood in the stool
- bringing up food
- severe chest pain
- cool, pale skin
- diarrhea
- difficulty swallowing
- earache
- fainting
- fever
- repeated heartburn
- increased sweating
- loss of appetite
- loss of vision
- rapid breathing
- chest tightness
- weight loss
- bloody diarrhea
- cold, pale, or blue-colored fingers or toes
- confusion
- fainting
- one-sided weakness
- seizures
- severe headache, dizziness, or vomiting
- severe stomach pain
- slurred speech
- tightness, pain, or pressure in the jaw, neck, or chest
- wheezing

Interactions

It is very important that the healthcare provider and pharmacist be informed of any and all prescription and nonprescription medicines, herbs, or dietary supplements being used by the patient.

Drugs

A total of 98 drugs are known to interact with almotriptan: 50 drugs have major interactions, 44 interact moderately, and 4 have minor interactions. SSRIs, such as **fluoxetine**, and SNRIs, such as **duloxetine**, **sibutramine**, **escitalopram**, or **paroxetine**, can increase the risk of serotonin syndrome. Other drugs that interact significantly with almotriptan include:

- azole antifungals such as **ketoconazole**
- HIV protease inhibitors such as **ritonavir**
- macrolide antibiotics such as **erythromycin**
- monoamine oxidase inhibitors (MAOIs), such as **phenelzine**, taken within the previous 14 days
- verapamil
- other 5-HT₁ receptor agonists such as **eletriptan** or **rizatriptan** taken within the past 24 hours
- certain other migraine drugs, such as the ergot alkaloid **ergotamine**, taken within the previous 24 hours

Food and other substances

The healthcare provider should be consulted before drinking grapefruit juice while taking almotriptan, as the juice may affect the potency of the medication. Alcohol, as well as certain medications, may increase drowsiness or dizziness caused by almotriptan.

Resources

BOOKS

Smith, Howard S., Marco Pappagallo, and Stephen M. Stahl. *Essential Pain Pharmacology: The Prescriber's Guide*. New York: Cambridge University, 2012.

PERIODICALS

Pringsheim, Tamara, and Werner J. Becker. "Triptans for Symptomatic Treatment of Migraine Headache." *British Medical Journal* 348, no. 7953 (2014): g2285.

WEBSITES

AHFS Consumer Medication Information. "Almotriptan." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a603028.html> (accessed January 15, 2015).

Micromedex. "Almotriptan (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/almotriptan-oral-route/description/drg-20061618> (accessed January 15, 2015).

Migraine Awareness Group: A National Understanding for Migraineurs (MAGNUM). "AXERT® (Almotriptan Malate Tablets)." <http://www.migraines.org/treatment/proaxert.htm> (accessed February 18, 2015).

Wolters Kluwer Health, Inc. "Almotriptan." Drugs.com. <http://www.drugs.com/cdi/almotriptan.html> (accessed January 15, 2015).

ORGANIZATIONS

American Headache Society, 19 Mantua Road, Mount Royal, NJ 08061, (856) 423-0043, Fax: (856) 423-0082, ahshq@talley.com, <http://www.americanheadachesociety.org/>.

M.A.G.N.U.M., Inc., National Migraine Association, 100 North Union Street, Suite B, Alexandria, VA 22314, (703) 349-1929, comments@migraines.org, <http://www.migraines.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Alprazolam

Definition

Alprazolam is a tranquilizer. It belongs to a group of drugs called benzodiazepines. In the United States, alprazolam is sold under the brand name Xanax.

Purpose

The U.S. Food and Drug Administration (FDA) has approved alprazolam to treat anxiety, panic disorder, and anxiety associated with depression.



Alprazolam, 0.5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Off-label use

Occasionally, alprazolam is used to treat alcohol withdrawal, but it is not FDA approved for this use and is not normally the first drug given when treating alcohol withdrawal symptoms.

Description

Alprazolam is classified as a benzodiazepine. Benzodiazepines are sedative-hypnotic drugs that help to relieve nervousness, tension, and other anxiety symptoms by slowing the central nervous system. To do this, they block the effects of a specific chemical involved in the transmission of nerve impulses in the brain, decreasing the excitement level of the nerve cells.

All benzodiazepines cause sedation, including drowsiness and reduced mental alertness. However, one benefit of alprazolam is that it causes somewhat less drowsiness than many other benzodiazepine drugs.

Alprazolam comes in scored and multiscored tablets in doses of 0.25, 0.5, 1, and 2 milligrams (mg), as well as a 1 mg per milliliter (mL) solution.

Recommended dosage

The recommended initial adult dose for anxiety is 0.25–0.5 mg taken three times daily. This dosage may be increased every three to four days to a maximum total of 4 mg daily. Dosages for alcohol withdrawal usually total 2–2.5 mg daily, given in several small doses throughout the day.

The starting dose for treating panic disorder is 0.5 mg three times daily. This dosage may be increased every three to four days until the total daily dosage ranges from 2 to 10 mg. The total amount should be divided into at least three even daily doses. Average doses for anxiety associated with depression range from 2.5 to 3 mg daily, divided into even doses.

Precautions

Because alprazolam is a nervous system and respiratory depressant, it should not be taken with other depressants, such as alcohol, other sedatives and related drugs, sleeping pills, or tranquilizers. People taking this drug should not drive, operate dangerous machinery, or engage in hazardous activities that require mental alertness, at least until they see how the drug affects them. Some patients taking alprazolam have engaged in behaviors such as “sleep driving,” or operating a vehicle while sleeping, with no recollection of the event.

Alprazolam should be used under close physician supervision in patients with a history of substance abuse

KEY TERMS

Anxiety—A psychological state characterized by strong feelings of worry, nervousness, apprehension, or agitation; may also be accompanied by physical symptoms, including sweating, tension, and increased pulse.

Benzodiazepines—A group of central nervous system depressants used to relieve anxiety or to induce sleep.

Central nervous system—The part of the nervous system that includes the brain and spinal cord.

Depressant—Any psychoactive substance that lowers the function or activity level of a specific part of the body or brain. Depressants are sometimes referred to as “downers.”

Depression—A mental state characterized by excessive sadness and loss of interest in life; other symptoms may include altered sleep or eating patterns, loss of concentration, agitation, lack of energy, and, in severe cases, attempts at self-harm or suicide.

Panic disorder—An anxiety disorder in which an individual experiences sudden, debilitating attacks of intense fear.

Withdrawal—Referring to a group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

and related disorders. Like other benzodiazepines, alprazolam can be habit forming. Risk and severity of dependence appear greater in patients taking doses larger than 4 mg daily. However, smaller doses may cause dependence if alprazolam is taken longer than 12 weeks. After four months, patients should be evaluated to see if they need to continue taking alprazolam.

Suddenly discontinuing alprazolam after several weeks may cause uncomfortable symptoms of withdrawal. Withdrawal symptoms tend to occur in people who have taken alprazolam for three months or longer and may include seizures, anxiety, nervousness, and headache. Patients should discuss with their healthcare provider how to gradually discontinue alprazolam use to avoid such symptoms.

Geriatric

The dose of alprazolam must be carefully regulated and individualized in the elderly (over age 60).

Pregnant or breastfeeding

Alprazolam should not be used by women who are pregnant.

Other conditions and allergies

Alprazolam should not be used by patients who have narrow-angle glaucoma or are allergic to this or any other benzodiazepine drug.

Doses must be carefully regulated in patients with liver or kidney disease or who are taking other medications used to treat mental disorders.

Side effects

The most common side effects of alprazolam include sedation, dizziness, drowsiness, insomnia, and nervousness. The intensity of these side effects usually declines gradually and subsides in about eight weeks. A drop in blood pressure and an increase in heart rate may also occur in people who are taking alprazolam.

Decreased sex drive, menstrual disorders, and both weight gain and weight loss have been associated with use of alprazolam. Gastrointestinal side effects such as stomach upset, nausea, vomiting, and dry mouth may be alleviated by eating frequent, small meals or chewing sugarless gum. Alprazolam has been associated with both diarrhea and constipation, as well as tremor, muscle cramps, vision disturbances, rash, amnesia and amnesic disorders, or memory loss.

Interactions

Alprazolam interacts with a long list of other medications. Anyone starting this drug should review the other medications they are taking, including herbs and supplements, with their physician and pharmacist for possible interactions.

Drugs

The most severe interactions occur with antifungal medications, such as **ketoconazole**, itraconazole, and **fluconazole**. These are associated with alprazolam toxicity (excessive sedation, fatigue, slurred speech, slowed reactions, and other types of psychomotor impairment). These medications should not be used concurrently (at the same time).

Estrogens (female hormones), **erythromycin** (an antibiotic), fluoxetine (Prozac, Sarafem), cimetidine (Tagamet), isoniazid, and disulfiram (Antabuse) can increase the effects of alprazolam. **Carbamazepine** can make alprazolam less effective. When alprazolam is combined with other sedative drugs (tranquilizers, sleeping pills) or alcohol, its depressant effects are more intense. These combinations should be avoided.

Food and other substances

Patients taking alprazolam should avoid eating grapefruit or drinking grapefruit juice due to potential adverse side effects.

Resources

BOOKS

Lacy, Charles F. *Drug Information Handbook with International Trade Names Index*. Hudson, OH: Lexi-Comp, Inc., 2011.
Pharmacia and Upjohn Company Staff. *Product Information: Xanax, Alprazolam*. Kalamazoo, MI: Pharmacia and Upjohn Company, 2011.

PERIODICALS

Moylan, S., et al. "The Role of Alprazolam for the Treatment of Panic Disorder in Australia." *Australian & New Zealand Journal of Psychiatry* 46, no. 3 (2012): 212–24. <http://dx.doi.org/10.1177/0004867411432074> (accessed February 17, 2015).
van Marwijk, Harm, et al. "Alprazolam for Depression." *Cochrane Database of Systematic Reviews* 7, art. no. CD007139 (2012). <http://dx.doi.org/10.1002/14651858.CD007139.pub2> (accessed February 17, 2015).

OTHER

U.S. Food and Drug Administration. *Xanax* [prescribing information]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/018276s044,021434s0061bl.pdf (accessed February 17, 2015).

WEBSITES

Healthwise. "Alprazolam." University of Michigan Health System. <http://www.uofmhealth.org/health-library/d00168a1> (accessed February 17, 2015).
Leger, Donna Leinwand. "Alprazolam Misuse Still Sending Tens of Thousands to Emergency Rooms." *USA Today*, May 22, 2014. <http://www.usatoday.com/story/news/nation/2014/05/21/xanax-sends-people-to-emergency-room/9391719/> (accessed February 17, 2015).
Micromedex. "Alprazolam (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/alprazolam-oral-route/description/drg-20061040> (accessed February 17, 2015).
National Health Service (NHS). "Alprazolam." UK Department of Health. <http://www.nhs.uk/conditions/anxiety/pages/MedicineOverview.aspx?condition=Depression&medicine=Alprazolam&preparation=Alprazolam%20250microgram%20tablets> (accessed February 17, 2015).

ORGANIZATIONS

National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (866) 615-6464, TTY: (866) 415-8051, <http://www.nimh.nih.gov/>.
U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Ajna Hamidovic, PharmD

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Altace see **Ramipril**

Amaryl see **Glimepiride**

Ambien see **Zolpidem**

Amitriptyline

Definition

Amitriptyline is a medication used to treat various forms of depression and nerve pain (neuropathic pain) and to prevent migraine headaches.

Purpose

Amitriptyline helps relieve depression and pain. In addition to neuropathic pain, it is sometimes prescribed to help treat pain associated with cancer and for various types of chronic pain. This medication, usually given at bedtime, also helps patients sleep better.

Description

Amitriptyline medication is one of several tricyclic antidepressants, so called because of the three-ring chemical structure common to these drugs. It acts to block reabsorption of neurotransmitters (chemicals that transmit nerve messages in the brain). Amitriptyline and the other tricyclic antidepressants are primarily used to treat depression but are increasingly being replaced by a newer and more effective



Amitriptyline, 75 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Depression—A mental state characterized by excessive sadness and loss of interest in life; other symptoms may include altered sleep or eating patterns, loss of concentration, agitation, lack of energy, and, in severe cases, attempts at self-harm or suicide.

Methylphenidate—A mild central nervous system stimulant that is used to treat hyperactivity.

Monoamine oxidase inhibitors (MAOIs)—A group of antidepressant drugs that decrease the activity of monoamine oxidase, a neurotransmitter found in the brain that affects mood.

Neuropathic pain—State of pain related to the nervous system; also known as neurogenic pain.

Urinary retention—Excessive storage of urine in the body.

group of antidepressant drugs called selective serotonin reuptake inhibitors (SSRIs). Tablets are available in 10, 25, 50, 75, 100, and 150 milligram (mg) doses.

U.S. brand names

Amitriptyline is sold in the United States under the brand names Elavil and Endep.

Recommended dosage

The usual adult dose for pain management ranges from 10 mg to 150 mg at bedtime. Patients are generally started on a low dose, and the amount may be increased as needed. Bedtime dosing helps the patient sleep. Healthcare providers generally prescribe 75–150 mg for depression. It is given at bedtime or in divided doses during the day. It may take 30 days for the patient to feel less depressed. Pain relief is usually noticed sooner than mood change.

If the nightly dose is missed, it should not be taken the next morning. Taking amitriptyline during waking hours could result in noticeable side effects. Patients should check with their healthcare provider if the daily dose is missed. Those on more than one dose per day should take a missed dose as soon as it is remembered but should not take two doses at the same time.

While amitriptyline is usually administered orally, injectable amitriptyline is available. It should not be used in this form long term; patients should switch to tablets as soon as possible.

Pediatric

Adolescents usually receive a lower dosage than adults.

Geriatric

Side effects, such as a dry mouth and drowsiness, may make it difficult to increase the dose in older adults.

Precautions

Patients should not stop taking this medication suddenly. The dose should be decreased gradually and then discontinued. If the drug is stopped abruptly, the patient may experience headache, nausea, or discomfort throughout the body, along with a worsening of the original symptoms. The effects of the medication last for three to seven days after it has been stopped. Patients may need to stop this medication before surgery.

For adolescents and adults up to age 24, amitriptyline carries an increased risk of developing suicidal thoughts while taking the drug. Patients taking amitriptyline should be monitored for signs of worsening depression or other worrisome symptoms, such as increased agitation or aggression, panic attacks, extreme irritability, or frenzied behavior. If these symptoms are experienced by the patient or observed by a caregiver, the patient's healthcare provider should be contacted.

Patients should not drive or operate machinery or appliances while under the influence of this drug. Alcohol and other central nervous system depressants can increase drowsiness.

Patients' skin may become more sensitive to the sun while taking amitriptyline, so direct sunlight should be avoided by wearing protective clothing and applying sunscreen with a protective factor (SPF) of 15 or higher.

Pediatric

This medication should not be given to children under 12 years of age.

Geriatric

Amitriptyline may increase the risk of falls in older adults.

Pregnant or breastfeeding

Pregnant women should discuss the risks and benefits of this medication with their healthcare provider, as fetal deformities have been associated with taking this drug during pregnancy. Women should not breastfeed while using amitriptyline.

Other conditions and allergies

Amitriptyline should not be given to anyone with allergies to the drug or to patients recovering from a heart attack.

Amitriptyline should be administered with caution to patients with glaucoma, seizures, urinary retention, overactive thyroid, poor liver or kidney function, alcoholism, asthma, digestive disorders, enlarged prostate, seizures, or heart disease.

Patients with schizophrenia may develop an increase in psychiatric symptoms.

Amitriptyline may produce an increase in the blood glucose levels of patients with diabetes.

Side effects

Common side effects include dry mouth, drowsiness, constipation, and dizziness or light-headedness when standing. Sucking on ice cubes or sugarless hard candy may help combat the dry mouth. Increased fiber in the diet and additional fluids may help relieve constipation. Dizziness is usually caused by a drop in blood pressure when suddenly changing position. Patients should slowly rise from a sitting or lying position if dizziness is noticed.

Amitriptyline may produce blurry vision, irregular or fast heartbeat, high or low blood pressure, and heart palpitations. It may increase appetite, cause weight gain, or produce an unpleasant taste in the mouth. It may also cause diarrhea, vomiting, or heartburn. Taking this medication with food may decrease digestive side effects. Other less likely side effects include muscle tremors, nervousness, impaired sexual function, sweating, rash, itching, hair loss, ringing in the ears, and changes in the makeup of the patient's blood, including bone marrow suppression.

Geriatric

Older patients are usually more prone to some side effects, such as drowsiness, dizziness, mental confusion, blurry vision, dry mouth, difficulty urinating, and constipation. Taking a lower dose may help resolve these problems.

Interactions

Patients should always tell all of their healthcare providers (including dentists) that they are taking this medication. It may decrease the effectiveness of some drugs used to treat high blood pressure and should not be taken with other antidepressants, **epinephrine** and other adrenaline-type drugs, and **methylphenidate**. Patients should not take over-the-counter medications without checking with their healthcare provider.

Drugs

Patients taking the monoamine oxidase inhibitors (MAOIs) tranylcypromine (Parnate) or phenelzine (Nardil)—different types of antidepressants—should not use amitriptyline in combination. Amitriptyline should

also not be taken with cimetidine (Tagamet) or phenylephrine (Neo-Synephrine).

Herbs and supplements

Patients taking amitriptyline should avoid the dietary supplements St. John's wort, belladonna, henbane, and scopolia.

Food and other substances

Alcohol may increase the sedative effect of amitriptyline. Black tea may decrease the absorption of this drug. Patients should ingest the drug and tea at least two hours apart.

Resources

BOOKS

- Consumer Reports and American Society of Health-System Pharmacists. *Consumer Reports Complete Drug Reference*, 2009 ed. Yonkers, NY: Consumers Reports, 2009.
- Mosby's *Drug Reference for Health Professions*. 5th ed. St. Louis, MO: Mosby, 2015.

PERIODICALS

- Kalita, J., et al. "An Open Labeled Randomized Controlled Trial of Pregabalin Versus Amitriptyline in Chronic Low Backache." *Journal of the Neurological Sciences* 342, nos. 1–2 (2014): 127–132. <http://dx.doi.org/10.1016/j.jns.2014.05.002> (accessed February 17, 2015).
- Vezmar, S., et al. "Pharmacokinetics and Efficacy of Fluvoxamine and Amitriptyline in Depression." *Journal of Pharmacological Sciences* 110, no. 1 (2009): 98–104.

WEBSITES

- AHFS Consumer Medication Information. "Amitriptyline." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682388.html> (accessed February 17, 2015).
- Micromedex. "Amitriptyline (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/amitriptyline-oral-route/description/drg-20072061> (accessed February 17, 2015).
- National Multiple Sclerosis Society. "Elavil." <http://www.nationalmssociety.org/Treating-MS/Medications/Elavil> (accessed February 17, 2015).

ORGANIZATIONS

- National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (866) 615-6464, TTY: (866) 415-8051, <http://www.nimh.nih.gov/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Amlodipine

Definition

Amlodipine besylate is a drug that is used to treat high blood pressure (hypertension) and angina (chest pain due to reduced blood flow to the heart). It is sometimes prescribed with other antihypertensive medications.

Purpose

Amlodipine besylate is prescribed as a treatment for hypertension, chronic stable angina, and vasospastic angina.

High blood pressure is a common condition, affecting nearly 30% of American adults. Chronic stable angina, also known as angina pectoris, affects more than 10 million Americans. It can cause pressure, squeezing, or pain beneath the breastbone, sometimes accompanied by discomfort in other upper-body locations, including the neck, shoulder, arm, back, or jaw. Chronic stable angina typically occurs when an individual is engaging in physical activity or is under stress, then dissipates when the activity or stress stops. Vasospastic angina, also called Prinzmetal or variant angina, is similar to chronic stable angina, except that patients experience symptoms that are cyclical, usually occurring in early morning, rather than during stress or physical activity.



Amlodipine, 10 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

Amlodipine besylate is one of a group of drugs known as long-acting dihydropyridine-type (DHP) calcium channel blockers. Calcium channel blockers are designed to prevent the mineral calcium from entering the cells making up the walls of the blood vessels and of the heart. By disrupting the movement of calcium, calcium channel blockers decrease the force of contraction of these muscle cells and allow the arteries to widen. The widening of these blood vessels lowers blood pressure. Amlodipine also increases blood flow to the heart muscle and blocks coronary artery spasms, which can help patients who have vasospastic or chronic stable angina.

U.S. brand names

Amlodipine besylate is sold under the brand name Norvasc in the United States. Amlodipine besylate is also sold as a combination drug under other brand names, including Caduet (amlodipine besylate and **atorvastatin**) and Lotrel (amlodipine besylate and **benazepril HCl**).

International brand names

Amlodipine besylate is sold under the brand name Norvasc in many countries. It is also sold under several other names, including:

- Abesyl
- Abis
- Abloom
- Amdipin
- Sandoz Amlodipine
- Normodipine

Origins

Norvasc, the primary brand name for amlodipine besylate, was approved by the U.S. Food and Drug Administration (FDA) for the treatment of hypertension, chronic stable angina, and vasospastic angina in 1991. It is currently approved and prescribed in dozens of countries around the world. It is administered in tablet form.

Recommended dosage

The dosage of amlodipine besylate typically begins at 5 milligrams (mg) once a day. The dose may be increased to as much as 10 mg once per day, as warranted. Usually, the dosage is increased slowly over one to two weeks, and the patient is monitored so that the dose may be personalized to the patient. In some cases, the healthcare provider may start the prescription

at the lower dosage of 2.5 mg daily. This may occur if other antihypertensive medications are prescribed concurrently, the patient is small or frail, or the patient has a liver disorder.

Pediatric

For patients 6–17 years old, the dosage of amlodipine besylate is 2.5–5 mg daily. The effect of the drug on younger children is unknown.

Geriatric

Healthcare providers may begin elderly patients at the lower dose (compared with younger adults) of 2.5 mg once daily.

Precautions

The concentration of amlodipine for each patient is usually determined over several days—often as long as two weeks—so that the correct dosage can be determined. This is especially important for patients who have severe hepatic impairment (reduced liver function).

Some individuals, notably those with severe aortic stenosis (a narrowed aortic valve in the heart), may experience symptomatic hypotension, which is low blood pressure accompanied by such symptoms as dizziness or nausea. In addition, those who have certain cardiovascular disorders may experience a heightening of their symptoms. Disorders include angina, acute myocardial infarction (heart attack), and especially obstructive coronary artery disease (plaque-induced narrowing of arteries to the heart).

Pediatric

The effect of amlodipine besylate on children less than six years of age is unknown, and therefore the drug should not be used in this age group.

Geriatric

Elderly patients taking amlodipine besylate in combination with diltiazem (an antihypertensive drug) should be monitored for symptoms of hypotension and edema (swelling).

Pregnant or breastfeeding

Although no major, well-controlled studies have been conducted that show risks to the mother or fetus, healthcare providers should still prescribe amlodipine besylate only if they feel confident that the benefits outweigh any potential risks. Likewise, no major, well-controlled studies have been conducted that show risks to breastfeeding infants. Nonetheless, it is

recommended that mothers stop taking the drug while they are nursing.

Side effects

In some cases, patients who are beginning a regimen of the medication or who start taking a higher dose may experience a heart attack or may find that their angina worsens. Under those circumstances, the patient should contact the prescribing physician immediately or report to a hospital emergency room.

Most common side effects associated with amlodipine besylate are mild to moderate. They may include:

- irregular heartbeat (arrhythmia)
- fast heartbeat (tachycardia)
- edema, especially swelling of the legs or ankles
- abnormal muscle movement, including muscle rigidity or tremor
- lethargy, including extreme sleepiness
- stomach pain or nausea
- dizziness
- feeling of warmth in the face (flushing)

Many other side effects have been reported with amlodipine, including blurred vision, tingling feelings, chills or cold sweats, diarrhea, and unusual bleeding or bruising. Most of these dissipate as the body adjusts to the medication. Any prolonged side effects, as well as side effects that raise concern to the patient or a caregiver, should be reported to the treating physician.

Other conditions and allergies

Individuals who are allergic to amlodipine or to the inactive ingredients in amlodipine besylate preparations should not take the medication.

Interactions

Patients should discuss with their healthcare provider possible interactions between amlodipine besylate and any other medications they are taking.

Drugs

Cyclosporine (Neoral, Sandimmune) and **tacrolimus** (Prograf), both of which are prescribed to transplant patients, and the cholesterol-lowering medication **simvastatin** (Zocor) are known to interact with amlodipine besylate. When used in combination with amlodipine besylate, the dosage of simvastatin is limited to 20 mg daily. In addition, all patients, especially elderly patients, who have hypertension and take CYP3A4 inhibitors should be monitored for

KEY TERMS

Acute myocardial infection—Heart attack.

Angina—Chest pain due to reduced blood flow to the heart.

Aortic stenosis—A narrowed aortic valve in the heart.

Calcium channel blocker—One of a number of medications designed to disrupt the movement of calcium in certain muscle cells, which can cause blood vessels to dilate and the heart to pump less forcefully.

Hepatic impairment—Reduced liver function.

Hypertension—High blood pressure.

Hypotension—Abnormally low blood pressure.

Obstructive coronary artery disease—Plaque-induced narrowing of arteries to the heart.

symptoms of hypotension (abnormally low blood pressure) and edema. CYP3A4 is the abbreviation for cytochrome P450 3A4. Many medications can inhibit CYP3A4. This includes the calcium channel blocker **diltiazem**, which is a medication for hypertension treatment.

An overdose of amlodipine besylate should be reported to the doctor or other medical professional immediately, as it can cause the blood pressure to drop to dangerously low levels. If the patient is unable to reach a medical professional, he or she should call the Poison Control Center at (800) 222-1222 or report to an emergency room without delay.

Herbs and supplements

No specific interactions are noted, but patients should still inform their healthcare providers about any herbs or supplements they are taking.

Foods and other substances

Alcohol can reduce blood pressure, which may intensify side effects. Alcohol consumption should be discussed with the healthcare provider before taking amlodipine besylate.

Resources

BOOKS

Kaplan, Norman M., and Ronald G. Victor. "Treatment of Hypertension: Drug Therapy" In *Kaplan's Clinical*

Hypertension. 11th ed. Philadelphia: Wolters Kluwer, 2015.

Mann, Samuel J. *Hypertension and You: Old Drugs, New Drugs, and the Right Drugs for Your High Blood Pressure*. Plymouth, MA: Rowman & Littlefield, 2012.

PERIODICALS

Clavijo, G. A., I. V. de Clavijo, and C. W. Weart. "Amlodipine: A New Calcium Antagonist." *American Journal of Health-System Pharmacy* 51, no. 1 (1994): 59–68.

Naito, Takafumi, et al. "Amlodipine Passage into Breast Milk in Lactating Women with Pregnancy-Induced Hypertension and Its Estimation of Infant Risk for Breastfeeding." *Journal of Human Lactation*. (December 1, 2014): e-pub ahead of print. Available at: <http://dx.doi.org/10.1177/0890334414560195> (accessed January 29, 2015).

WEBSITES

American Heart Association. "Angina Pectoris (Stable Angina)." Heart.org. http://www.heart.org/HEARTORG/Conditions/HeartAttack/SymptomsDiagnosisofHeartAttack/Angina-Pectoris-Stable-Angina_UCM_437515_Article.jsp# (accessed January 11, 2015).

"Norvasc." Drugs.com. <http://www.drugs.com/norvasc.html> (accessed January 11, 2015).

Hopkins, William, and Lewis J. Rubin. "Treatment of Pulmonary Hypertension in Adults." UpToDate.com. <http://www.uptodate.com/contents/treatment-of-pulmonary-hypertension-in-adults> (accessed January 11, 2015).

Mayo Clinic staff. "Amlodipine (Oral Route): Side Effects." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/amlodipine-oral-route/side-effects/drug-20061784> (accessed January 11, 2015).

Pfizer. "NORVASC—Amlodipine Besylate Tablet." http://labeling.pfizer.com/Show_Labeling.aspx?id=562#section-8.1 (accessed January 11, 2015).

U.S. Food and Drug Administration. "Norvasc (Amlodipine Besylate) Tablets." FDA.gov. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm204020.htm> (accessed January 11, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org/>.

American Society of Hypertension, 45 Main Street, Suite 712, Brooklyn, NY 11201, (212) 696-9099, Fax: (347) 916-0267, <http://www.ash-us.org/>.

National Heart, Lung, and Blood Institute Health Information Center, PO Box 30105, Bethesda, MD 20824, (301) 592-8573, Fax: (301) 592-8563, nhlbiinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov/>.

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Amlodipine/valsartan

Definition

This drug combination brings together two medications: amlodipine besylate and valsartan. Combination **amlodipine** besylate/valsartan is used to treat high blood pressure, also known as hypertension, in patients whose hypertension cannot be adequately treated with other medications. Amlodipine besylate is a calcium channel blocker, and valsartan is an angiotensin II receptor antagonist.

Purpose

Individually, amlodipine is used to treat high blood pressure and angina, and valsartan is used to treat high blood pressure and congestive heart failure. Valsartan is also used to lessen the risk of heart-attack fatalities in patients who have left ventricular dysfunction, which is a reduced ability to pump blood by one of the four chambers of the heart. Healthcare providers prescribe combination amlodipine besylate/valsartan to treat high blood pressure in patients whose hypertension has not previously been controlled with other angiotensin receptor blockers or calcium channel blockers. The combination drug is also used to treat hypertension in those patients who experienced dose-limiting side effects, such as edema (swelling), dizziness, or flushing (warmth in the face), with either valsartan or amlodipine alone.



Exforge (amlodipine/valsartan, 5 mg/160 mg). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

Amlodipine besylate/valsartan is administered as a tablet that is taken orally. The two drugs in combination amlodipine besylate/valsartan function differently. The one-pill combination is designed to provide the hypertension-fighting attributes of both medications, thereby fighting blood pressure with two complementary approaches.

Amlodipine besylate

Amlodipine besylate is a type of drug known as a long-acting dihydropyridine-type (DHP) calcium channel blocker. Calcium channel blockers prevent calcium from entering the muscle cells of the heart and of blood vessel walls. By blocking calcium, these drugs reduce the contraction of muscle cells and allow arteries to widen, which in turn lowers blood pressure.

Amlodipine also increases blood flow to the heart muscle and stops spasms of the coronary artery, which is beneficial for patients who have chronic stable angina or vasospastic angina. Chronic stable angina, also known as angina pectoris, affects more than 10 million Americans. It can cause pressure, squeezing, or pain beneath the breastbone, sometimes accompanied by discomfort in other upper-body locations, including the neck, shoulder, arm, back, or jaw. Chronic stable angina typically occurs when the person is engaging in physical activity or is under stress, then dissipates when the activity or stress stops. Vasospastic angina, also called Prinzmetal or variant angina, is similar to chronic stable angina, but the symptoms are cyclical, usually occurring in early morning, rather than being tied to stress or physical activity.

Valsartan

Valsartan is an angiotensin II receptor antagonist (also known as an angiotensin receptor blocker, or ARB). Angiotensin II receptor antagonists help to regulate a particular hormone system (the renin-angiotensin-aldosterone system) that controls blood pressure as well as the fluid balance in the body. One of the participants in the hormone system is a peptide (a small, protein-like molecule) called angiotensin II, which causes blood vessels to constrict. Valsartan prevents angiotensin II from binding to its associated receptor—called the type 1 angiotensin receptor (AT₁)—on blood vessels. If the angiotensin II cannot bind, it does not have its constricting effect on the blood vessels. As a consequence, the blood vessels do not narrow, which keeps blood pressure from rising.

U.S. brand names

Combination amlodipine besylate/valsartan is sold in the United States under the brand name Exforge, which is produced by Novartis Pharmaceuticals. The company

also makes Exforge HCT, which adds **hydrochlorothiazide**, a diuretic. Diuretics, often called “water pills,” are medications that promote the excretion of water through increased urine production. The removal of excess water in the body can help to lower blood pressure.

International brand names

Combination amlodipine/valsartan is sold under a number of names internationally. They include:

- Amlosartan
- Amlovaltan
- Amval
- Camoval
- Copalia
- Dafiro
- Diovan Amlor
- Disarval
- Reovan-A
- Imprida
- Valaxam
- Vartalan AM

Origins

The U.S. Food and Drug Administration (FDA) accepted Exforge for review in 2006. This followed clinical trials demonstrating its usefulness in lowering blood pressure. Exforge was the first medication of its kind, offering a single tablet that combined amlodipine besylate and valsartan. The FDA tentatively approved Exforge for the treatment of hypertension in late 2006, and in the spring of 2007, it granted final approval.

Recommended dosage

The recommended dosage varies by individual. The prescribing physician generally takes a slow and measured approach, recommending increasing dosages until the patient’s blood pressure is controlled. Exforge is available in several formulations, including either 5 milligrams (mg) or 10 mg of amlodipine besylate, combined with 160 mg or 320 mg of valsartan. These formulations are written as: 5/160 mg, 10/160 mg, 5/320 mg, and 10/320 mg. The maximum dosage is 10 mg/day amlodipine besylate and 320 mg/day valsartan.

Pediatric

Safety and efficacy for combination amlodipine besylate/valsartan have not been established for children, so it is not prescribed for this age group.

Geriatric

Dosage recommendations are the same for older adults as they are for younger adults.

Precautions

Patients with anuria (inability to pass urine) should not take combination amlodipine besylate/valsartan. Physicians should take special care in prescribing this drug to patients who have heart failure, have had a recent myocardial infarction, are undergoing surgery, or are undergoing dialysis. Patients should be monitored for excessive lowering of the blood pressure (hypotension).

Pregnant or breastfeeding

Combination amlodipine/valsartan falls within the FDA pregnancy category C during the first trimester and category D during the second and third trimesters. Category D indicates a risk to the fetus, so as soon as a woman learns she is pregnant, she should discontinue the drug. Amlodipine besylate/valsartan has been associated with fetal health issues including hypotension, underdevelopment of the skull (hypoplasia), anuria, renal failure (sometimes irreversible), and death. It is further recommended that women not take the drug while they are nursing.

Other conditions and allergies

Individuals with allergic reactions to either of the medications in combination amlodipine besylate/valsartan should not take this medication.

Side effects

The most common side effects associated with combination amlodipine besylate/valsartan are headache and a slightly increased blood urea nitrogen (BUN) level, which is an indicator of kidney function (an abnormally high level suggests a kidney problem). Less common side effects include:

- peripheral edema, usually in the lower legs
- common cold or other upper-respiratory infection
- cough
- dizziness
- increased potassium levels
- anxiety
- drowsiness
- nausea or diarrhea
- abdominal pain

Rare side effects include a dizzy spell upon standing (orthostatic hypotension), fainting, and ringing or noise in the ears (tinnitus).

KEY TERMS

Acute myocardial infection—Heart attack.

Angina—Chest pain due to reduced blood flow to the heart.

Angiotensin II receptor antagonists—Drugs that regulate a particular hormone system (the renin-angiotensin-aldosterone system) that controls blood pressure as well as the fluid balance in the body.

Aortic stenosis—A narrowed aortic valve in the heart.

Calcium channel blocker—One of a number of medications designed to disrupt the movement of calcium in certain muscle cells, which can cause blood vessels to dilate and the heart to pump less forcefully.

Edema—Swelling caused by fluid retention.

Hypertension—High blood pressure.

Hypotension—Abnormally low blood pressure.

Obstructive coronary artery disease—Plaque-induced narrowing of arteries to the heart.

Pregnancy category—A system of classifying drugs for their use during pregnancy. Category A: Controlled human studies have identified no fetal risk. Category B: Animal studies indicate no fetal risk, but there are no human studies, or adverse effects have been found in animals but not in well-controlled human studies. Category C: No adequate animal or human data is available, or adverse effects have been found in animal studies, but no human data is available. Category D: Evidence of fetal risks exists, but the benefits outweigh the risks. Category X: Evidence of fetal risks exists, and the risks outweigh any benefits.

Some individuals, notably those with severe aortic stenosis (a narrowed aortic valve in the heart), may experience symptomatic hypotension, which is low blood pressure accompanied by such symptoms as dizziness or nausea. In addition, those who have certain cardiovascular disorders may experience a heightening of their symptoms. These disorders include angina, acute myocardial infarction (heart attack), and especially obstructive coronary artery disease (plaque-induced narrowing of arteries to the heart).

Patients who have any other health conditions should discuss the potential ramifications of a regimen of combination amlodipine besylate/valsartan before beginning to take the new drug. They should also notify their prescribing doctor of any health or medication changes while on the

drug. Patients should immediately notify their healthcare provider if they experience edema in the hands or feet, symptoms of heart attack, unexplained muscle pain, dark-colored urine, or any other troubling or new symptoms.

Geriatric

Elderly patients taking **diltiazem** (an antihypertensive drug) should be monitored for symptoms of hypotension and edema while taking combination amlodipine besylate/valsartan.

Interactions

Patients should discuss with their healthcare provider possible interactions between combination amlodipine besylate/valsartan and any other medications they are taking.

Drugs

Individuals who are taking aliskiren (Tekturna) or dantrolene (Dantrium) should not take combination amlodipine besylate/valsartan. Aliskiren is a drug used to treat hypertension. Dantrolene is a muscle relaxant that is used to treat, prevent, or reduce the risk of malignant hyperthermia (severely high body temperature).

Individuals and their healthcare providers should discuss alternatives for combination amlodipine besylate/valsartan if they are taking other drugs, including:

- **benazepril** (Lotensin)
- **captopril** (Capoten)
- **diltiazem** (Cardizem)
- **enalapril** (Vasotec)
- **fosinopril** (Monopril)
- **idelalisib** (Zydelig)
- **ivacaftor** (Kalydeco)
- **lisinopril** (Prinivil)
- **lithium** (Lithane)
- **moexipril** (Univasc)
- **nefazodone** (Serzone)
- **perindopril** (Aceon)
- **pirfenidone** (Esbriet)
- **quinapril** (Accupril)
- **ramipril** (Altace)
- **simvastatin** (Zocor)
- **trandolapril** (Mavik)

If the patient is taking these or other drugs, including aspirin, **atorvastatin** (Lipitor), **ibuprofen**, or many others that may interact with combination amlodipine besylate/valsartan, the patient should be closely monitored to ensure that he or she experiences no adverse effects.

Herbs and supplements

Potassium supplements and salt substitutes should not be used without consent from the prescribing doctor.

Foods and other substances

Alcohol can reduce blood pressure, which may intensify side effects. Alcohol consumption should be discussed with the treating physician before beginning to take combination amlodipine besylate/valsartan.

Resources

BOOKS

- Kaplan, Norman M., and Ronald G. Victor. "Treatment of Hypertension: Drug Therapy." In *Kaplan's Clinical Hypertension*. 11th ed. Philadelphia: Wolters Kluwer, 2015.
- Mann, Samuel J. *Hypertension and You: Old Drugs, New Drugs, and the Right Drugs for Your High Blood Pressure*. Plymouth: Rowman & Littlefield, 2012.

PERIODICALS

- Armario, Pedro, and Bernard Waeber. "Therapeutic Strategies to Improve Control of Hypertension." *Journal of Hypertension* 31, suppl. 1 (2013): S9–S12.
- Habib, G. B., and S. S. Basra. "Are There Any New Pharmacologic Therapies on the Horizon to Better Treat Hypertension? A State-of-the-Art Paper." *Journal of Cardiovascular Pharmacology and Therapeutic* 19, no. 6 (2014): 516–25.

WEBSITES

- American College of Cardiology. "Amlodipine and Valsartan." *Cardiosmart.org*. <https://www.cardiosmart.org/Healthwise/d066/62/d06662> (accessed January 11, 2015).
- Drugs.com. "Amlodipine/valsartan." <http://www.drugs.com/cdi/amlodipine-valsartan.html> (accessed January 11, 2015).
- Drugs.com. "Exforge." <http://www.drugs.com/pro/exforge.html> (accessed January 11, 2015).
- Novartis Pharmaceuticals. "About Exforge and Exforge HCT." *Exforge.com*. <http://www.exforge.com/c/exforge-high-bp> (accessed January 11, 2015).
- Mayo Clinic staff. "Amlodipine and Valsartan (Oral Route)." *MayoClinic.org*. <http://www.mayoclinic.org/drugs-supplements/amlodipine-and-valsartan-oral-route/description/drg-20071029> (accessed January 11, 2015).
- Medscape staff. "Valsartan/Amlodipine." *Medscape Reference*. <http://reference.medscape.com/drug/exforge-valsartan-amlodipine-342469#5> (accessed January 11, 2015).
- RxList.com. "Exforge." <http://www.rxlist.com/exforge-drug/indications-dosage.htm> (accessed January 11, 2015).
- U.S. Food and Drug Administration. "Exforge (Amlodipine/Valsartan) Tablets." *FDA.gov*. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm258792.htm> (accessed January 11, 2015).

ORGANIZATIONS

- American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org/>.

American Society of Hypertension, 45 Main Street, Suite 712, Brooklyn, NY 11201, (212) 696-9099, Fax: (347) 916-0267, <http://www.ash-us.org/>.

National Heart, Lung, and Blood Institute (NHLBI) Health Information Center, PO Box 30105, Bethesda, MD 20824, (301) 592-8573, Fax: (301) 592-8563, nhlbiinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov/>.

Leslie A Mertz, PhD

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Amoxicillin

Definition

Amoxicillin is an antibiotic drug in the family of penicillin drugs.

Purpose

Amoxicillin is used to treat bacterial infections primarily of the ears, lungs, sinus, skin, and urinary tract that are sensitive to penicillin-like drugs. Amoxicillin may be combined with other agents to treat the bacteria that cause stomach ulcers. Amoxicillin destroys bacteria such as *H. influenzae*, *E. coli*., *N. gonorrhea*, and *Streptococcus pneumoniae*.

Many organisms have developed a characteristic called "resistance," which is the ability to destroy amoxicillin and prevent its therapeutic effect. To combat this, amoxicillin is often combined in a formulation with clavulanic acid, which prevents the organisms from destroying the active ingredient. This combination is sold in the United States as Augmentin and has its own unique properties.

Off-label use

Amoxicillin may be used off label in children to treat community-acquired pneumonia and Group A strep throat infections. It is also used to prevent endocarditis (an infection of the endocardium in the heart) in vulnerable individuals and anthrax in individuals who have had documented exposure. Amoxicillin may treat infections in artificial joints, brain infections due to Lyme disease, and lung infections in patients who do not have cystic fibrosis.

Description

Amoxicillin is available in pill, capsule, and liquid suspension forms. The medication is taken by mouth and must be prescribed by a physician. Amoxicillin is used internationally and is on the World Health Organization's



Amoxicillin, 875 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

list of essential medicines. It is also frequently used in veterinary medicine.

U.S. brand names

Amoxicillin is sold under the brand name Moxatag. It is also manufactured as a generic by many different companies.

Canadian brand names

In Canada, amoxicillin is sold as:

- Apo-Amoxi
- Mylan-Amoxicillin
- Novamoxin
- NTP-Amoxicillin
- Nu-Amoxi
- PHL-Amoxicillin
- PMS-Amoxicillin
- Pro-Amox-250
- Pro-Amox-500

International brand names

Amoxicillin is sold under several hundred brand names internationally. In some countries, amoxicillin is only one component of the medication, and there are other medications included in the formulation. In some locations, it is available only for veterinary, not human, use.

Recommended dosage

Recommended dosages are based on the amount of amoxicillin needed to treat the infection. In general, recommended adult dosages are 250–500 milligrams (mg) every 8 hours, 500–875 mg twice daily, or 775 mg extended-release tablets once daily. Other dosing formats may be followed for specific infections or circumstances.

Pediatric

Recommended dosages for children are as follows:

- Children under the age of three months are dosed in the range of 20–30 mg per kilogram (kg, or 2.2 lb.) of body weight per day, divided into two doses administered every 12 hours.
- Children over the age of three months who weigh less than 88 lb. (40 kg) are dosed in the range of 20–45 mg/kg/day, in divided doses taken either every 8 or every 12 hours.
- Children over the age of three months and weighing more than 88 lb. (40 kg) are dosed as adults.
- Other dosing formats may be followed for specific infections or circumstances.

Precautions

The following precautions apply to all individuals.

- Individuals who are allergic to amoxicillin (e.g., Amoxil, Trimox, Wymox), amoxicillin/clavulanic acid, any form of penicillin, or any cephalosporin drugs should not take amoxicillin.
- Amoxicillin (and all antibiotics) should be taken for the entire length of the prescription. Failure to take a complete course of the medication can result in return of symptoms.
- Amoxicillin can be taken with or without food.
- Use over a long period of time may increase the risk of developing another fungal or bacterial infection (secondary infection).
- *C. difficile*-associated diarrhea and pseudomembranous colitis have both been associated with long-term use of amoxicillin, even months after the drug has been discontinued.
- Amoxicillin makes the skin more sensitive to sun exposure and tanning lights, resulting in more easily (and potentially severely) burned skin.

Women taking **oral contraceptives** should ask their healthcare providers if they need to use a second form of contraception while taking amoxicillin, because the drug can interfere with the effectiveness of the birth control pill.

KEY TERMS

Anaphylaxis—A severe, systemic allergic reaction that can be potentially life threatening.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Pregnancy category—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk, but there are no human studies, or there are adverse effects in animals but not in well-controlled human studies. Category C: No adequate human or animal studies exist, or adverse fetal effects have been seen in animal studies, but there is no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk, and risks outweigh any benefits.

Resistance—A characteristic developed by some organisms that allows them to escape the effects of certain antibiotics.

Use of amoxicillin for treating severe sore throat associated with infectious mononucleosis carries an extremely high risk of developing a rash, so an alternate form of treatment is advised.

Pregnant or breastfeeding

Amoxicillin has not been well studied in pregnant women. It is classified as a pregnancy category B drug. Women who are pregnant or breastfeeding should tell their doctor before taking amoxicillin. This drug can pass into breast milk and may cause diarrhea, yeast infections, or allergic reactions in the nursing child.

Other conditions and allergies

Individuals with a history of kidney problems or on dialysis should tell their doctor before taking this drug. Dosage reductions may be necessary.

People with phenylketonuria should not use the chewable tablets, as they contain phenylalanine.

Individuals with a history of severe allergies, asthma, or prior reactions involving anaphylaxis, hives,

or the severe swelling called angioedema are at higher risk for serious reactions to amoxicillin.

Side effects

Serious and sometimes fatal reactions can occur in individuals who are allergic to penicillin and penicillin-like drugs. Anyone who has had a severe reaction to any drug should alert the physician before taking this drug.

The most common adverse side effects of amoxicillin for all age groups tend to be mild. They include:

- upset stomach
- loose stools or diarrhea
- nausea and vomiting

These side effects should be brought to the attention of a healthcare provider if they do not go away within a few days. Whitish vaginal discharge or white coating of the tongue and inside of the mouth should also be reported to a healthcare provider.

Symptoms such as wheezing, difficulty breathing or swallowing, or severe skin rash or hives may indicate a serious allergic reaction and require immediate medical attention. Individuals experiencing these symptoms should immediately call their healthcare provider or go to the emergency room.

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herb, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Amoxicillin is known to interact with the following pharmaceutical drugs. Other interactions are possible. An individual who develops any unusual or unexpected symptoms should contact a physician.

- Amoxicillin may increase the blood levels and possible toxic effects of **methotrexate** and probenecid.
- Amoxicillin may decrease the blood levels and therapeutic effects of the bacillus Calmette–Guérin (BCG) vaccine, mycophenolate, sodium picosulfate, and typhoid vaccine.
- Amoxicillin's blood levels and risk of toxicity may be increased by simultaneous use of **allopurinol** or vitamin K antagonists (such as **warfarin**).
- Amoxicillin's blood levels and effectiveness may be decreased by **tetracycline** drugs.

Resources

BOOKS

Bennett, John E., Raphael Dolin, and Martin J. Blaser. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. London: Churchill Livingstone, 2015.

Cherry, J., et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Saunders, 2013.

Drug Information Handbook. 23rd ed. Hudson: Lexi-Comp, 2014.

Magill, Alan, J., et al. *Hunter's Tropical Medicine and Emerging Infectious Disease*. Philadelphia: Saunders, 2012.

Rang, H. P., et al. *Rang & Dale's Pharmacology*. 7th ed. London: Churchill Livingstone, 2011.

WEBSITES

AHFS Consumer Medication Information. "Amoxicillin." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a685001.html> (accessed February 10, 2015).

Physicians' Desk Reference. "Amoxicillin." PDR Health. <http://www.pdrhealth.com/drugs/amoxicillin> (accessed February 10, 2015).

U.S. Food and Drug Administration. "Amoxicillin (Amoxil, Larotid, Trimox, Wymox) Use by Pregnant and Lactating Women." <http://www.fda.gov/drugs/emergencypreparedness/bioterrorismdrugpreparedness/ucm072124.htm> (accessed February 10, 2015).

ORGANIZATIONS

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rosalyn S. Carson-DeWitt, MD
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Amoxicillin/clavulanic acid

Definition

Amoxicillin and clavulanic acid, also called amoxicillin clavulanate, is an antibacterial drug composed of amoxicillin and clavulanate potassium. Amoxicillin is a beta-lactam antibiotic in the family of aminopenicillin drugs. Clavulanic acid is a beta-lactamase inhibitor. Bacteria tend to develop resistance to beta-lactam antibiotics by producing beta-lactamase, an enzyme that breaks down the antibiotic's structure. Beta-lactamase



Amoxicillin/clavulanic acid, 875 mg/125 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

inhibitors help combat this resistance by preventing the production of beta-lactamase.

Purpose

Amoxicillin/clavulanic acid is used to treat bacterial infections primarily of the ears, lungs, sinus, skin, and urinary tract that are sensitive to penicillin-like drugs. The amoxicillin destroys bacteria such as *H. influenzae*, *Escherichia coli*, *Neisseria gonorrhea*, and *Streptococcus pneumoniae*, which are responsible for *H. influenzae* type b (Hib) disease, *E. coli* infections, gonorrhea, pneumonia, and strep infections, respectively. The clavulanic acid prevents the bacteria from destroying the amoxicillin, making the drug more effective than amoxicillin alone.

Description

Amoxicillin/clavulanic acid was invented in Britain in the late 1970s and was patented in the United States in 1979. Since then, various forms and doses of the drug have been approved by the U.S. Food and Drug Administration (FDA). All formulations must be prescribed by a physician.

Amoxicillin/clavulanic acid is taken orally (by mouth) and is available in the following forms and strengths:

- chewable: 200/28.5 milligrams (mg), 400/57 mg
- tablets (film coated): 250/125 mg, 500/125 mg, and 875/125 mg

- extended-release tablets: 1,000/62.5 mg
- powder for suspension (liquid): 125/31.25 mg, 200/28.5 mg, 250/62.5 mg, 400/57 mg, and 600/42.9 per 5 milliliters (mL)

Amoxicillin/clavulanic acid is used internationally. It is on the World Health Organization's list of essential medicines. It is also frequently used in veterinary medicine but is banned for use in food animals (e.g., cattle) in the United States and Europe.

U.S. brand names

In the United States, common brand names include Augmentin (the name given to it by its inventor), Augmentin XR (extended release), and Augmentin-ES600.

International brand names

Amoxicillin/clavulanic acid is sold under more than 60 brand names internationally.

Recommended dosage

Recommended dosages are based on the amount of amoxicillin needed to treat the infection. Recommended adult dosages are 500 mg every 8–12 hours, 250 mg every 8 hours, 875 mg every 12 hours, or 2,000 mg every 12 hours.

Pediatric

Children weighing more than 88 lb. (40 kg) are dosed as adults. The recommended dosage for children weighing less than 88 lb. (40 kg) is 20–45 mg/kg every 8–12 hours.

The only recommended formulation for infants under the age of three months is an oral suspension containing 125 mg/5 mL.

Precautions

The following precautions apply to all individuals:

- If the individual switches from tablet form to another (e.g., from a standard tablet to a chewable tablet or to an extended-release tablet), the dosage instructions may change. The tablets are not interchangeable. The amount of amoxicillin in each type of tablet may be the same, but the amount of clavulanic acid is different in each type of tablet.
- This drug should be taken for the entire length of the prescription. Failure to take a complete course of the medication can result in the return of symptoms.
- Amoxicillin/clavulanic acid should be taken on a full stomach, because clavulanic acid can cause stomach

KEY TERMS

Jaundice—A condition in which bilirubin, a waste product caused by the normal breakdown of red blood cells, builds up in the body faster than the liver can break it down. People with jaundice develop yellowish skin, and the whites of their eyes become yellow. The condition can occur in newborns and people with liver damage.

Pregnancy category—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk, but there are no human studies, or adverse effects have been seen in animals but not in well-controlled human studies. Category C: No adequate human or animal studies exist, or adverse fetal effects have been seen in animal studies, but there is no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk, and risks outweigh any benefits.

Streptococcal infections—Also called strep infections; a group of diseases caused by *Streptococci* bacteria, including strep throat, scarlet fever, impetigo, toxic shock syndrome, cellulitis, meningitis, and blood infections.

upset. Taking this drug with food reduces the likelihood of upset stomach.

- Individuals with a history of liver problems, jaundice, or kidney problems should tell their healthcare provider before taking this drug. Dosage reduction may be necessary.
- Individuals with gonorrhea should discuss the use of this drug with their healthcare provider.

Pediatric

Children weighing less than 88 lb. (40 kg) should not take 250 mg tablets because of the high amount of clavulanic acid that they contain.

Pregnant or breastfeeding

Amoxicillin/clavulanic acid has not been well studied in pregnant women. This drug is a pregnancy category B drug, which means that there is not enough data to confirm that the drug does not have adverse effects on a fetus. Women who are pregnant or breastfeeding should tell their doctor before taking

amoxicillin and clavulanic acid. This drug can pass into breast milk and may cause diarrhea, yeast infection, or allergic reaction in the nursing child.

Other conditions and allergies

Individuals who are allergic to amoxicillin (e.g., Amoxil, Trimox, Wymox) or any form of penicillin should not take amoxicillin/clavulanic acid. In addition, individuals with allergies to any drugs in the cephalosporin class of antibiotics may experience a reaction to amoxicillin/clavulanic acid. To avoid reactions, the prescribing physician should be made aware of all of a patient's possible medication allergies.

Side effects

Serious and sometimes fatal reactions can occur in individuals who are allergic to penicillin and penicillin-like drugs. Anyone who has had a severe reaction to any drug should alert the physician before taking this drug.

The most common adverse side effects of amoxicillin/clavulanic acid for all age groups tend to be mild. They include:

- loose stools or diarrhea
- nausea and vomiting
- mild skin rash

These side effects should be brought to the doctor's attention if they do not go away within a few days.

A doctor should be notified immediately if any of these less common but more serious side effects occur:

- severe skin rash, itching, or hives
- yellowing of the skin
- vaginal itching or discharge (females)
- seizures
- abdominal pain with fever

Wheezing or difficulty breathing or swallowing may indicate a severe allergic reaction and requires immediate medical attention. If these effects occur, call the doctor or go to the emergency room.

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbal or dietary supplements, and foods. Interactions can increase or decrease the effectiveness of amoxicillin/clavulanic acid or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Amoxicillin/clavulanic acid is known to interact with the following pharmaceutical drugs:

- **Allopurinol** (Lopurin, Zyloprim) may result in skin rash.
- **Probenecid** (Benemid), used to treat gout, may allow toxic levels of amoxicillin to accumulate in the bloodstream.
- **Oral contraceptives** (birth control pills) may be less effective during the time amoxicillin/clavulanic acid is taken.
- Other antibiotics (e.g., **erythromycin**, **doxycycline**, sulfamethoxazole, and their relatives) taken while amoxicillin/clavulanic acid is taken may decrease amoxicillin/clavulanic acid's effectiveness.
- **Methotrexate** (Trexall) increases the risk of side effects.

Other interactions are possible. An individual who develops any unusual or unexpected symptoms should contact a physician.

Resources

PERIODICALS

Haeseker, Michiel. "Is the Standard Dose of Amoxicillin-Clavulanic Acid Sufficient?" *BMC Pharmacology and Toxicology* 15 (July 21, 2014). <http://dx.doi.org/10.1186/2050-6511-15-38> (accessed January 23, 2015).

WEBSITES

"Amoxicillin and Clavulanate Potassium." Drugs.com. <http://www.drugs.com/monograph/amoxicillin-and-clavulanate-potassium.html> (accessed December 31, 2014).

MedlinePlus. "Amoxicillin and Clavulanic Acid." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a685024.html> (accessed December 31, 2014).

U.S. National Library of Medicine. "Amoxicillin-Clavulanate." LiverTox.gov. <http://livertox.nih.gov/Amoxicillin-Clavulanate.htm> (accessed January 23, 2015).

World Health Organization. "Amoxicillin + Clavulanic Acid." *WHO Model Prescribing Information: Drugs Used in Bacterial Infections*. <http://apps.who.int/medicinedocs/en/d/Js5406e/16.2.html> (accessed January 23, 2015).

ORGANIZATIONS

Alliance for the Prudent Use of Antibiotics (APUA), 136 Harrison Avenue, M&V Suite 811, Boston, MA 02111, (617) 636-0966, apua@tufts.edu, <http://www.tufts.edu/med/apua>.

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Tish Davidson, AM

REVIEWED BY GREGORY A. PRATT, RPH

Amoxil see **Amoxicillin**

Amphetamine/dextroamphetamine see
Dextroamphetamine

Antivert see **Meclizine**

Aricept see **Donepezil**

Aripiprazole

Definition

Aripiprazole is a newer-generation antipsychotic medication.

Purpose

Aripiprazole can be used short term to treat acute psychotic and manic states and agitation in dementia, as well as long term to treat chronic psychotic disorders such as schizophrenia. The symptoms of schizophrenia include hallucinations, delusions, paranoia, and social withdrawal. In the past, these conditions were typically treated with conventional antipsychotic drugs, such as phenothiazine, thioxanthene, and butyrophenone neuroleptics.

Although aripiprazole is primarily indicated for the treatment of adults, some studies suggest that it also may be effective for children and adolescents with bipolar disorder. Researchers recommend a lower dose in younger patients. There is a risk of increased suicidal thoughts or actions, especially in children and

adolescents taking aripiprazole and in patients with bipolar disorder.

Description

Aripiprazole is part of a class of drugs called atypical antipsychotics. Drugs in this class, which include **clozapine**, **olanzapine**, quetiapine, **risperidone**, and **ziprasidone**, are called “atypical” because of their relatively lower risk of certain types of adverse side effects compared with traditional antipsychotic drugs.

The exact mechanism by which aripiprazole and other atypical antipsychotic drugs work is unknown. Scientists believe that schizophrenia is caused by an imbalance of dopamine in the brain. Dopamine is a neurotransmitter that affects movement and balance. The theory is that aripiprazole acts as a partial agonist and antagonist, meaning that it binds to dopamine receptors in the brain and partially activates these receptors while preventing dopamine from binding to and fully activating them. Conventional antipsychotic drugs, by contrast, act as full antagonists. These drugs completely block dopamine receptors and significantly interfere with dopamine transmission, which can cause severe movement side effects. Aripiprazole also affects another neurotransmitter, serotonin, which is involved in regulating mood and is also imbalanced in individuals with schizophrenia.

Although studies suggest that aripiprazole works well to treat psychotic conditions such as schizophrenia, less research has been conducted on how its effectiveness compares to that of conventional antipsychotic drugs.

U.S. brand names

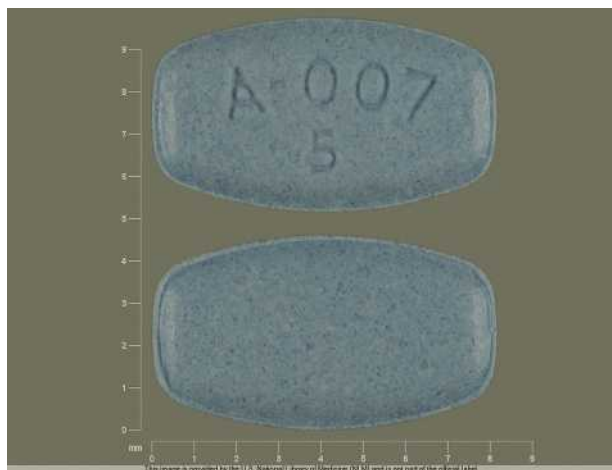
Aripiprazole is sold under the brand name Abilify.

Origins

It was approved by the U.S. Food and Drug Administration (FDA) in 2002 to treat schizophrenia symptoms. Aripiprazole is also FDA approved as a therapy for individuals with bipolar disorder who have had episodes of acute mania or mixed episodes of mania and depression but who have subsequently been stabilized for at least six weeks.

Recommended dosage

Aripiprazole is available only by prescription. It is taken once a day by mouth as either a tablet or an oral solution. The oral solution is designed for older patients who have difficulty swallowing a tablet. Tablets range in strength from 2 to 30 milligrams (mg). The oral solution



Abilify (aripiprazole), 5 mg. (U.S. National Library of Medicine, Pillbox)

KEY TERMS

Atypical antipsychotic—A class of newer-generation antipsychotic medications that are used to treat schizophrenia and other psychotic disorders.

Bipolar disorder—A mental disorder that causes extreme emotional shifts, from mania (elation or hyperactivity) to depression.

Delusions—False beliefs held by a person despite evidence to the contrary.

Dementia—A loss of mental ability, often occurring with age, that can interfere with a person's ability to think clearly and function independently.

Dopamine—A chemical messenger in the brain that regulates movement and balance.

Extrapyramidal—Related to the motor system in the brain, which controls movement and coordination.

Hallucinations—Perceptions of things (seeing, hearing, feeling, smelling, or tasting) that do not exist.

Mania—A mood disorder in which an individual may become impulsive or irritable and may exercise extremely poor judgment.

Neuroleptic malignant syndrome—A rare response to certain antipsychotic drugs, which can raise the body temperature to potentially life-threatening levels.

Neurotransmitter—A naturally occurring chemical in the body that carries chemical messages to nerve cells, often by transmitting nerve impulses. Central nervous system well-being is dependent on a balance among the neurotransmitters acetylcholine, dopamine, serotonin, and norepinephrine.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer these drugs, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Paranoia—Condition in which an individual has an irrational suspicion about another person or situation.

Partial agonist—A substance that partially activates a receptor in the brain while blocking the neurotransmitter for that receptor from binding to it.

Schizophrenia—A mental disorder in which an individual experiences hallucinations and delusions and displays unusual behavior.

Serotonin—A chemical messenger in the brain that affects mood and emotion.

is available in a 1 mg per milliliter (mL) solution. Aripiprazole can be taken with or without food. Some patients start on a low dose, and then their doctor increases the dose after approximately two weeks.

Precautions

Patients always need to read the accompanying medication guide before taking a prescribed drug. Aripiprazole may increase the risk for diabetes, and individuals who develop extreme thirst, frequent urination, or other diabetes symptoms while taking the drug should see a doctor for assessment.

Because this medication may cause drowsiness and can impair judgment and motor skills, individuals who take it should take precautions when operating a motor vehicle or machinery. Alcohol can increase the sedative effects and is not advised for use in individuals who are taking aripiprazole. Also, individuals who take this drug should use caution when exercising, because aripiprazole can affect the body's ability to regulate temperature, potentially leading to overheating and dehydration.

This drug can increase the risk for a rare condition called neuroleptic malignant syndrome (NML). This condition, which is sometimes caused by drugs that interfere with the dopamine pathway, can raise body temperatures to potentially life-threatening levels.

Aripiprazole can cause significant weight gain and the development of metabolic syndrome, the main characteristics of which are high cholesterol, increased blood pressure, insulin resistance or tolerance, or diabetes. Some practitioners use the diabetes drug **metformin** in patients who appear to be developing this syndrome, in an effort to avoid the development of diabetes and cardiovascular disease.

Geriatric

Aripiprazole is not approved for the treatment of psychosis in elderly patients with dementia. The FDA in 2005 released a public health advisory warning patients and doctors against using aripiprazole and other atypical antipsychotics off label. In studies, these drugs significantly increased the risk of death in older patients with dementia compared with placebo. Most of

the deaths were associated with heart failure or infections such as pneumonia. In June 2008, the FDA required all manufacturers of antipsychotic drugs to create a warning label with information about this risk. Atypical antipsychotics also have been associated with an increased risk for stroke in elderly patients with dementia-related psychosis.

Pregnant or breastfeeding

Women who are pregnant, who intend to become pregnant, or who are nursing should ask their doctor before taking or discontinuing this drug. There is an increased risk for extrapyramidal symptoms, which are a group of involuntary muscle movement disorders, and withdrawal symptoms in newborns whose mothers took aripiprazole during their third trimester of pregnancy. Symptoms include abnormal muscle tone, tremor, difficulty breathing and feeding, and agitation.

Other conditions and allergies

Because of potential drug interactions, individuals who are taking aripiprazole should tell their doctor if they have or are taking medications for any of the following conditions:

- Alzheimer's disease
- anxiety
- depression
- diabetes
- heart disease or heart failure
- high or low blood pressure
- human immunodeficiency virus (HIV)
- irritable bowel disease
- mental illness
- Parkinson's disease
- seizures
- stroke or mini-stroke
- ulcers

Side effects

Aripiprazole and other atypical antipsychotic drugs tend to cause fewer neurological side effects than the older antipsychotic drugs. In particular, they have a lower risk of extrapyramidal symptoms. However, the drug does have side effects. The most common side effects with aripiprazole are:

- anxiety
- constipation
- difficulty sleeping
- dizziness

- drowsiness
- headache
- nausea
- nervousness
- numbness
- tremor
- vomiting
- weight gain

Interactions

To avoid interactions, patients should tell their physicians about all of the drugs they are currently taking, including supplements.

Drugs

Aripiprazole can have potentially dangerous interactions with the following drugs:

- **famotidine**
- valproate
- lithium
- dextromethorphan
- **warfarin**
- **omeprazole**
- **lorazepam**

Food and other substances

Individuals taking aripiprazole should not consume alcoholic beverages.

Resources

BOOKS

- Mondimore, Francis Mark. *Bipolar Disorder: A Guide for Patients and Families*. 2nd ed. Baltimore: Johns Hopkins University Press, 2006.
- Stahl, Stephen M. *The Prescriber's Guide: Stahl's Essential Psychopharmacology*. 4th ed. Cambridge: Cambridge University Press, 2011.
- Torrey, E. Fuller. *Surviving Schizophrenia: A Manual for Families, Patients, and Providers*. 6th ed. New York: Harper Perennial, 2013.

PERIODICALS

- Raoufinia, Arash, et al. "Initiation of Aripiprazole Once-Monthly in Patients with Schizophrenia." *Current Medical Research & Opinion* (February 5, 2015): e-pub ahead of print. <http://dx.doi.org/10.1185/03007995.2015.1006356> (accessed February 23, 2015).

WEBSITES

- AHFS Consumer Medication Information. "Aripiprazole." American Society of Health-System Pharmacists.

Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a603012.html> (accessed February 23, 2015).
National Alliance on Mental Illness. "Aripiprazole (Abilify)." [http://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Aripiprazole-\(Abilify\)](http://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Aripiprazole-(Abilify)) (accessed February 23, 2015).

ORGANIZATIONS

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.
National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.
National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

Stephanie N. Watson

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Aristocort see **Triamcinolone**

Armodafinil

Definition

Armodafinil is a type of medication called a central nervous system stimulant. The central nervous system (CNS) includes the brain, spinal cord, and nerves. By stimulating the CNS—or, more precisely, affecting certain substances in the brain—the drug can promote wakefulness.

Purpose

A number of conditions, behaviors, or circumstances can cause people to have trouble sleeping at night or especially to have trouble staying awake during the day. For example, nighttime wakefulness and daytime sleepiness may be caused by shift work that keeps a person's internal sleep-and-wake clock out of sync with their work schedule (shift work disorder), or they may result from medical conditions such as narcolepsy, which is characterized by brief periods of sudden, deep sleep that can be associated with hallucinations and loss of muscle control. Another cause of daytime sleepiness is a sleep disturbance called obstructive sleep apnea, which is characterized by moments of blockage of the upper airway during sleep. The use of armodafinil can help ease sleepiness associated with these disorders.



Armodafinil (Nuvigil), 150 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

Armodafinil comes in tablet form and is available only by prescription. It was developed as a modified version of a similar drug called **modafinil**, but armodafinil can last longer and at a lower dose. The drug is considered a controlled substance, which means that it can be obtained only through a pharmacist with a doctor's prescription. The medication has the potential to be abused or lead to drug dependence, but it has been approved by the U.S. Food and Drug Administration (FDA) for specific medical uses, including improving wakefulness in people who have narcolepsy, obstructive sleep apnea, or shift work disorder.

U.S. brand names

In the United States, armodafinil is sold under the brand name Nuvigil.

Recommended dosage

Armodafinil comes in 50, 150, 200, and 250 milligram (mg) tablet strengths. Dosage depends on the purpose of its use. For narcolepsy or obstructive sleep apnea, adults can take between 150 mg and 250 mg once each morning. Adults with shift work disorder can take 150 mg once each day about one hour before their work shift begins.

Geriatric

Older patients (65 years and older) may need a lower dose of armodafinil than other adults.

Other conditions and allergies

Patients who have problems with liver function may also require a lower dose of armodafinil.

Precautions

Some people who take armodafinil have developed a severe rash when taking the medicine. It is important for anyone considering the medication to inform the doctor of all allergies, especially a known allergy to a similar medication called modafinil (Provigil). People with a history of certain heart valve problems should not use armodafinil. Because the drug can be abused, it is important to inform the doctor about any past problems with alcohol or drug abuse. It is important to avoid driving a vehicle or operating machinery until patients know how armodafinil affects them.

Pediatric

Armodafinil is not approved for use in children for any medical reason, and there are no clinical trial results to show whether the drug is safe or works in children.

Geriatric

Older patients who use armodafinil may need to have lower doses and may require closer monitoring of the drug's effects than other adults.

Pregnant or breastfeeding

Armodafinil is in the FDA pregnancy category C, which means that it has not been tested adequately in pregnant women, but studies in animals have shown that the medicine could be harmful to a fetus. The medicine is also released in breast milk. A woman who is pregnant should continue using armodafinil only if she and her doctor decide that the benefits of the medication outweigh potential risks to her unborn child. Mothers who want to breastfeed should decide whether to continue using the drug and not nurse their infants or to discontinue the medication while breastfeeding.

Other conditions and allergies

People who know they are allergic to modafinil should not take armodafinil.

Side effects

Armodafinil can cause several side effects. These include:

- dizziness
- headache

KEY TERMS

Angina—Chest pain and pressure that occurs when not enough blood flows to the heart muscle.

Narcolepsy—A problem with the nervous system that causes attacks of daytime sleep and extreme sleepiness.

Obstructive sleep apnea (OSA)—A potentially life-threatening condition characterized by episodes of breathing cessation during sleep alternating with snoring or disordered breathing. The low levels of oxygen in the blood of patients with OSA may eventually cause heart problems or stroke.

Shift work disorder—A sleep disorder caused by rotating work shift patterns or working nontraditional hours.

- problems with concentration or attention
- trouble falling asleep or staying asleep
- stomach problems such as pain, nausea, or vomiting
- heartburn
- shaking in any part of the body that will not stop
- numbness or tingling in the hands and feet

More serious side effects can occur and may indicate a severe allergic reaction. A doctor should be notified immediately if any of the following effects are noticed:

- blisters or peeling of skin
- rash
- sores in the mouth
- hives and itching
- swelling around the eyes, face, lips, mouth
- swelling of the arms, feet, or lower legs
- problems breathing or swallowing
- weakness
- chest pain
- pounding heart or irregular heartbeat

Interactions

Armodafinil can cause interactions with several drugs or substances that may affect how well the armodafinil or another drug works. Sometimes taking another drug or herbal remedy or drinking alcohol at the same time as taking a medication can intensify the drug's effects or cause unwanted side effects.

Drugs

Several drugs can interact with armodafinil. Some of the more serious interactions include:

- Taking armodafinil and the antidepressant **citalopram** (Celexa) at the same time can increase side effects such as irregular heartbeat.
- The combination of **clopidogrel** (Plavix), a drug used to help prevent blood clots or other heart and blood vessel problems, and armodafinil can reduce the effects of clopidogrel.
- Armodafinil and ranolazine (Ranexa), which is used to treat angina, can interact by reducing the levels of ranolazine in the blood and lessening its effectiveness.
- Use of armodafinil with certain steroidal contraceptives can lessen the effects of the contraceptives. Patients should discuss additional or alternative methods of contraception with their doctors.

Food and other substances

It is recommended to avoid drinking alcohol while taking armodafinil. Anyone with a past or current issue with drug or alcohol dependence should tell their healthcare provider.

Resources

PERIODICALS

Sonka, Karel, and Marek Susta. "Diagnosis and Management of Central Hypersomnias" *Therapeutic Advances in Neurological Disorders* 5, no. 5 (2012): 297–305.

WEBSITES

AHFS Consumer Medication Information. "Armodafinil." American Society of Health-System Pharmacists. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a607067.html> (accessed January 28, 2015).

"Armodafinil." Drugs.com. <http://www.drugs.com/cdi/armodafinil.html> (accessed January 28, 2015).

National Sleep Foundation. "Medical Treatments for Shift Work Disorder." <http://sleepfoundation.org/shift-work/content/medical-treatments-shift-work-disorder> (accessed January 28, 2015).

"Nuvigil." Cephalon, Inc. <http://nuvigil.com/Default.aspx> (accessed January 28, 2015).

U.S. National Library of Medicine. "Armodafinil." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2c824d4c-2309-4e2a-bc74-aa8d80a5c454> (accessed February 18, 2015).

ORGANIZATIONS

National Heart, Lung, and Blood Institute, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbiinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov/>.

National Sleep Foundation, 1010 N. Glebe Road, Suite 310, Arlington, VA 22201, (703) 243-1697, nsf@sleepfoundation.org, <http://sleepfoundation.org/>.

Teresa G. Odle, BA, ELS

REVIEWED BY KEVIN GLAZA, RPH

Asmanex see **Mometasone**

Aspirin

Definition

Aspirin is a medicine that relieves pain and reduces fever.

Purpose

Aspirin is used to relieve many kinds of minor aches and pains, including headache, toothache, muscle pain, menstrual cramps, joint pain related to arthritis, and aches associated with cold and flu symptoms. Some people take over-the-counter aspirin daily to reduce the risk of stroke, heart attack, or other heart problems. It is also prescribed in higher doses.

Description

Aspirin, also known as acetylsalicylic acid, is commonly sold over the counter and comes in many



Aspirin, 325 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

forms, from the familiar white tablets to chewing gum and rectal suppositories. Coated, chewable, buffered, and delayed-release forms are available; prescription aspirin is typically extended release. Aspirin is also often combined with other medications, both prescription and over the counter.

Aspirin belongs to a group of drugs called salicylates. Other members of this group include sodium salicylate, choline salicylate, and magnesium salicylate. These drugs are more expensive and often no more effective than aspirin, but they may have fewer gastrointestinal side effects. Aspirin is quickly absorbed into the bloodstream and provides relatively long-lasting pain relief. Aspirin also reduces inflammation. Researchers believe these effects come about because aspirin blocks the production of pain-producing chemicals called prostaglandins.

In addition to relieving pain and reducing inflammation, aspirin also lowers fever by acting on the part of the brain that regulates temperature. The brain then signals the blood vessels to widen, which allows heat to leave the body more quickly.

Recommended dosage

Aspirin comes in 81, 325, and 500 milligram (mg) tablets.

Adults

PAIN OR FEVER. To relieve pain or reduce fever, one to two tablets may be taken every three to four hours, up to six times per day.

STROKE. To reduce the risk of stroke, one tablet is taken four times a day, or two tablets twice a day.

HEART ATTACK. Individuals should check with their physician for the proper dose and number of times per week aspirin should be taken, if at all, to reduce the risk of heart attack (cardiac arrest).

Pediatric

Parents should check with their child's healthcare provider regarding the proper dosage.

Precautions

Aspirin, even children's aspirin, should never be given to children or teenagers with flulike symptoms or chickenpox. Aspirin can cause Reye syndrome, a life-threatening condition that affects the nervous system and liver. As many as 30% of children and teenagers who develop Reye syndrome die, and those who survive may have permanent brain damage.

KEY TERMS

Inflammation—Pain, redness, swelling, and heat that usually develop in response to injury or illness.

NSAIDs—Nonsteroidal anti-inflammatory drugs. Includes drugs that relieve pain and reduce inflammation, such as ketoprofen and ibuprofen.

Polyp—A lump of tissue protruding from the lining of an organ, such as the nose, bladder, or intestine. Polyps can sometimes block the passages in which they are found.

Prostaglandin—A hormone-like chemical produced in the body. Prostaglandins have a wide variety of effects and may be responsible for the production of some types of pain and inflammation.

Reye syndrome—A life-threatening disease that affects the liver and the brain and sometimes occurs after a viral infection, such as flu or chickenpox. Children or teenagers who are given aspirin for flu or chickenpox are at increased risk of developing Reye syndrome.

Rhinitis—Inflammation of the membranes inside the nose.

Salicylates—A group of drugs that includes aspirin and related compounds. Salicylates are used to relieve pain, reduce inflammation, and lower fever.

Because aspirin can increase the risk of excessive bleeding, no one should take aspirin for more than ten days in a row—for any purpose—unless told to do so by a physician. Anyone with a fever should not take aspirin for more than three days without a physician's consent. Do not take more than the recommended daily dosage.

Aspirin should not be taken before surgery, as it can increase the risk of excessive bleeding. Anyone who is scheduled for surgery should check with his or her surgeon to find out how long before surgery to avoid taking aspirin.

Aspirin can cause stomach irritation. To reduce the likelihood of that problem, aspirin may be taken with food or milk or a full 8-ounce glass of water. Taking coated or buffered aspirin instead of regular aspirin may also help.

Aspirin that has a vinegary smell is too old and ineffective and should be safely discarded.

Pregnant or breastfeeding

Pregnant women should consult their healthcare provider before taking aspirin, as the drug can cause bleeding problems in both the mother and the developing

fetus and can cause the infant's weight to be too low at birth. Aspirin also passes into breast milk.

Other conditions and allergies

People in the following categories should not use aspirin without first checking with their physician:

- people with a history of bleeding problems
- people who are taking blood-thinning drugs, such as warfarin (Coumadin)
- people with a history of ulcers
- people with a history of asthma, nasal polyps, or both (increases the risk of an allergy to aspirin)
- people who are allergic to fenoprofen, **ibuprofen**, indomethacin, **ketoprofen**, meclofenamate sodium, naproxen, sulindac, tolmetin, or the orange food-coloring tartrazine (also increases the likelihood of an aspirin allergy)
- people with acquired immune deficiency syndrome (AIDS) or an AIDS-related complex who are taking zidovudine (AZT)
- people with liver damage or severe kidney failure

Pediatric

Parents should check with a physician before giving aspirin to a child under 12 years of age for arthritis, rheumatism, or any condition that requires long-term use of the drug.

Side effects

The most common side effects include stomachache, heartburn, loss of appetite, and small amounts of blood in stools. Less common side effects are rashes, hives, fever, vision problems, liver damage, thirst, stomach ulcers, and bleeding. People who are allergic to aspirin or those who have asthma, rhinitis, or polyps in the nose may have trouble breathing after taking aspirin.

Individuals should stop taking aspirin immediately and call a physician if any of these symptoms develop:

- ringing or buzzing in the ears
- hearing loss
- dizziness
- stomach pain that does not go away

Interactions

Aspirin may increase, decrease, or change the effects of many drugs.

Drugs

Aspirin can make drugs such as **methotrexate** (Rheumatrex) and valproic acid (Depakote, Depakene)

more toxic. If taken with blood-thinning drugs, such as **warfarin** and dicumarol, aspirin can increase the risk of excessive bleeding. Aspirin counteracts the effects of other drugs, such as angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, which lower blood pressure, and medicines used to treat gout (probenecid and sulfinpyrazone). Blood pressure may drop unexpectedly and cause fainting or dizziness if aspirin is taken along with nitroglycerin tablets. Aspirin may also interact with diuretics, diabetes medicines, other nonsteroidal anti-inflammatory drugs (NSAIDs), seizure medications, and steroids. Anyone who is taking these drugs should ask his or her physician whether they can safely take aspirin.

Food and other substances

Alcohol consumption can worsen stomach irritation.

Resources

PERIODICALS

- Desai, D., H. M. Ahmed, and E. D. Michos. "Preventing Cardiovascular Disease in Patients with Diabetes: Use of Aspirin for Primary Prevention." *Current Cardiology Reports* 17, no. 3 (2015): 566.
- Fang, J., et al. "Use of Low-Dose Aspirin as Secondary Prevention of Atherosclerotic Cardiovascular Disease in US Adults (from the National Health Interview Survey, 2012)." *American Journal of Cardiology* (January 14, 2015): e-pub ahead of print. <http://dx.doi.org/10.1016/j.amjcard.2015.01.014> (accessed February 17, 2015).
- Sinha, G., et al. "More Evidence That Aspirin Lowers Cancer Risk." *Journal of the National Cancer Institute* 107, no. 1 (2015): 495. <http://dx.doi.org/10.1093/jnci/dju495> (accessed February 17, 2015).

WEBSITES

- AHFS Consumer Medication Information. "Aspirin." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682878.html> (accessed February 17, 2015).
- Harvard Health Publications. "New Guidelines Refine Aspirin Prescription." Harvard Medical School. <http://www.health.harvard.edu/heart-health/new-guidelines-refine-aspirin-prescription> (accessed February 17, 2015).
- Memorial-Sloan Kettering Cancer Center. "Common Medications Containing Aspirin and Other Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)." <http://www.mskcc.org/cancer-care/patient-education/resources/common-medications-containing-aspirin-and-other-nonsteroidal-anti-inflammatory-drugs-nsa> (accessed February 17, 2015).
- U.S. Food and Drug Administration. "Aspirin for Reducing Your Risk of Heart Attack and Stroke: Know the Facts." <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/SafeDailyUseofAspirin/ucm291433.htm> (accessed February 17, 2015).

ORGANIZATIONS

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Nancy Ross-Flanigan

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Aspirin/extended-release dipyridamole

Definition

The combination of **aspirin** and extended-release dipyridamole is in a class of drugs called antiplatelet agents. Antiplatelet agents keep blood clots from forming in blood vessels. Such clots can cut off blood flow to the heart and brain, which leads to heart attacks and strokes, respectively. Combination aspirin and extended-release dipyridamole is designed to reduce blood clotting in vessels leading to the brain.

Purpose

The combination of aspirin and extended-release dipyridamole is used for individuals who are at risk for having a stroke and for individuals who have already had

a transient ischemic attack or stroke and are at risk for another.

Description

The combination of aspirin and extended-release dipyridamole is designed to inhibit the clumping of platelets, which are cells that circulate in the blood. When a blood vessel is damaged, as occurs in a cut, the platelets attach to the site, begin releasing chemicals that attract more platelets, and start clumping together (aggregation) to form a clot. Aspirin, also known as acetylsalicylic acid, works by inhibiting the production of thromboxane, a platelet enzyme that helps platelets bind to one another and form the clot. Dipyridamole has its effect on another enzyme, known as phosphodiesterase, which normally breaks down the chemical cyclic adenosine monophosphate (cAMP). cAMP prevents platelets from clumping, and dipyridamole elevates cAMP levels by blocking phosphodiesterase. In addition, dipyridamole dilates the blood vessels. Studies have shown that the combination of aspirin and extended-release dipyridamole is more effective in preventing blood clots than either aspirin or dipyridamole alone.

Combination aspirin/extended-release dipyridamole is prescribed to reduce the risk of stroke in people who have had a stroke or a transient ischemic attack (TIA) due to thrombosis, which is the formation of a blood clot inside a blood vessel. TIAs are also sometimes called “mini-strokes.” A TIA produces the same symptoms as a stroke but usually lasts just a few minutes, and the patient experiences no permanent damage.

Combination aspirin/dipyridamole is administered as a capsule that is taken orally.

U.S. brand names

Combination aspirin/extended-release dipyridamole is sold under the trade name Aggrenox in the United States.

International brand names

Combination aspirin/extended-release dipyridamole is sold internationally under the trade name Asasantin.

Origins

During the development of Aggrenox, a multinational clinical trial was conducted in more than 7,000 patients in Europe. That trial demonstrated that the combination aspirin/dipyridamole was more effective than either aspirin or dipyridamole alone in reducing stroke risk among patients with a history of transient or complete stroke. Boehringer Ingelheim Pharmaceuticals, Inc., submitted a new drug application to the U.S. Food



Aggrenox (aspirin/extended-release dipyridamole, 25 mg/200 mg). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Antiplatelet agents—Compounds that prevent blood clots from forming in blood vessels.

Blood clot—A dense mat formed by certain components of the bloodstream to prevent blood loss.

Cyclic adenosine monophosphate (cAMP)—A compound that prevents platelets from clumping.

Phosphodiesterase—An enzyme that breaks down the chemical known as cyclic adenosine monophosphate (cAMP).

Platelets—Cells that circulate in the blood and are involved in blood clotting.

Stroke—Irreversible damage to the brain caused by insufficient blood flow to the brain as the result of a blocked artery. Damage can include loss of speech or vision, paralysis, cognitive impairment, and death.

Thrombosis—The formation of a blood clot inside a blood vessel.

Thromboxane—A platelet enzyme that helps platelets bind to one another and form a blood clot.

Transient ischemic attack (TIA)—A disorder that causes the same symptoms as a stroke but usually lasts just a few minutes and causes no permanent damage.

and Drug Administration (FDA) for Aggrenox in December 1998 for its use in reducing the risk of stroke in “patients who have transient ischemia of the brain or completed ischemic stroke due to thrombosis.” Based on the results of the multinational clinical trial, the FDA approved the drug as safe and effective for use as noted in the application.

Recommended dosage

The adult dosage for combination aspirin/extended-release dipyridamole contains 25 milligrams (mg) of aspirin and 200 mg extended-release dipyridamole, taken by mouth once in the morning and once in the evening. Each pill is taken whole with a glass of water. A missed dose should not be doubled up with the next dose.

Pediatric

Safety and efficacy for combination aspirin/extended-release dipyridamole have not been established for children, so it is not prescribed for this age group.

Geriatric

Dosage recommendations are the same for older adults as they are for younger adults. Older patients do sometimes have greater sensitivity to various medicines, however, so healthcare providers generally monitor them more carefully when beginning any new prescription.

Precautions

Patients should discuss with their healthcare provider what they can expect with regard to bleeding, as combination aspirin/dipyridamole inhibits clotting. In addition, individuals who are scheduled to have any dental work or heart tests should notify their dentists and physicians that they are using combination aspirin/extended-release dipyridamole. During heart tests, patients may be injected with dipyridamole, and the additional dose could be harmful. In some cases, the treating physician may have the patient stop taking the drug in advance of undergoing the test or the dental work.

All patients should be monitored for gastrointestinal ulcers and bleeding when they are taking combination aspirin/dipyridamole.

Geriatric

Individuals who are taking any other medications should notify the prescribing doctor of these medications before starting a regimen of combination aspirin/extended-release dipyridamole due to the risk of drug interactions.

Pregnant or breastfeeding

Combination aspirin/extended-release dipyridamole is in the FDA pregnancy category D from the third trimester of pregnancy through labor and delivery. Category D indicates a risk to the fetus, so as soon as a woman learns she is pregnant, she should consult with her healthcare provider about stopping her prescription. Combination aspirin/extended-release dipyridamole should be used with caution by nursing mothers, as it is excreted in breast milk.

Other conditions and allergies

Patients with hypersensitivity to aspirin, dipyridamole, or any product ingredients or with a known allergy to nonsteroidal anti-inflammatory drugs (NSAIDs) should not take combination aspirin/extended-release dipyridamole.

Patients who have severe renal failure, liver dysfunction, asthma, rhinitis, nasal polyps, or a history of active peptic ulcer disease should not take combination aspirin/extended-release dipyridamole. Those with coronary artery disease should be advised that the drug can lead

to new or intensified chest pain. Aspirin may exacerbate hives (urticaria), the hive-like swelling known as angioedema, or bronchospasm (airway spasms). In addition, patients with abnormally low blood pressure (hypotension) should discuss how the drug will impact them.

Side effects

Common side effects include headache (sometimes severe), abdominal pain, indigestion, nausea, and diarrhea. Less common side effects include:

- fatigue or weakness
- vomiting
- joint or back pain
- arthritis
- muscle pain
- nose bleeds
- amnesia
- convulsions
- bruising
- coughing or infection of the upper respiratory tract
- hemorrhoids
- anemia
- cardiac failure
- fainting

Use of combination aspirin/extended-release dipyridamole has also been associated with angina pectoris (chest pain due to coronary heart disease), confusion, skin rash, liver failure, acute anaphylaxis (a severe, whole-body allergic reaction), dehydration, low blood glucose levels (hypoglycemia), and unusually high or low blood potassium levels (hyper- or hypokalemia, respectively).

Geriatric

No specific additional side effects are noted for older adults. Since they are more likely to have additional health conditions, however, the healthcare provider should take these into account before prescribing combination aspirin/extended-release dipyridamole and while the patient is taking the drug.

Pregnant or breastfeeding

Side effects in mothers include prolonged pregnancy or labor and increased bleeding before and during birth. Low-birth-weight newborns and stillbirths have been reported.

Interactions

Because combination aspirin/extended-release dipyridamole contains two drugs, interactions may occur with

either of the two. Although many people take aspirin, it does interact with a number of drugs, and patients should not discount these interactions.

Drugs

Patients who are taking theophylline (a bronchodilator used to treat asthma and other lung conditions), mifepristone (a synthetic steroid used to end a pregnancy), or ticagrelor (designed to treat hypertension) should not also take combination aspirin/extended-release dipyridamole. Interactions may occur between combination aspirin/extended-release dipyridamole and a variety of additional drugs. These include:

- adenosine, which is used to treat irregular heartbeat and is also sometimes administered during stress tests
- anagrelide, which is used to treat essential thrombocytosis (also called essential thrombocythemia), or excessive production of platelets
- angiotensin-converting-enzyme (ACE) inhibitors, which are used to treat high blood pressure (hypertension), cardiovascular disease, and kidney (renal) diseases
- anticoagulants, which are used to prevent blood clotting
- anticonvulsants, which are used to treat epileptic seizures and sometimes neuropathic pain and bipolar disorder
- beta-blockers (also known as beta-adrenergic antagonists), which are used to treat hypertension, cardiac arrhythmias (abnormal heartbeat), and other cardiovascular conditions
- carbonic anhydrase inhibitors, which are used to treat such conditions as glaucoma, epilepsy, and osteoporosis
- cholinesterase inhibitors, which are used to treat such conditions as Alzheimer's disease and myasthenia gravis (a neuromuscular disease that causes muscle weakness)
- diuretics (also known as water pills), which promote urine production and are used to treat various heart, liver, and kidney conditions as well as hypertension
- NSAIDs, which are used to reduce pain, fever, and inflammation

Herbs and supplements

No specific interactions are noted, but patients should still inform their healthcare providers about any herbs or supplements they are taking.

Foods and other substances

Patients should discuss alcohol consumption with their doctor before beginning combination aspirin/extended-release dipyridamole. Consumption of alcohol may put patients at increased risk of bleeding.

Resources

BOOKS

Adrianne, Sarah, and Michael T. Torbey. "Antithrombotic Therapy in the Prevention of Stroke and Transient Ischemic Attack." In *The Stroke Book*, edited by Michael T. Torbey and Magdy H. Selim. 2nd ed. Cambridge: Cambridge University Press, 2013.

Eisert, Wolfgang G. "Dipyridamole." In *Platelets*, edited by Alan Michelson. 3rd ed. San Diego: Academic Press, 2013, pp. 1155–70.

PERIODICALS

Becker, Daniel E. "Antithrombotic Drugs: Pharmacology and Implications for Dental Practice." *Anesthesia Progress* 60, no. 2 (2013): 72–80.

Buitrago, Ivan. "Syncope During a Pharmacologic Nuclear Stress Test." *Cleveland Clinic Journal of Medicine* 81, no. 5 (2014): 279–80.

Kent, Tiffany L., and Philip L. Custer. "Bleeding Complications in Both Anticoagulated and Nonanticoagulated Surgical Patients." *Ophthalmic Plastic & Reconstructive Surgery* 29, no. 2 (2013): 113–17.

OTHER

American Heart Association. "What Are Anticoagulants and Antiplatelet Agents?" Heart.org. https://www.heart.org/idc/groups/heart-public/@wcm/@hcm/documents/downloadable/ucm_300338.pdf (accessed January 11, 2015).

Boehringer Ingelheim Pharmaceuticals, Inc. "Highlights of Prescribing Information." Bidocs.boehringer-ingelheim.com. <http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Aggrenox+Caps/Aggrenox.pdf> (accessed January 11, 2015).

Center for Drug Evaluation and Research. "Application Number: 020884." Accessdata.fda.gov. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20884_AGGRENOX_APPROV.PDF (accessed January 11, 2015).

WEBSITES

Boehringer Ingelheim Pharmaceuticals, Inc. "Taking Aggrenox." Aggrenox.com. <https://www.aggrenox.com/taking-aggrenox> (accessed January 11, 2015).

"Dipyridamole/Aspirin." Drugs.com. <http://www.drugs.com/ppa/dipyridamole-aspirin.html> (accessed January 11, 2015).

Mayo Clinic staff. "Aspirin and Dipyridamole (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/aspirin-and-dipyridamole-oral-route/description/drug-20061846> (accessed January 11, 2015).

MedlinePlus. "Aspirin and Extended-Release Dipyridamole." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699053.html> (accessed January 11, 2015).

Medscape Reference. "Aspirin/dipyridamole (Rx)—Aggrenox." <http://reference.medscape.com/drug/aggrenox-aspirin-dipyridamole-342148> (accessed January 11, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org/>.

American Society of Hypertension, 45 Main Street, Suite 712, Brooklyn, NY 11201, (212) 696-9099, Fax: (347) 916-0267, <http://www.ash-us.org/>.

National Heart, Lung, and Blood Institute Health Information Center, PO Box 30105, Bethesda, MD 20824, (301) 592-8573, Fax: (301) 592-8563, nhlbiinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov/>.

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Atacand see **Candesartan**

Atenolol

Definition

Atenolol is a cardiovascular drug known as a beta-blocker. This drug both relaxes blood vessels and slows heart rate.

Purpose

Patients take atenolol as directed by their doctors to treat high blood pressure (hypertension) and angina pectoris (chest pain due to reduced blood flow to the heart). Healthcare professionals may also use atenolol to improve the survival rate in patients who have just suffered a heart attack.

Description

Beta-blockers are a class of commonly used medications that have an effect on chemicals known as catecholamines. A major catecholamine is **epinephrine** (also called adrenaline), which is a hormone secreted by the adrenal glands (which sit on top of the kidneys). When a person is under stress—this includes short-term stress, such as watching a close and important football game, or long-term stress, such as continuing deadlines at work—nerves in the adrenal glands trigger the release of epinephrine. Epinephrine quickly spreads, binding at certain sites (called the beta-adrenergic receptors) throughout the body. Once bound, epinephrine causes such responses as increased heart rate and muscle strength, elevated blood pressure and heightened sugar metabolism and, in so doing, prepares the body to take action against the stressor.

Beta-blockers step in to prevent epinephrine from binding, inhibiting the hormone's effects. Different



Atenolol, 25 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

beta-blockers obstruct the effects of epinephrine at different locations in the body. Atenolol is a beta-blocker that keeps epinephrine from binding to the beta-adrenergic receptors in the cardiac muscle and stops epinephrine from telling the heart to beat faster and harder. In particular, atenolol targets a subset of receptors known as beta-1 adrenergic receptors. By limiting the binding of epinephrine, atenolol lowers blood pressure and slows heart rate. In patients who have angina pectoris, it also reduces chest pain.

Prescription atenolol is sold as tablets, which are taken by mouth. Depending on the formulation, it may be available as 25, 50 or 100 milligram (mg) tablets. For patients who have just suffered a heart attack, healthcare professionals may administer atenolol intravenously and via tablets.

Atenolol is often prescribed with other hypertension/angina medications, and in some cases it is formulated as a combined medication with such hypertension/angina medications as chlorthalidone, **amlodipine**, or **nifedipine**.

U.S. brand names

The primary brand name for atenolol is Tenormin.

International brand names

Tenormin is the primary brand name internationally. It is also sold as a generic drug under many labels.

Additional names under which atenolol is sold internationally include:

- Abloc
- Apo-Atenol
- Atenol
- AteHexal
- Aten
- Betacard
- Cardioblock
- Catenol
- Normaten
- Noten
- Ormidol
- Tenalol
- Therabloc
- Vascoten

Origins

One of the first beta-blockers with significant medical effects was **propranolol**. Discovered by Scottish pharmacologist Sir James Whyte Black in 1962, the drug was put to use to treat angina pectoris. This work led to the Nobel Prize in Physiology or Medicine, which Black received in 1988. Other beta-blockers followed, and among them was atenolol.

Atenolol was developed by the Stuart Company, a division of the British company Imperial Chemical Industries (now called Zeneca). The Stuart Company introduced atenolol in 1976. The U.S. Food and Drug Administration (FDA) initially approved the drug in 1981. It is now sold around the world for the management of patients who have hypertension or angina pectoris. In emergency rooms, it is also used to reduce the risk of death due to heart attack.

Recommended dosage

Atenolol is sold as pills, which patients are directed to take with a full glass of water and at the same time each day. The normal adult dose for angina pectoris is 50 mg daily initially. If needed, the doctor may increase the dosage to 100 mg or even 200 mg per day. For the treatment of hypertension, the normal dose is 50 mg daily. If necessary, the doctor may increase the dosage to 100 mg daily.

Precautions

Once a patient who has coronary artery disease has begun a regimen of atenolol, he or she should not abruptly stop the medication. This is especially important for patients who are taking the drug to manage angina, but the recommendation should also be followed by

individuals who are taking the drug to treat hypertension. Stopping the drug regimen abruptly can have serious consequences, including severe angina attacks, ventricular arrhythmias (rapid heartbeats originating in the ventricles, which are the heart's lower chambers), and heart attack. When a physician does decide to stop a patient's use of atenolol, he or she will carefully monitor the patient and advise the patient to limit physical activity.

Patients who have scheduled major surgery should discuss their use of atenolol with the prescribing physician and with the surgeon to determine the best course of action.

Patients should inform their doctors of all of their preexisting health conditions as well as any new conditions that arise while taking atenolol. In addition, they should be sure to inform their doctors about any medications, vitamins, and herbal supplements they are taking, so they understand any potential interactions.

Pediatric

Safety and efficacy for atenolol have not been established for children, so it is rarely prescribed for this age group.

Geriatric

Dosage recommendations are the same for older adults as they are for younger adults. However, older patients generally have a greater number of concomitant health conditions that may be affected by atenolol, so healthcare providers typically monitor them more carefully when beginning a new prescription and may start them on the low end of the dosage range.

Pregnant or breastfeeding

Atenolol is in the FDA pregnancy category D, which indicates a risk to the fetus. Lower birth weight is associated with the use of atenolol by expectant mothers during the second or third trimester of pregnancy. As soon as a woman learns she is pregnant, she should consult with her doctor about stopping her prescription. As noted, the patient should not stop taking the drug on her own, as this can cause health problems and may even lead to a heart attack.

Atenolol should be used with caution by nursing mothers, as it is released in breast milk and has been associated with hypoglycemia (low blood glucose) and bradycardia (slow heart rate) in newborns.

Other conditions and allergies

Doctors should use caution when prescribing atenolol to patients who have diabetes, impaired kidney function, or an overactive thyroid, and atenolol should

KEY TERMS

Angina—Chest pain due to reduced blood flow to the heart. There are two types: stable angina (angina pectoris) and unstable angina. The chest pain of angina pectoris is typically associated with physical activity or stress, while the pain of unstable angina can occur at any time.

Beta-blockers—Members of a class of commonly used medications that have an effect on chemicals known as catecholamines, which include epinephrine.

Bradycardia—Abnormally slow heart rate.

Bronchospastic disease—Any disease that causes spasms in the bronchi, which are airways within the lungs.

Epinephrine—Also called adrenaline, epinephrine is a stress-triggered hormone that causes such responses as increased heart rate and muscle strength, elevated blood pressure, and heightened sugar metabolism.

Hypertension—High blood pressure.

Hypoglycemia—Abnormally low blood glucose (blood sugar).

Hypotension—Abnormally low blood pressure.

not be prescribed to individuals with untreated pheochromocytoma (a rare adrenal gland tumor). Individuals who have a bronchospastic disease such as asthma or chronic obstructive pulmonary disease (COPD) should take atenolol only under certain conditions. If a patient cannot use or does not respond to other hypertensive medications and needs to regulate his or her blood pressure, the doctor may prescribe atenolol. In this case, the doctor will carefully monitor the patient to help ensure that he or she does not experience adverse effects.

Persons with allergic reactions to atenolol or any of the compounds used in making the tablets should not take this medication.

Side effects

Side effects of atenolol are generally mild and temporary, disappearing once the body adapts to the medication. These include:

- dizziness (especially upon standing)
- light-headedness
- vertigo
- fatigue or general tiredness

- diarrhea
- nausea

Some patients have experienced other side effects, such as:

- hypotension (abnormally low blood pressure)
- bradycardia
- blurred vision
- difficulty breathing

Patients should discuss side effects with their doctor or pharmacist and understand which side effects warrant medical attention.

Interactions

Patients should discuss with their healthcare provider possible interactions between atenolol and any other medications, vitamins, or supplements they are taking.

Drugs

Interactions may occur with atenolol and numerous drugs. These include:

- amiodarone, another anti-arrhythmia medication
- calcium channel blockers, which are drugs that disrupt the movement of calcium in certain muscle cells, causing blood vessels to dilate and the heart to pump less forcefully
- catecholamine-depleting drugs
- digitalis glycosides, which are cardiovascular drugs
- disopyramide, a medication to treat arrhythmia
- prostaglandin synthetase-inhibiting drugs

Herbs and supplements

No specific interactions are noted, but patients should still inform their doctors about any herbs or supplements they are taking.

Foods and other substances

Patients are advised to take atenolol with a glass of water rather than with apple or orange juice. These juices can affect the body's absorption of the drug. In addition, patients should refrain from drinking juice within four hours of taking atenolol. Patients should discuss alcohol consumption with their doctor, as alcohol can cause drowsiness, which may be exacerbated by atenolol.

Resources

BOOKS

Kaplan, Norman M., and Ronald G. Victor. "Treatment of Hypertension: Drug Therapy." In *Kaplan's Clinical Hypertension*. 11th ed. Philadelphia: Wolters Kluwer, 2015.

Mann, Samuel J., *Hypertension and You: Old Drugs, New Drugs, and the Right Drugs for Your High Blood Pressure*. Plymouth, UK: Rowman & Littlefield, 2012.

PERIODICALS

Abdullayev, Vasif, and Gulzar Aliyeva. "The Beta-Blockers in Combined Treatment of Coronary Heart Disease in Patients with Chronic Obstructive Pulmonary Disease (COPD)." *European Respiratory Journal* 42, suppl. 57 (2013): P3684.

Armario, Pedro, and Bernard Waeber. "Therapeutic Strategies to Improve Control of Hypertension." *Journal of Hypertension* 31, suppl. 1 (2013): S9–S12.

Habib, G. B., and S. S. Basra. "Are There Any New Pharmacologic Therapies on the Horizon to Better Treat Hypertension? A State-of-the-Art Paper." *Journal of Cardiovascular Pharmacology and Therapeutics* 19, no. 6 (2014): 516–25.

OTHER

AstraZeneca. "Tenormin Tablets [prescribing information]." <http://www1.astrazeneca-us.com/pi/tenormin.pdf> (accessed January 29, 2015).

WEBSITES

"Atenolol Pregnancy and Breastfeeding Warnings." Drugs.com. <http://www.drugs.com/pregnancy/atenolol.html> (accessed January 29, 2015).

Datapharm. "Atenolol (Atenolol 100 mg Tablets)." UK National Health Service. <http://www.nhs.uk/medicine-guides/pages/MedicineOverview.aspx?condition=Heart%20rhythm%20disorders&medicine=atenolol> (accessed January 29, 2015).

Mayo Clinic staff. "Atenolol (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/atenolol-oral-route/description/drg-20071070> (accessed January 29, 2015).

MedlinePlus. "Atenolol." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a684031.html> (accessed January 29, 2015).

U.S. National Library of Medicine. "Drug Record: Atenolol." LiverTox. <http://livertox.nih.gov/Atenolol.htm> (accessed January 29, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org/>.

American Society of Hypertension, 45 Main Street, Suite 712, Brooklyn, NY 11201, (212) 696-9099, Fax: (347) 916-0267, <http://www.ash-us.org/>.

National Heart, Lung, and Blood Institute Health Information Center, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, (301) 592-8563, nhlbiinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov/>.

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Ativan see **Lorazepam**

Atomoxetine

Definition

Atomoxetine is a medication used to treat attention deficit hyperactivity disorder (ADHD). Atomoxetine belongs to a class of drugs known as selective norepinephrine reuptake inhibitors, which specifically act on the neurological signaling chemical norepinephrine. Norepinephrine is a type of neurotransmitter involved in normal brain function and has an effect on mood and concentration.

Purpose

Atomoxetine is used to treat some of the symptoms of ADHD in both adults and children. Atomoxetine is often used for patients with ADHD who develop too many side effects from stimulants or who cannot tolerate stimulants due to coexisting anxiety or substance abuse. Patients with Tourette syndrome may find that the stimulant medications used to treat ADHD worsen their tics; atomoxetine is useful in this scenario because it can treat the symptoms of ADHD without worsening coexisting tics. For patients with ADHD who also have coexisting depression, atomoxetine may have some antidepressant properties, though it has not officially been approved for use in treating depression. The decision to use atomoxetine alone or in combination with other drugs depends on the medical profile of the patient and individual health parameters.



Strattera (atomoxetine), 60 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

Atomoxetine has a therapeutic mechanism of action that is focused on the modulation of the natural body chemical norepinephrine. Norepinephrine is a type of neurotransmitter in the nervous system, a chemical that neurons use to signal one another in complex pathways for normal brain and body functioning. Neurotransmitters such as norepinephrine bind to chemical receptors on the surface of neurons (brain cells). Once bound to a receptor, the neurotransmitters affect physiological processes. The receptors activate a sequence of cellular events known as chemical cascades or signaling pathways. Neurotransmitter signaling pathways are responsible for many regulatory processes, including neuronal signaling that affects mood and concentration.

It is believed that a decrease in norepinephrine signaling contributes to disorders such as ADHD and depression. The brain has discrete physiological areas that impact different functions of the mind and body. The area of the brain known as the prefrontal cortex affects attention span, judgment, response to external stimuli, memory, motor function, and impulse control. It is believed that increases in the available amounts of norepinephrine (and to a small degree dopamine) by drugs such as atomoxetine improve the symptoms of ADHD in the prefrontal cortex. Atomoxetine seems to function to improve the symptoms of ADHD without psychostimulation.

U.S. brand names

Atomoxetine is sold under the brand name Strattera.

Origins

Atomoxetine was the first nonstimulant drug approved by the U.S. Food and Drug Administration for the treatment of ADHD, though the stimulants remain the mainstay of ADHD therapy.

Recommended dosage

Atomoxetine is taken as an oral medication, usually in the morning, and often requires several weeks of therapy before ADHD symptoms improve. For adults, the dose is usually started at 40 milligrams (mg) for a few days, to allow the patient to adjust to the medication, and is then increased to 80 mg a day. Some patients will require the maximum dose of 100 mg a day for the best effect, but this dose should not be attempted until the patient does well on the 80 mg dose for three to four weeks.

Pediatric

Children six years old and older and heavier than 154 lb. (70 kg) follow the same regimen as adults but

KEY TERMS

Attention deficit hyperactivity disorder (ADHD)—A condition characterized by lack of concentration, impulsive or inappropriate behavior (relative to age level), and hyperactivity.

Bipolar disorder—Psychiatric mood disorder characterized by periods of manic behavior that may alternate with periods of depression; previously known as manic depressive disorder.

Dopamine—A type of neurotransmitter involved in regulation of concentration, impulse control, judgment, mood, attention span, psychostimulation, and disease states such as addiction, ADHD, and depression.

Mania—Physiological state of hyperactivity experienced by patients with certain psychiatric illnesses involving inappropriately elevated mood, pressured speech, poor judgment, and sometimes psychotic episodes.

Monoamine oxidase inhibitor (MAOI)—Type of antidepressant medication that affects various kinds of neurotransmitters.

Neurotransmitter—A chemical messenger that travels through the body and acts in the nervous system. Neurotransmitter signaling is responsible for a wide range of bodily processes and is often the target of medications involving the brain and cardiovascular system.

Neurotransmitter receptor—A physical recipient for chemicals called neurotransmitters. Receptors sit on the surface of cells that make up body tissues; once bound to the neurotransmitter, they initiate the

chemical signaling pathway associated with neurotransmitters.

Norepinephrine—A type of neurotransmitter involved in regulation of concentration, impulse control, judgment, mood, attention span, psychostimulation, and disease states such as ADHD and depression.

Prefrontal cortex—Area of the brain involved in attention span, judgment, response to external stimuli, memory, motor function, and impulse control.

Selective norepinephrine reuptake inhibitors—Drug class that acts to specifically inhibit the reuptake of norepinephrine with little effect on other types of neurotransmitters, thereby decreasing side effects associated with broader-acting drugs.

Stimulant—A type of psychoactive substance that increases alertness or wakefulness. Stimulants may be prescribed to treat disorders such as autism or attention deficit hyperactivity disorder but are also illegally abused.

Tic—Involuntary movements (such as twitching or facial grimacing) or vocalizations (such as throat clearing or barking) associated with Tourette syndrome.

Tourette syndrome—An inherited neuropsychiatric disorder characterized by the development of both motor and vocal tics. The tics are preceded by a feeling of tension or urgency in the affected individual until the tic behavior is performed and relieves the perceived feeling of tension.

may have doses divided throughout the day to reduce the amount taken at any one time. Children who are older than six years and less than 70 kg are dosed based on weight. The usual starting dose is 0.5 mg per 2.2 lb. (1 kg) a day for several days, increased to 1.2 mg per kg per day. The maximum dose in this population is 1.4 mg per kg per day.

Other conditions and allergies

Some patients have altered metabolism of atomoxetine and require a slower pace for increasing the dose. Patients with liver impairment may not metabolize atomoxetine well and will require lower doses or may not be able to use the drug.

Precautions

Patients are frequently reassessed for the need for treatment, as drugs for ADHD are avoided unless absolutely necessary. The dose chosen depends on individual patient response to the medication regarding its effectiveness and the occurrence of adverse effects. Patients are given the lowest possible effective dose to avoid the development of adverse effects. Slowly increasing the dose over time helps with minimizing side effects, and some side effects lessen with continued use. Clinicians weigh the potential for benefit with atomoxetine treatment against the potential undesirable outcomes when making treatment decisions.

Rare but serious reactions include very high blood pressure (hypertension), glaucoma, loss of consciousness,

heart arrhythmias, heart attack, stroke, seizures, liver toxicity, and sudden death. Some patients develop increased aggressiveness, psychosis, mania, or suicidality in the first weeks of use before the intended therapeutic effects take place. Patients taking atomoxetine are monitored closely for behavioral changes, especially when starting treatment or after dose changes.

Pediatric

Children are especially at risk for behavioral side effects.

Pregnant or breastfeeding

Atomoxetine is classified as category C for pregnancy, which means that either there are no adequate human or animal studies or adverse fetal effects have been found in animal studies but there is no available human data. The decision whether to use category C drugs in pregnancy is generally based on weighing the critical needs of the mother against the risk to the fetus. Other, lower category agents are used whenever possible. The safety of atomoxetine use during breastfeeding is unknown, so its use is not recommended.

Other conditions and allergies

Atomoxetine may be contraindicated (should not be used) or may require caution in patients with uncontrolled hypertension, liver function impairment or liver disease, kidney function impairment, glaucoma, heart conditions or abnormalities, or seizure disorder. Kidney and liver function as well as blood pressure may be monitored while taking atomoxetine. Atomoxetine is discouraged from use in patients with bipolar disorder, as it is more likely to induce a state of mania in these individuals than in those without bipolar disorder.

Side effects

Atomoxetine has many adverse effects. It usually takes several weeks of medication for the treatment effect to occur, while the undesirable side effects may occur at the onset of treatment. Sensitivity to atomoxetine varies among patients, and some patients may find that even lower doses are more than their body system can tolerate. Common reactions include dry mouth, abdominal pain, nausea and vomiting, constipation, insomnia, sleep disorders and abnormal dreams, decreased appetite, changes in urination, erectile dysfunction, changes to the menstrual cycle, drowsiness, numbness and tingling in the extremities, dizziness, fatigue, hot flashes, increased blood pressure and heart rate, sweating, and palpitations.

Interactions

Patients should make their doctor aware of all medications and supplements they are taking before using atomoxetine. Drugs that affect the liver may alter the metabolism of atomoxetine, resulting in too much or too little of the drug in the body. This could lead to increased side effects or even toxic doses. Likewise, atomoxetine may affect the metabolism of other drugs, leading to greater or lower doses than therapeutically desired.

Drugs

Certain drugs may cause toxicity when used with atomoxetine, either through additive effects or through inhibition of metabolism, causing toxic levels of atomoxetine in the blood. Drugs that may cause toxicity with atomoxetine include:

- antidepressants such as **bupropion** and **duloxetine**
- the antiulcer drug cimetidine
- cinacalcet, used to treat some endocrine disorders
- some anticancer drugs, such as **imatinib** and nilotinib
- the heart drug amiodarone
- certain antibiotics, such as **linezolid**
- antipsychotics such as **haloperidol** and thioridazine

Antidepressants called monoamine oxidase inhibitors (MAOIs) also increase the amounts of norepinephrine and dopamine left in the body and cannot be used concurrently with atomoxetine, as the combination may cause overstimulation of the central nervous system and toxicity. Switching drug treatment from an MAOI to atomoxetine may require a waiting period of up to two weeks between drugs. The antidepressant drug maprotiline may also have additive effects with atomoxetine that cause toxicity.

Herbs and supplements

It is unknown which herbal supplements interact with atomoxetine. Patients should consult their health-care provider before taking any herbs or other dietary supplements.

Food and other substances

Using alcohol while taking atomoxetine may create toxic reactions in the body and should be avoided. Caffeine may also cause toxicity.

Resources

BOOKS

Brunton, Laurence L., et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill Medical, 2011.

Stargrove, Mitchell Bebel, et al. *Herb, Nutrient, and Drug Interactions: Clinical Implications and Therapeutic Strategies*. St. Louis: Mosby, 2007.

PERIODICALS

Asherson, P., et al. "The Effects of Atomoxetine on Emotional Control in Adults with ADHD: An Integrated Analysis of Multicenter Studies." *European Psychiatry* (January 30, 2015): e-pub ahead of print. <http://dx.doi.org/10.1016/j.eurpsy.2014.12.002> (accessed February 23, 2015).

Bro, S. P., et al. "Adverse Pregnancy Outcomes after Exposure to Methylphenidate or Atomoxetine during Pregnancy." *Clinical Epidemiology* 7 (January 29, 2015): 139–47.

WEBSITES

Micromedex. "Atomoxetine (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/atomoxetine-oral-route/description/drg-20066904> (accessed February 23, 2015).

U.S. Food and Drug Administration. "Atomoxetine (Marketed as Strattera) Information." <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107912.htm> (accessed February 23, 2015).

ORGANIZATIONS

American College of Neuropsychopharmacology, 5034-A Thoroughbred Lane, Brentwood, TN 37027, (615) 324-2360, Fax: (615) 523-1715, acnp@acnp.org, <http://www.acnp.org/default.aspx>.

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.

Mental Health America, 2000 N. Beauregard Street, 6th Floor, Alexandria, VA 22311, (703) 684-7722, (800) 969-6642, Fax: (703) 684-5968, <http://www1.nmha.org/>.

Maria Eve Basile, PhD

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Atorvastatin

Definition

Atorvastatin belongs to a family of drugs called 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, more commonly known as statins.

Purpose

Atorvastatin is used to decrease the amount of cholesterol the body produces by interfering with an enzyme in the liver needed to produce cholesterol. It reduces the level of low-density lipoprotein (LDL, or "bad" cholesterol) and increases levels of high-density



Lipitor (atorvastatin), 40 mg. (© Cengage Learning®.)

lipoprotein (HDL, or "good" cholesterol) in the blood. It also lowers the level of triglycerides (fats) in the blood. By reducing LDL cholesterol and triglycerides and increasing HDL cholesterol, atorvastatin helps reduce the risk of coronary artery disease, stroke, and heart attack.

Description

Atorvastatin is a white, elliptical tablet that comes in strengths of 10, 20, 40, and 80 milligrams (mg). It is taken by mouth once daily at the same time each day. It can be taken with or without food.

Atorvastatin is also a component of two other drugs. Caudet contains atorvastatin and amlodipine, a blood-pressure-lowering drug, and Liptruzet contains atorvastatin and ezetimibe, a drug that reduces the absorption of cholesterol in the small intestine.

Origins

Atorvastatin was first invented in the Parke-Davis pharmaceutical laboratory. It was sold exclusively by Pfizer under the name Lipitor (atorvastatin calcium) from 1996 until its patent expired in November 2011. During this time, it became the world's best-selling drug. In 2012, after Pfizer's patent expired, a generic form of the drug became available.

KEY TERMS

Cholesterol—A waxy substance made by the liver and also acquired through diet. High levels in the blood may increase the risk of cardiovascular disease.

Pregnancy category—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk, but there are no human studies, or adverse effects have been seen in animals but not in well-controlled human studies. Category C: No adequate human or animal studies exist, or adverse fetal effects have been seen in animal studies but there is no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk. Risks outweigh any benefits.

Triglycerides—A type of fat found in the blood. High levels of triglycerides can increase the risk of coronary artery disease.

Recommended dosage

Dosage varies with the degree to which cholesterol needs to be reduced and the response of the individual to the drug. Often the initial dosage is 10 mg or 20 mg once daily. The initial dosage is monitored and can be adjusted in two to four weeks until the desired cholesterol readings are obtained. People who require severe reductions in LDL cholesterol may start at a higher dosage. Maximum recommended dosage is 80 mg once daily.

Because the drug is taken to reduce the risk of coronary artery disease, individuals normally stay on the drug continuously once the correct dosage is reached. The drug should not be stopped without consulting a physician.

Pediatric

The maximum recommended dosage for children ages 10–17 is 20 mg per day. Higher dosage in children has not been studied.

Precautions

The following precautions apply to all individuals.

- Alcohol consumption can increase the risk of serious side effects. Individuals should tell their doctor if they

drink more than two alcoholic drinks per day. Daily alcohol use should be avoided while on this drug.

- Before taking atorvastatin, individuals should tell the doctor about any drug or food allergies.
- Women should tell their doctor if they plan to become pregnant. This drug should never be taken during pregnancy or while breastfeeding. It is essential to use effective birth control while taking this drug.
- Tell the doctor of any history of liver disease, kidney disease, thyroid disease, diabetes, low blood pressure, muscle weakness, or seizures.

Pediatric

Atorvastatin should not be given to children under 10 years old.

Pregnant or breastfeeding

Women who are pregnant, trying to become pregnant, or breastfeeding should not take atorvastatin. The drug is a pregnancy category X drug, which means that it will cause harm to the developing fetus.

Other conditions and allergies

Individuals with HIV/AIDS who are taking the protease inhibitors tipranavir (Aptivus) plus ritonavir (Norvir) and individuals who have hepatitis C and are taking telaprevir (Incivek) should not take atorvastatin. Individuals taking other drugs for HIV/AIDS and hepatitis C should review their medications with their doctor. If atorvastatin is prescribed, it should be given only at the lowest dose necessary.

Side effects

Serious allergic reactions to atorvastatin are rare. Severe rash or itching; swelling, especially of the face or tongue; trouble breathing; and severe dizziness are all signs of an allergic reaction and require immediate medical attention. Call a doctor or go to the emergency room if these symptoms appear after taking atorvastatin.

Side effects that are serious and require prompt medical attention, but that are uncommon, include:

- dark urine or yellowing of the skin, which may indicate liver damage
- stomach pain, nausea, and persistent vomiting
- chest pain
- extreme tiredness or weakness
- loss of appetite
- unusual amount of bruising or bleeding
- flulike symptoms and fever

Muscle pain, tenderness, and weakness, especially muscle pain that persists after the drug is stopped, may indicate a rare breakdown of skeletal muscle called rhabdomyolysis, especially if they are accompanied by fever and changes in urine output.

Milder and less serious side effects include:

- constipation, diarrhea, or gas
- headache
- mild joint pain
- confusion or memory impairment (both rare)

Geriatric

Older individuals are more likely to develop skeletal muscle breakdown, which can lead to kidney failure. At greatest risk are older adults who already have kidney problems or a low-functioning thyroid (hypothyroidism).

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbal or dietary supplements, and foods. Interactions can increase or decrease the effectiveness of atorvastatin or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Atorvastatin is known to interact with the following pharmaceutical drugs:

- drugs used to treat fungal infections, such as **fluconazole** (Diflucan), itraconazole (Sporanox), **ketconazole** (Nizoral), or voriconazole (Vfend)
- **diltiazem** (Cardizem, Cartia, Dilacor, Diltia, Diltzac, Taztia, Tiazac) and other drugs used to treat heart conditions such as digoxin (Lanoxin), nicardipine (Cardene), quinidine (Quin-G), and verapamil (Calan, Covera, Ioptin, Verelan)
- **spironolactone** (Aldactone, Aldactazide)
- certain antibiotics, such as **clarithromycin** (Biaxin), **erythromycin** (EES, EryPed, Ery-Tab, Erythrocin), dalfopristin/quinupristin (Synercid), rifampin (Rifater, Rifadin, Rifamate), and telithromycin (Ketek)
- **gemfibrozil** (Lopid), fenofibric acid (Fibricor, Trilipix), or **fenofibrate** (Antara, Fenoglide, Lipofen, Lofibra, Tricor, Triglide)
- many HIV/AIDS medications, including darunavir (Prexista), fosamprenavir (Lexiva), ritonavir (Norvir), lopinavir/ritonavir (Kaletra), nelfinavir (Viracept), saquinavir (Invirase), and tipranavir (Aptivus)
- drugs containing niacin

- drugs that suppress the functioning of the immune system, such as steroids, **cyclosporine** (Gengraf, Neoral, Sandimmune), sirolimus (Rapamune), or **tacrolimus** (Prograf), as well as many cancer medications
- telaprevir (Incivek)

Other interactions are possible. An individual who develops any unusual or unexpected symptoms should contact a physician.

Herbs and supplements

Red yeast rice products should be avoided. When taken with atorvastatin, they increase the chance of developing serious side effects.

Niacin supplements should be avoided.

Foods and other substances

Consuming large quantities of grapefruit or grapefruit juice should be avoided while taking atorvastatin.

Resources

BOOKS

- Estren, Mark James. *Statins: Miraculous or Misguided?* Berkeley, CA: Ronin, 2013.
- Roberts, Barbara H. *The Truth about Statins: Risks and Alternatives to Cholesterol-Lowering Drugs*. New York: Gallery Books, 2012.

PERIODICALS

- “High-Dose Atorvastatin Is Superior to Moderate-Dose Simvastatin in Preventing Peripheral Arterial Disease.” *Heart* (January 16, 2015): e-pub ahead of print. <http://dx.doi.org/10.1136/heartjnl-2014-306906> (accessed January 23, 2015).

WEBSITES

- “Atorvastatin.” Drugs.com. <http://www.drugs.com/atorvastatin.html> (accessed December 31, 2014).
- MedlinePlus. “Atorvastatin.” U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a600045.html> (accessed December 31, 2014).
- Pfizer. “Lipitor.” Lipitor.com. <http://www.lipitor.com> (accessed December 31, 2014).

ORGANIZATIONS

- American College of Cardiology, Heart House, 2400 N Street NW, Washington, DC 20037, (202) 375-6000, ext. 5603, (800) 253-4636, ext. 5603, Fax: (202) 375-7000, resource @acc.org, <http://www.acc.org/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Tish Davidson, AM

REVIEWED BY GREGORY A. PRATT, RPh

Atripla see **Efavirenz/emtricitabine/tenofovir**

Atrovent see **Ipratropium**

Augmentin see **Amoxicillin/clavulanic acid**

Avapro see **Irbesartan**

Avastin see **Bevacizumab**

Avelox see **Moxifloxacin**

Avodart see **Dutasteride**

Avonex see **Interferon beta 1a**

Axert see **Almotriptan**

Azithromycin

Definition

Azithromycin is an antibiotic drug in the family of macrolide drugs.

Purpose

Azithromycin treats a variety of infections, including infections of the ears, throat, lungs, sinuses, skin, and gastrointestinal and genitourinary tracts. Some of the organisms it is effective against include *Haemophilus*

influenzae, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Mycobacterium avium*.

Description

Azithromycin is available in tablet, liquid suspension, and injectable (intravenous) forms. The medication is taken by mouth or through an intravenous (IV) line and must be prescribed by a physician. Azithromycin is used internationally and is on the World Health Organization's list of essential medicines. It is also frequently used in veterinary medicine.

U.S. brand names

Azithromycin is sold under the brand names Zithromax, Zithromax Tri-Pak, Zithromax Z-Pak, and Zmax. It is also manufactured as a generic by many different companies.

Canadian brand names

Azithromycin is sold as Apo-Azithromycin, Apo-Azithromycin Z, Ava-Azithromycin, Dom-Azithromycin, PRO-Azithromycin, Zithromax, and Zmax SR.

International brand names

Azithromycin is sold under a large variety of brand names internationally, including Abacten, Astro, Avzeth, Cetaxim, Hemomycin, Ultreon, and Zeto. In some countries, azithromycin is only one component of the medication, and there are other medications included in the formulation.

Recommended dosage

Recommended dosages are based on the amount of azithromycin needed to treat the infection. Dosing schedules depend on the specific infection being treated and range from one single large dose to three-, five-, seven-, or ten-day courses of medication. Azithromycin is dosed once per day, and single doses range in strength from 250 to 2,000 milligrams (mg). Dosing schedules often instruct that a double dose is taken on the first day, followed by a single dose on subsequent days until the prescription is gone. Azithromycin can be taken with or without food. It is important to read and follow the prescription instructions.

Pediatric

Pediatric dosing also depends on the infection being treated. In general, children are dosed by weight, with dosages ranging from 5 to 30 mg per kilogram (kg, or 2.2 lb.) of body weight per day and most treatment regimens requiring only a single dose each day.



Azithromycin, 250 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Anaphylaxis—A severe, systemic allergic reaction that can be potentially life threatening.

Macrolides—A class of antibiotic drugs, named for the macrolide ring within a macrolide drug's structure.

Pregnancy category—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk, but no human studies exist, or adverse effects have been seen in animals but not in well-controlled human studies. Category C: No adequate human or animal studies exist, or adverse fetal effects have occurred in animal studies but there is no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk, and risks outweigh any benefits.

Precautions

The following precautions apply to all individuals:

- Individuals should not take azithromycin if they are allergic to azithromycin or other macrolide-type drugs (e.g., azalide or ketolide) or have developed jaundice and liver problems when taking azithromycin in the past.
- This drug should be taken for the entire length of the prescription. Failure to take a complete course of the medication can result in return of symptoms.
- Individuals with a history of kidney or liver problems or on dialysis should tell their doctor before taking this drug.
- Use over a long period of time can increase the risk of developing another fungal or bacterial infection.
- *C. difficile*—associated diarrhea and pseudomembranous colitis have both been associated with long-term use of azithromycin, even months after the drug has been discontinued.
- Individuals with a history of severe allergies, asthma, or previous reactions involving anaphylaxis, hives, or severe swelling (angioedema) are at higher risk for serious reactions to azithromycin.
- Individuals looking to take azithromycin for the severe sore throat associated with infectious mononucleosis have an extremely high risk of developing a rash, so azithromycin use should be avoided.

- Women taking **oral contraceptives** should ask their healthcare providers if they need to use a second form of contraception while on azithromycin, as this drug can interfere with the effectiveness of the birth control pill.

- Azithromycin makes the skin more sensitive to sun exposure and tanning lights, resulting in more easily (and potentially severely) burned skin.

Geriatric

Although the risk of azithromycin-induced heart-related side effects may be increased in the elderly, no dosage adjustment is necessary.

Pregnant or breastfeeding

Azithromycin has not been well studied in pregnant women. This drug is a pregnancy category B drug. Women who are pregnant or breastfeeding should tell their doctor before taking azithromycin. This drug can pass into breast milk and may cause low appetite, diarrhea, rash, and sleepiness in the nursing child.

Other conditions and allergies

Azithromycin should be used only for individuals whose illness is mild and who do not have any of the following pre-existing conditions that might require more robust therapy:

- cystic fibrosis
- hospital-acquired infections
- bacteria in the bloodstream (bacteremia)
- severe enough illness to require hospitalization
- elderly or debilitated patients
- immunosuppression, immunodeficiency, or non-working/absent spleen

Other conditions that require careful attention during treatment with azithromycin include:

- Sexually transmitted infections, such as gonorrhea and syphilis; symptoms may be masked while using azithromycin. If these infections are suspected, then testing should be accomplished before beginning azithromycin treatment.
- People with liver disorders should be given azithromycin with caution, and treatment should be stopped immediately if they develop symptoms of hepatitis (jaundice, weakness, nausea and vomiting, abdominal cramping fever).
- People with myasthenia gravis should use azithromycin cautiously, as this medication may worsen the disorder.

- People with kidney disorders may have a higher risk of gastrointestinal problems while using azithromycin.

Side effects

Serious and sometimes fatal reactions can occur in individuals who are allergic to penicillin and penicillin-like drugs. Anyone who has had a severe reaction to any drug should alert the physician before taking this drug.

The most common adverse side effects of azithromycin for all age groups tend to be mild. They include:

- upset stomach
- loose stools or diarrhea
- nausea and vomiting

These side effects should be brought to the doctor's attention if they do not go away within a few days. Whitish vaginal discharge or white coating of the tongue and inside of the mouth should also be reported to the doctor.

A doctor should be notified immediately if any of these less common but more serious side effects occur:

- hoarse voice
- severe skin rash, itching, or hives or blistering or separating skin
- swelling
- yellowing of the skin or the whites of the eyes (symptoms of jaundice)
- vaginal itching or discharge
- seizures
- abdominal pain with fever
- sensation of an extra, skipped, or fast heartbeat
- dizziness, fainting
- severe or bloody diarrhea, even if it occurs two months after ending azithromycin treatment
- easy bruising or bleeding
- very dark urine
- severe muscle weakness or unusual loss of muscle control
- wheezing or difficulty breathing or swallowing

Wheezing and difficulty breathing and swallowing may indicate a severe allergic reaction and require immediate medical attention. Individuals experiencing these effects should immediately call the doctor or go to the emergency room.

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herb, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects.

Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Azithromycin is known to interact with the following pharmaceutical drugs. Other interactions are possible. An individual who develops any unusual or unexpected symptoms should contact a physician.

- Due to increased risk of cardiovascular complications, avoid using azithromycin in conjunction with amiodarone, ivabradine, mifepristone, pimozone, and terfenadine.
- Azithromycin may increase blood levels and toxic effects of **atorvastatin**, cardiac glycosides, **cyclosporine**, ivermectin, lovastatin, quinine, rilpivirine, **rivaroxaban**, **simvastatin**, **tacrolimus**, and vitamin K antagonists (such as **warfarin**).
- Azithromycin may decrease blood levels and therapeutic effects of the bacillus Calmette–Guérin (BCG) vaccine, sodium picosulfate, and the typhoid vaccine.
- Serum concentration and toxic effects of azithromycin may be increased by nelfinavir.

Resources

BOOKS

- Bennett, John E., Raphael Dolin, and Martin J. Blaser. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. London: Churchill Livingstone, 2014.
- Cherry, J., et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Saunders, 2013.
- Drug Information Handbook*. 23rd ed. Hudson: Lexi-Comp, 2014.
- Rang, H. P., et al. *Rang & Dale's Pharmacology*. 7th ed. London: Churchill Livingstone, 2011.

PERIODICALS

- Mori, F., et al. "Azithromycin Anaphylaxis in Children." *International Journal of Immunopathology and Pharmacology* 27, no. 1 (2014): 121–26.
- Ray, Wayne A., et al. "Azithromycin and the Risk of Cardiovascular Death." *New England Journal of Medicine* 366 (May 17, 2012): 1881–90.

WEBSITES

- Micromedex. "Azithromycin (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/azithromycin-oral-route/description/drg-20072362> (accessed February 14, 2015).
- U.S. Food and Drug Administration. "FDA Drug Safety Communication: Azithromycin (Zithromax or Zmax) and the Risk of Potentially Fatal Heart Rhythms." <http://www.fda.gov/Drugs/DrugSafety/ucm341822.htm> (accessed February 14, 2015).

U.S. National Library of Medicine. *Drugs and Lactation Database (LactMed)*. <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm> (accessed February 14, 2015).

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

ORGANIZATIONS

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

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Azulfidine see **Sulfasalazine**

B

Baclofen

Definition

Baclofen is a drug that is classified as a skeletal muscle relaxant and an antispastic.

Purpose

Baclofen acts on the nerves in the spinal cord and is used in the treatment of spastic movement disorders, primarily multiple sclerosis and spinal cord injuries. Baclofen may be taken orally or delivered by intrathecal injection to help relax certain muscles and relieve muscle spasms, cramping, and tightness associated with diseases or injuries that affect the spinal cord. It may also be used to treat chronic neuropathic pain. It is not used to relieve ordinary muscle soreness occurring as a result of exercise or strain.

Off-label use

Baclofen has been used to treat hiccups and gastroesophageal reflux disease (GERD). The drug is also being investigated for treating alcoholism and alcohol withdrawal syndrome but is not yet approved for these uses.

Description

Baclofen is a white to off-white, relatively odorless crystalline powder that can be prepared as a tablet, suspended in solution as an injectable drug, or compounded into a topical cream. As such, it can be administered orally, directly into the spinal fluid by injection, intrathecally using a pain pump implanted under the skin, or transdermally (applied directly to the skin). When taken orally, the drug is absorbed rapidly and is distributed widely throughout the body to ease muscle spasms and relieve associated pain. Intrathecal injection of baclofen bathes the spinal cord in the drug solution to decrease the number and severity of muscle

spasms, improve muscle movement, and relieve pain. Although it is used for muscle relaxation and pain relief, it has not been shown to have potential for addiction, as do other drugs with similar functions.

Studies have shown that patients experience different effects from the drug and that dosage may need to be exceptionally high in some patients, especially in children with severe spastic disease. High doses, however, often cause adverse effects that require discontinuing baclofen therapy. The same dosage and the same route of administration are not effective uniformly in all patients. If oral administration is not effective, intrathecal administration may be tried. However, the injectable form may not have any effect on the nervous system in some patients. Because of the uncertain effectiveness in individual patients, physicians typically begin treatment slowly with a low test dose and then increase the dosage gradually until the patient responds. The drug is also discontinued slowly, with gradual reductions in dosage and close observation, since some patients exhibit withdrawal symptoms if baclofen is discontinued abruptly.

U.S. brand names

Baclofen is sold in the United States under the trade name Lioresal. Other trade names include Gablofen, Lyflex, Beklo, Kemstro, and Baclosan.

Origins

Baclofen was originally developed as a drug for treating epilepsy. However, results of the initial clinical trials for epilepsy treatment were disappointing. Instead, investigators observed that baclofen therapy decreased spasticity in some patients. The drug was then developed to treat muscle spasms and spasticity and was approved by the U.S. Food and Drug Administration (FDA) for those purposes only. The mechanism of action of baclofen has not been fully explained, but the drug is



Baclofen, 10 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

known to inhibit mono- and polysynaptic nervous system reflexes arising in the spine.

Recommended dosage

Baclofen is available as 10 and 20 milligram (mg) tablets to be taken orally or in an injectable form. The injection must be administered by a healthcare professional or used with a pain pump implanted in the abdomen for timed delivery of the prescribed dosage directly into spinal fluid. It is also sometimes compounded into a cream for topical treatment of muscle spasms and related pain.

The initial oral dose for adult patients is 5 mg, taken three times a day for three days. On subsequent days, the dosage is 15 mg orally, taken three times a day for three days, and then 20 mg orally three times a day thereafter. The maintenance dose is between 40 mg and 80 mg per day, divided in four doses throughout the day.

When the drug is delivered by injection for muscle spasm or trigeminal neuralgia, it is injected into the fluid-filled intrathecal space under a membrane that covers the brain and spinal cord using a method called barbotage. The injectable drug is delivered slowly for at least one minute, and then fluid is drawn back into the syringe. The first dose is 50 micrograms (mcg) suspended in 1 milliliter (mL) of fluid, increased to 75 mcg for the second dose and 100 mcg for the third dose. When a positive response is noted, the test dose can be doubled and administered over 24 hours. After that, the dose may

be reduced again incrementally. Most patients receive 300–800 mcg per day.

Precautions

Since baclofen is associated with dizziness and drowsiness in some patients, activities that require alertness should be avoided, including driving motor vehicles or operating machinery of any kind.

Baclofen cannot be discontinued abruptly since withdrawal symptoms may occur in some patients, especially patients who have had long-term (three to four months) treatment. Withdrawal symptoms can be as simple as nausea, dizziness, and insomnia or as severe as hallucinations, confusion, delusions, agitation, fluctuation of consciousness, memory impairment, anxiety, psychosis, mania, mood disturbances, behavioral disturbances, hyperthermia, tachycardia, seizures, tremors, autonomic dysfunction, and rebound spasticity (return of symptoms). Withdrawal can be avoided by discontinuing the drug slowly with tapered dosages.

Geriatric

Adults older than age 65 may be more sensitive to the side effects of baclofen, especially drowsiness, sleep disorders, mental changes such as confusion, and mood changes such as depression or anxiety.

Pregnant or breastfeeding

Pregnant women should receive baclofen only when absolutely needed, and the risks and benefits of baclofen therapy should be reviewed with the physician before taking the drug. Baclofen does pass into breast milk, and the physician should be consulted before beginning a course of baclofen.

Other conditions and allergies

Baclofen is not recommended for use in people with Parkinson's disease or in those who have had stroke. It is also given with caution to anyone with a history of kidney disease, mental or mood disorders, brain disorders, or seizures. It is not indicated for epilepsy treatment or for skeletal muscle spasm resulting from rheumatic disorders. It has not yet been approved for use in treating cerebral palsy, although this is being clinically evaluated. Before taking baclofen, patients should report any previous or current illnesses to the physician.

Serious allergic reactions to baclofen administration are rare. Before taking baclofen, patients should inform their physicians about any known allergies or previous allergic reactions. During baclofen therapy, any symptoms such as rash or itching; swelling of the face, tongue,

KEY TERMS

Barbotage—Barbotage is the alternating injection and withdrawal of a fluid used to administer an injectable therapeutic or anesthetic agent into an area of the spine called the intrathecal space.

Intrathecal injection—An injection delivered into the intrathecal space, which is the fluid-filled space between thin layers of tissue that cover the spinal cord.

Multiple sclerosis—A degenerative nervous system disorder in which the protective covering of the nerves in the brain are damaged, leading to tremor and paralysis.

Neuropathic pain—State of pain related to the nervous system; also known as neurogenic pain.

Spasms—Sudden involuntary muscle movement or contraction.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

or throat; dizziness; or difficulty breathing should be reported to the physician immediately.

Side effects

Possible side effects that may occur during baclofen therapy are tiredness or drowsiness, difficulty sleeping, nausea, constipation, headache, or a feeling of weakness. More serious side effects may include confusion, depression, hallucinations, changes in mood or behavior, heart symptoms, seizures, and autonomic nervous system dysfunction.

An overdose of baclofen produces symptoms such as enlarged pupils, vomiting, weakness, sleepiness, itching of the skin (pruritus), slowed breathing, seizures, and coma. Patients or their caregivers are urged to report such symptoms immediately.

Interactions

To help avoid drug interactions, patients should inform their physicians about all prescription and nonprescription drugs being taken, including over-the-counter medications and herbs or supplements.

Drugs

Certain drugs or supplements may alter baclofen activity in the body and increase or decrease its effectiveness. Interactions may also increase the risk of

certain side effects and severe adverse reactions. The main drugs to avoid are:

- other drugs that cause drowsiness, including antihistamines (e.g., **diphenhydramine**), sleeping aids, and antianxiety medications (e.g., **alprazolam**, **diazepam**, **zolpidem**)
- other types of muscle relaxants, such as cyclobenzaprine, **methocarbamol**, and diazepam (Valium)
- narcotic pain relievers, such as codeine, meperidine, **morphine**, or **oxycodone**

Herbs and supplements

Herbs called nervines, which work on the central nervous system, should be avoided. These include, but are not limited to, St. John's wort, skullcap, and valerian.

Food and other substances

Alcohol consumption should be avoided when taking baclofen.

Resources

BOOKS

American Society of Health System Pharmacists. *AHFS Drug Information 2015*. Bethesda: ASHP, 2015.

PERIODICALS

Draulans, N., et al. "Intrathecal Baclofen in Multiple Sclerosis and Spinal Cord Injury: Complications and Long-Term Dosage Evolution." *Clinical Rehabilitation* 27, no. 12 (2013): 1137–43.

Heetla, H. W., et al. "The Incidence and Management of Tolerance in Intrathecal Baclofen Therapy." *Spinal Cord* 47, no. 10 (2009): 751–56.

Khan, A. A., et al. "Clinical Outcome and Complications of Intrathecal Baclofen Pump in Multiple Sclerosis Patients: A Retrospective Study." *NeuroRehabilitation* 27, no. 2 (2010): 117–20.

Liu, J., and L. N. Wang. "Baclofen for Alcohol Withdrawal." *The Cochrane Database of Systematic Reviews* 2, art. no. CD008502 (February 28, 2013). <http://dx.doi.org/10.1002/14651858.CD008502.pub3> (accessed March 3, 2015).

Veerakumar, A., J. J. Cheng, and A. Sunshine. "Baclofen Dosage after Traumatic Spinal Cord Injury: A Multidecade Retrospective Analysis." *Clinical Neurology and Neurosurgery* 129 (2015): 50–56.

WEBSITES

AHFS Consumer Medication Information. "Baclofen." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682530.html> (accessed March 3, 2015).

PubMed Health. "Baclofen." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682530.html> (accessed March 3, 2015).

ORGANIZATIONS

American Society for Clinical Pharmacology and Therapeutics,
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Bactrim see **Sulfamethoxazole/trimethoprim**

Bactroban see **Mupirocin**

Base Filmtab see **Erythromycin**

Benadryl see **Diphenhydramine**

Benazepril

Definition

Benazepril (also known as benazepril hydrochloride or benazepril HCl) is a type of medication known as an angiotensin-converting enzyme (ACE) inhibitor. It is prescribed for the treatment of high blood pressure (hypertension), but it may also be recommended for other uses.

Purpose

Benazepril HCl is primarily prescribed for the treatment of hypertension. Doctors may also recommend it for other uses, including the treatment of congestive heart failure and heart attacks or the prevention of certain diabetes-associated complications of the kidney and of the retina, the light-sensitive tissue of the eye.

Description

Benazepril HCl is an ACE inhibitor. ACE inhibitors work by inhibiting angiotensin-converting enzyme. This enzyme is a hormone that is part of the renin-angiotensin system, which regulates both blood pressure and the balance of fluid in the body. Within this system, angiotensin-converting enzyme converts one type of hormone, called angiotensin I, into a second hormone known as angiotensin II. Angiotensin II stimulates muscles in the blood vessels, causing the blood vessels to constrict and thereby lessening the space through which blood can flow. At the same time, angiotensin II also increases the volume of fluid in the blood. As a result of these actions, more blood is moving through narrower vessels, causing blood pressure to increase.

ACE inhibitors help to lower blood pressure by curbing the hormone conversion and reducing the production of angiotensin II. Benazepril HCl is sometimes combined with other medications, such as



Benazepril, 20 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

amlodipine besylate or **hydrochlorothiazide**, to reduce blood pressure.

Benazepril HCl is sold as tablets, which are taken by mouth. Depending on the formulation, it may be available as 5, 10, 20, or 40 milligram (mg) tablets.

U.S. brand names

Benazepril HCl is sold in the United States under the brand name of Lotensin.

Canadian brand names

Benazepril HCl is sold in Canada under such names as Lotensin and Cibacen.

International brand names

Internationally, benazepril HCl is sold under a number of brand names. These include:

- Benazep
- Briem
- Cibace
- Cibacen
- Lisonid
- Lotensin
- Pu Li Duo
- Tatsujipin
- Tenkuoren
- Zaprace
- Zinadril

KEY TERMS

ACE inhibitor—A drug that disrupts the ability of angiotensin-converting enzyme (ACE) to produce the hormone angiotensin II, which raises blood pressure.

Angioedema—A condition signified by pronounced rapid, below-the-skin swelling; somewhat similar to hives.

Angiotensin II—A hormone that causes blood vessels to constrict and increases the volume of fluid in the blood, which together cause blood pressure to increase.

Angiotensin-converting enzyme—Often abbreviated to ACE, this enzyme is a hormone that is part of the renin-angiotensin system, which regulates both blood pressure and the balance of fluid in the body.

Diuretic—A drug designed to encourage excretion of urine in people who accumulate excess fluid, such as individuals with high blood pressure or heart conditions.

Hypertension—High blood pressure.

Renal—Relating to the kidney.

Origins

The history of ACE inhibitors is attributed to work performed by scientists at Takeda Chemical Industries in Osaka, Japan. In 1982, these scientists noted inhibition of angiotensin II. Other pharmaceutical companies began developing their own ACE inhibitors, including benazepril HCl, which were found to help lower blood pressure. Lotensin benazepril HCl tablets originally received U.S. Food and Drug Administration (FDA) approval in June 1991. The U.S. FDA approval for Lotensin HCT (the combination of benazepril HCl and hydrochlorothiazide) followed a year later in 1992.

Recommended dosage

Doctors typically prescribe a starting dose of 10 mg once a day for adults. This dosage may be adjusted until the optimal effects are attained.

Some patients may balk at taking a medication day in and day out for the rest of their lives, especially for a condition such as hypertension, which may not have noticeable symptoms. For this reason, it is important for patients to understand—and for doctors to reinforce—the importance of taking hypertension-fighting medications

at the dosage and for the duration recommended by the doctor. The duration may well be every day for the rest of the patient's life.

Pediatric

It is recommended that children younger than six years old not use benazepril HCl. For children six years and older, the doctor will determine the dosage based on each child's weight, needs, and other factors. The safety of doses greater than 0.6 mg per kilogram (kg, or 2.2 lb.) of body weight in pediatric patients has not been studied.

Geriatric

No special dosage recommendations are made for older patients. Since older patients are more likely to have reduced kidney function, however, their doctors may be more conservative in dosage of benazepril.

Precautions

Patients with severe congestive heart failure or a history of kidney (renal) problems may experience an increased risk of impaired renal function. For this reason, such patients should be carefully monitored, especially when they begin a new prescription of benazepril HCl.

Pediatric

It is recommended that children younger than six years old not use benazepril HCl. Children who have a glomerular filtration rate less than 30 milliliters (mL) in one minute, which is a measure indicating poor functioning of the kidneys, should not use benazepril HCl.

Geriatric

Older patients are more likely to have a greater number of health problems than younger adults, so they should become fully aware of potential side effects—especially the signs that may accompany life-threatening side effects—before beginning benazepril HCl. They should also be sure to notify their doctors about any health changes they experience. In addition, since older patients are more likely to have reduced kidney function, doctors should be especially vigilant in monitoring kidney function among this age group.

Pregnant or breastfeeding

Benazepril HCl is in the FDA pregnancy category D during the second and third trimesters, which indicates a risk to the fetus. Specifically, benazepril HCl may affect kidney function, can cause damage that includes skeletal deformities, and may lead to death of the developing fetus. As soon as a woman learns she is pregnant, she

should immediately consult with her doctor about stopping her prescription and perhaps beginning an alternative antihypertension treatment. Women should not stop benazepril without consulting their physician, as hypertension during pregnancy is a serious health consideration.

Other conditions and allergies

Patients who are sensitive to benazepril or any other ACE inhibitors should not take benazepril HCl. Individuals who have a history of angioedema (a condition signified by pronounced below-the-skin swelling) should also avoid benazepril HCl. Some patients undergoing therapy involving the administration of bee/wasp venom have experienced life-threatening reactions when also using benazepril HCl, so doctors may consider suspending the latter while the patient is receiving venom therapy.

Patients who are undergoing dialysis with high-flux membranes or the dialysis-like therapy known as LDL apheresis should discuss the use of benazepril HCl with their doctors, as adverse reactions have been reported. In addition, patients who are undergoing surgery or other care involving the use of anesthetics should inform their prescribing doctor and the doctor performing the surgery or care, as there is a heightened risk of hypotension (abnormally low blood pressure).

Side effects

This medication is generally well tolerated, but some patients do experience side effects. These may include:

- Headache.
- Dizziness.
- Persistent, nonproductive cough.
- Angioedema of the arms and legs; the face, including the lips and tongue; the intestines; and the voice box (larynx) as well as the glottis, which is the opening to the upper larynx. Angioedema can present a serious health threat when it interferes with breathing. Individuals who experience difficulty breathing should seek medical attention immediately. The angioedema side effect is more common among persons of African descent.
- Symptomatic hypotension, which is abnormally low blood pressure accompanied by such symptoms as dizziness or fainting. This is mainly associated with patients who are undergoing prolonged diuretic therapy, are on a salt-restrictive diet or dialysis, or are experiencing diarrhea or vomiting and among patients who have congestive heart failure.

- Low levels of neutrophils, which are infection-fighting blood cells, accompanied by fever or other symptoms of an infection.
- Jaundice (yellowing of the skin), which in rare instances may progress to a serious health threat.
- Hyperkalemia (increased potassium levels in the blood). For this reason, patients should discuss the use of potassium supplements or potassium-containing salt substitutes with their doctor.

Pediatric

Studies in children 6–16 years old have been conducted, and both the tolerance to the drug and the adverse effects in this age group were similar to those in adults. Nonetheless, parents may wish to discuss the potential for long-term effects of the medication on growth and development with the prescribing doctor.

Benazepril HCl carries a risk for kidney-development problems in infants younger than one year old and should not be used in this population.

Geriatric

Side effects in this age group are similar to those seen in younger adults. However, since older patients in general have more health problems than younger adults, doctors should be especially vigilant in monitoring them for side effects.

Interactions

Benazepril has some known interactions with drugs and other substances.

Drugs

Patients who take diuretics (sometimes called “water pills”), especially those who have just begun taking diuretics, may experience a drop in blood pressure when they begin taking benazepril HCl. In this case, doctors may recommend that the patient stop taking diuretics, increase salt intake, or reduce the dosage of benazepril HCl. For those patients who take thiazide diuretics, doctors will frequently monitor potassium levels, as benazepril HCl can cause potassium loss.

The use of benazepril HCl (and other ACE inhibitors) in conjunction with lithium therapy—and especially when diuretics are added—can result in increased serum (blood) lithium levels and symptoms of lithium toxicity, so doctors should administer these combinations with caution and should frequently monitor serum lithium levels in the patient. Lithium therapy is used to treat a number of illnesses, including bipolar disorder, depression, eating disorders, and anemia.

Herbs and supplements

Patients should not use potassium supplements while taking benazepril HCl without the consent and advice of the doctor. They should also alert their doctor about any vitamins or herbal supplements they are taking so that they understand any potential interactions.

Foods and other substances

Patients should not use salt substitutes while taking benazepril HCl without the consent and advice of the doctor. In addition, alcohol can reduce blood pressure, which may intensify side effects, so alcohol consumption should be discussed with the doctor before beginning to take benazepril HCl.

Resources

BOOKS

- Kaplan, Norman M., and Ronald G. Victor. "Treatment of Hypertension: Drug Therapy." In *Kaplan's Clinical Hypertension*. 11th ed. Philadelphia: Wolters Kluwer, 2015.
- Mann, Samuel J. *Hypertension and You: Old Drugs, New Drugs, and the Right Drugs for Your High Blood Pressure*. Plymouth, UK: Rowman & Littlefield, 2012.

PERIODICALS

- Gosmanova, Elvira O., and Csaba P. Kovesdy. "Adherence to Antihypertensive Medications: Is Prescribing the Right Pill Enough?" *Nephrology Dialysis Transplantation* (October 21, 2014). <http://dx.doi.org/10.1093/ndt/gfu330> (accessed January 30, 2015).
- Pinargote, Paulette, Denisse Guillen, and Juan C. Guarderas. "ACE Inhibitors: Upper Respiratory Symptoms." *BMJ Case Reports* (July 17, 2014). <http://dx.doi.org/10.1136/bcr-2014-205462> (accessed January 30, 2015).

OTHER

- Grylack, Lawrence. "One Year Post Exclusivity Adverse Event Review: Benazepril." U.S. Food and Drug Administration. http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4089s1_01_Benazepril.ppt (accessed January 30, 2015).
- Novartis. "Lotensin (Benazepril hydrochloride) Tablets." U.S. Food and Drug Administration. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019851s042lbl.pdf (accessed January 30, 2015).

WEBSITES

- "Benazepril." Drugs.com. <http://www.drugs.com/cdi/benazepril.html> (accessed January 30, 2015).
- Johns Hopkins Lupus Center. "Blood Pressure Medications (Anti-Hypertensives)." [Hopkinslupus.org](http://www.hopkinslupus.org/lupus-treatment/common-medications-conditions/blood-pressure-medications-antihypertensives/). <http://www.hopkinslupus.org/lupus-treatment/common-medications-conditions/blood-pressure-medications-antihypertensives/> (accessed January 30, 2015).
- Mayo Clinic staff. "Benazepril (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/benazepril-oral-route/description/drg-20069193> (accessed January 30, 2015).

MedlinePlus. "Benazepril." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a692011.html> (accessed January 30, 2015).

Novartis. "Lotensin (Benazepril hydrochloride) Tablets." U.S. Food and Drug Administration. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019851s042lbl.pdf (accessed January 30, 2015).

Physician's Desk Reference. "Lotensin." PDR Health. <http://www.pdrhealth.com/drugs/lotensin> (accessed January 30, 2015).

ORGANIZATIONS

- American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org/>.
- American Society of Hypertension, 45 Main Street, Suite 712, Brooklyn, NY 11201, (212) 696-9099, Fax: (347) 916-0267, <http://www.ash-us.org/>.
- National Heart, Lung, and Blood Institute Health Information Center, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, NHLBIinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov/>.

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Benazepril/ hydrochlorothiazide

Definition

Benazepril hydrochloride (sometimes shortened to simply benazepril) and **hydrochlorothiazide** (HCT) are two different compounds that are combined and prescribed for the treatment of high blood pressure (hypertension).

Purpose

Combination benazepril HCT is prescribed for the treatment of hypertension. It works by suppressing certain chemicals that would otherwise constrict blood vessels and increase blood volume. As a result of these actions, combination benazepril HCT lowers blood pressure.

Description

Benazepril hydrochloride and hydrochlorothiazide are different types of compounds. Benazepril hydrochloride is an angiotensin-converting enzyme (ACE) inhibitor, and hydrochlorothiazide is a type of diuretic.



Benazepril/hydrochlorothiazide, 20 mg/12.5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

ACE inhibitors work by curbing angiotensin-converting enzyme, which is a hormone that is part of a system (the renin-angiotensin system) that regulates blood pressure and the balance of fluid in the body. ACE plays its role in the system by converting one type of hormone, called angiotensin I, into a second hormone known as angiotensin II. Angiotensin II stimulates muscles in the blood vessels that cause them to constrict. When they constrict, blood has less space in which to course through the vessels, so blood pressure rises. Angiotensin II also increases the volume of fluid in the blood, so more blood is moving through narrow vessels, which heightens blood pressure even more. ACE inhibitors such as benazepril hydrochloride help to lower blood pressure by interfering with hormone conversion, thereby reducing the production of angiotensin II and lowering blood pressure.

Hydrochlorothiazide is a thiazide diuretic that keeps the body from absorbing too much salt, and this also serves to reduce the retention of water. Both water and salt are removed from the body through increased urination. Thiazide diuretics such as hydrochlorothiazide are used to treat hypertension because they reduce water retention, which lowers blood volume and causes blood pressure to drop.

Benazepril hydrochloride and hydrochlorothiazide are used together to increase their hypertension-fighting effect.

Benazepril HCT is sold as tablets, which are taken by mouth. Depending on the formulation, benazepril HCT may be available as a combination of 5, 10, or 20

milligrams (mg) of benazepril hydrochloride and 6.25, 12.5, or 25 mg of hydrochlorothiazide.

U.S. brand names

Benazepril HCT is sold in the United States under the brand name of Lotensin HCT.

International brand names

Internationally, benazepril HCT is sold under a number of brand names. These include:

- Benazeplus
- Briazide
- Cordibenz Plus
- Cibadrex
- Cibacen
- Lisonid HCT
- Lotensin HCT
- Zaprace-D
- Zinadiur

Origins

Scientists began studying ACE inhibitors and their medical uses in the 1980s. Diuretics, on the other hand, have been used to treat edema (swelling resulting from excess fluid in the body) since at least the sixteenth century. In the mid-twentieth century, scientists began developing thiazide diuretics for the treatment of hypertension. The U.S. Food and Drug Administration (FDA) approved Lotensin HCT (the combination of benazepril hydrochloride and hydrochlorothiazide) for the treatment of hypertension in 1992.

Recommended dosage

Doctors typically prescribe a starting dosage of 10 mg of benazepril hydrochloride and 12.5 mg of hydrochlorothiazide once a day for adults. This dosage may be adjusted until the optimal effects are attained. Patients should be informed about the need to take hypertensive drugs over the long term, even if they feel fine. Hypertension is often described as a “silent killer” because it carries no obvious symptoms.

Pediatric

The safety and effectiveness of benazepril HCT have not been verified in pediatric patients, so its use in this population is not recommended.

Geriatric

No special dosage recommendations are made for older patients, but because this population is more likely

KEY TERMS

ACE inhibitor—A drug that disrupts the ability of angiotensin-converting enzyme (ACE) to produce the hormone angiotensin II, which raises blood pressure.

Angioedema—A condition signified by pronounced rapid, below-the-skin swelling; somewhat similar to hives.

Angiotensin II—A hormone that causes blood vessels to constrict and increases the volume of fluid in the blood, which together cause blood pressure to increase.

Angiotensin-converting enzyme (ACE)—Often abbreviated to ACE, this enzyme is a hormone that is part of the renin-angiotensin system, which regulates both blood pressure and the balance of fluid in the body.

Diuretic—Also known as “water pills,” diuretics serve to reduce water retention through increased urination; they may be used to help control blood pressure.

Hypertension—High blood pressure.

Renal—Relating to the kidney.

to have reduced kidney function, doctors may be more conservative in dosage of benazepril HCT and more vigilant in monitoring patient progress.

Precautions

Patients with severe congestive heart failure or a history of kidney (renal) problems may experience an increased risk of impaired renal function. For this reason, such patients should be carefully monitored, especially when they begin a new prescription of benazepril HCT.

Pediatric

The use of benazepril HCT is not recommended in this age group.

Geriatric

Older patients are more likely to have a greater number of health problems than younger adults, so they should become fully aware of potential side effects—especially the signs that may accompany life-threatening side effects—before beginning benazepril HCT. They should also be sure to notify their doctors about any health changes they experience while taking the

medication. In addition, since older patients are more likely to have reduced kidney function, healthcare providers should be especially vigilant in monitoring kidney function among this age group.

Pregnant or breastfeeding

Benazepril HCT is in the FDA pregnancy category D during the second and third trimesters, which indicates a risk to the fetus. Specifically, benazepril HCT may affect kidney function, can cause other developmental damage, and may lead to the death of the fetus or the newborn. As soon as a woman learns she is pregnant, she should immediately consult with her doctor about stopping her prescription and perhaps beginning alternative antihypertensive treatment. Women should not stop benazepril HCT without consulting their physician, as hypertension during pregnancy is a serious and potentially life-threatening health consideration.

Other conditions and allergies

Patients who are sensitive to benazepril or any other ACE inhibitors, to hydrochlorothiazide, or to other sulfonamide-derived drugs should not take benazepril HCT. Patients with these sensitivities along with a history of allergy or bronchial asthma may be especially susceptible to adverse sensitivity reactions, so they and their doctors should be especially cautious.

Other individuals who should not take benazepril include those who are anuric (have suppressed urine production) and those who have a history of angioedema (a condition signified by pronounced below-the-skin swelling). Some patients undergoing therapy involving the administration of bee/wasp venom have experienced life-threatening reactions when also using ACE inhibitors, so patients should be sure to inform their doctors of any venom therapy.

Patients who are undergoing dialysis with high-flux membranes or the dialysis-like therapy known as LDL apheresis should discuss the use of benazepril HCT with their doctors, as adverse reactions have been reported. In addition, patients who are undergoing surgery or other care involving the use of anesthetics should inform the prescribing doctor and the doctor performing the surgery or care, as there is a heightened risk of hypotension (abnormally low blood pressure).

Side effects

This medication is generally well tolerated, but some patients do experience side effects. These may include:

- Headache.
- Dizziness.

- Fatigue.
- Persistent, nonproductive cough.
- Angioedema of the arms and legs; the face, including the lips and tongue; the intestines; and the voice box (larynx) as well as the glottis, which is the opening to the upper larynx. Angioedema can present a serious health threat when it interferes with breathing. Individuals who experience difficulty breathing should seek medical attention immediately. The angioedema side effect is more common among persons of African descent.
- Symptomatic hypotension, which is abnormally low blood pressure accompanied by such symptoms as dizziness or fainting. This is mainly associated with patients who are undergoing prolonged diuretic therapy, are on a salt-restrictive diet or dialysis, or are experiencing diarrhea or vomiting and among patients who have congestive heart failure.
- Low levels of neutrophils, which are infection-fighting blood cells, accompanied by fever or other symptoms of an infection.
- Jaundice (yellowing of the skin), which in rare instances may progress to a serious health threat.
- Hyperkalemia (increased potassium levels in the blood). For this reason, patients should discuss the use of potassium supplements or potassium-containing salt substitutes with their doctor.

Geriatric

Side effects in this age group are similar to those seen in younger adults. Since older patients generally have more health problems than younger adults, however, doctors will carefully monitor older patients for side effects, making prescription alterations as necessary.

Interactions

Benazepril HCT has some known interactions with drugs and other substances.

Drugs

Patients who have diabetes should not take benazepril HCT with the medication aliskiren (trade names include Tekturna and Rasilez), which is sometimes prescribed to treat hypertension.

The use of drugs containing benazepril hydrochloride (and other ACE inhibitors) in conjunction with lithium therapy—and especially when diuretics are added—can result in increased serum (blood) lithium levels and symptoms of lithium toxicity, so doctors should administer these combinations with caution and should frequently monitor serum lithium levels in the patient.

Lithium therapy is used to treat a number of illnesses, including bipolar disorder, depression, eating disorders, and anemia.

Herbs and supplements

Patients should not use potassium supplements while taking benazepril HCT without the consent and advice of the doctor. They should also alert the doctor about any vitamins or herbal supplements they are taking so they understand any potential interactions.

Foods and other substances

Patients should not use salt substitutes while taking benazepril HCT without the consent and advice of the doctor. In addition, alcohol can reduce blood pressure, which may intensify side effects, so alcohol consumption should be discussed with the doctor before beginning to take benazepril HCT.

Resources

BOOKS

- Kaplan, Norman M., and Ronald G. Victor. "Treatment of Hypertension: Drug Therapy." In *Kaplan's Clinical Hypertension*. 11th ed. Philadelphia: Wolters Kluwer, 2015.
- Mann, Samuel J. *Hypertension and You: Old Drugs, New Drugs, and the Right Drugs for Your High Blood Pressure*. Plymouth, UK: Rowman & Littlefield, 2012.

PERIODICALS

- Gosmanova, Elvira O., and Csaba P. Kovesdy. "Adherence to Antihypertensive Medications: Is Prescribing the Right Pill Enough?" *Nephrology Dialysis Transplantation* (October 21, 2014). <http://dx.doi.org/10.1093/ndt/gfu330> (accessed January 30, 2015).
- Pinargote, Paulette, Denisse Guillen, and Juan C. Guarderas. "ACE Inhibitors: Upper Respiratory Symptoms." *BMJ Case Reports* (July 17, 2014). <http://dx.doi.org/10.1136/bcr-2014-205462> (accessed January 30, 2015).
- Pizzi, Richard A. "Diuretics Redux." *Today's Chemist at Work*, July 2003, pp. 35–36. <http://pubs.acs.org/subscribe/archive/tcaw/12/i07/pdf/703health.pdf> (accessed January 30, 2015).

OTHER

- Grylack, Lawrence. "One Year Post Exclusivity Adverse Event Review: Benazepril." U.S. Food and Drug Administration. http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4089s1_01_Benazepril.ppt (accessed January 30, 2015).
- Novartis. "Lotensin (Benazepril Hydrochloride) Tablets." U.S. Food and Drug Administration. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019851s0421bl.pdf (accessed January 30, 2015).

WEBSITES

- "Hydrochlorothiazide." Drugs.com. <http://www.drugs.com/hydrochlorothiazide.html> (accessed January 30, 2015).
- Johns Hopkins Lupus Center. "Blood Pressure Medications (Anti-Hypertensives)." [Hopkinslupus.org](http://www.hopkinslupus.org/lupus-treatment/common-medication-conditions/blood-pressure-medications-antihypertensives/). <http://www.hopkinslupus.org/lupus-treatment/common-medication-conditions/blood-pressure-medications-antihypertensives/> (accessed January 30, 2015).
- "Lotensin HCT." Drugs.com. <http://www.drugs.com/cdi/lotensin-hct.html> (accessed January 5, 2015).
- Mayo Clinic staff. "Benazepril and Hydrochlorothiazide (Oral Route)." [MayoClinic.org](http://www.mayoclinic.org/drugs-supplements/benazepril-and-hydrochlorothiazide-oral-route/description/DRG-20069142). <http://www.mayoclinic.org/drugs-supplements/benazepril-and-hydrochlorothiazide-oral-route/description/DRG-20069142> (February 19, 2015).
- MedlinePlus. "Benazepril and Hydrochlorothiazide." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601025.html> (accessed January 30, 2015).
- U.S. Food and Drug Administration. "Lotensin HCT (benazepril HCl and Hydrochlorothiazide) Tablets." <http://www.fda.gov/safety/medwatch/safetyinformation/ucm262151.htm> (accessed January 30, 2015).

ORGANIZATIONS

- American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org/>.
- American Society of Hypertension, 45 Main Street, Suite 712, Brooklyn, NY 11201, (212) 696-9099, Fax: (347) 916-0267, <http://www.ash-us.org/>.
- National Heart, Lung, and Blood Institute Health Information Center, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, NHLBIinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov/>.

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Bendamustine

Definition

Bendamustine hydrochloride (Treanda) is an alkylating agent used in the treatment of chronic lymphocytic leukemia and B-cell non-Hodgkin lymphoma.

Purpose

Bendamustine hydrochloride is used to treat two types of cancer: chronic lymphocytic leukemia (CLL) and slow-growing (indolent) B-cell non-Hodgkin lymphoma (NHL).



Treanda (bendamustine HCl). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

CLL is a cancer of the white blood cells called lymphocytes. The disease develops in the bone marrow and blood. Cancerous (malignant) lymphocytes mature incorrectly or incompletely and live longer than normal so that they build up in the blood, usually over several years, before causing symptoms of CLL.

B-cell NHL is a cancer of B cells, which are a type of white blood cell that helps to fight infection by making antibodies. B-cell NHL develops in the lymph nodes and accounts for about 85% of all NHLs. Bendamustine hydrochloride is used specifically to treat indolent B-cell NHL that has progressed during or within six months of treatment with **rituximab** (Rituxan).

Description

Bendamustine hydrochloride is an alkylating agent that kills cells by binding with and linking deoxyribonucleic acid (DNA) strands. It is effective against both actively dividing and nondividing (quiescent) cells. The drug is an off-white powder that must be mixed with sterile water before use.

Bendamustine hydrochloride continues to be tested in clinical trials in the United States for use against other cancers and in combination with other therapies.

U.S. brand names

Bendamustine hydrochloride is sold in the United States under the brand name Treanda.

KEY TERMS

Anaphylaxis—A severe allergic reaction to a foreign substance (antigen) that a patient has had previous contact with, characterized by redness and swelling, itching, water buildup, and, in severe cases, extremely low blood pressure, lung spasms, and shock.

B cell—Type of lymphocyte (white blood cell) that creates antibodies to fight infection; also referred to as a B-cell lymphocyte.

Chronic lymphocytic leukemia (CLL)—A cancer characterized by an abnormal increase in mature lymphocytes, especially B cells, that primarily affects older adults.

Lymphocyte—A type of white blood cell that defends the body against infection and disease. Lymphocytes are found in the bloodstream, the lymphatic system, and lymphoid organs. The two main types of lymphocytes are the B cells (produced in the bone marrow) and the T cells (produced in the thymus).

Myelosuppression—A condition in which bone marrow activity is diminished, resulting in decreased platelet, red blood cell, and white blood cell counts.

Non-Hodgkin lymphoma—A cancer of the lymph system that causes the accumulation of large numbers of defective (cancerous) immune system cells.

International brand names

Bendamustine is marketed under the brand name Ribomustin in Germany.

Origins

The U.S. Food and Drug Administration (FDA) first approved Treanda for the treatment of CLL on March 20, 2008. It was approved for the treatment of B-cell NHL on October 31, 2008.

Recommended dosage

Bendamustine hydrochloride is infused intravenously (into a vein). The drug has different dosage regimens for treating CLL and B-cell NHL:

- For CLL, the standard dosage is 100 milligrams per square meter of body surface area (mg/m^2) infused over 30 minutes once a day for two consecutive days,

followed by 26 days when no drug is given. This 28-day cycle is repeated up to six times.

- For B-cell NHL, the standard dosage is $120 \text{ mg}/\text{m}^2$ infused over 60 minutes once a day for two consecutive days, followed by 19 days in which no drug is given. This cycle can be repeated up to eight times.

In both dosage regimens, the dose may be delayed or reduced if a decrease in red blood cells, platelets, or various types of white blood cells occurs. The dose also may be delayed or reduced if other serious side effects occur.

Pediatric

The safety and efficacy of this drug have not been determined in children.

Precautions

The following precautions should be observed:

- Severe decrease in the number of normal blood cells (myelosuppression) may occur. A decrease in the number of blood platelets (thrombocytopenia) may reduce the ability of the blood to clot and increase the risk of serious bleeding episodes. A decrease in the number of neutrophils (neutropenia) may impair the body's ability to fight infection. A decrease in the number of red blood cells (anemia) may reduce the ability of the blood to supply oxygen. Blood count should be monitored frequently. In severe cases, drug administration may need to be delayed or reduced.
- Infection, including pneumonia and systemic infection (sepsis), may occur and be serious enough to require hospitalization. Sepsis has resulted in patient deaths during clinical trials. Patients should immediately report any signs of infection to their physician.
- Infusion reactions are common with bendamustine hydrochloride. Common symptoms include fever, chills, and rash. If a severe infusion reaction occurs, bendamustine hydrochloride should be discontinued. In rare cases, anaphylaxis can occur, most often during the second or later cycle. Severe anaphylaxis can result in death. Individuals who are allergic to mannitol (Osmitol) are at high risk for anaphylaxis and should not be given bendamustine hydrochloride.
- Patients may experience tumor lysis syndrome that results in kidney (renal) failure and, if untreated, death. Blood chemistries should be monitored regularly.
- Serious skin rashes, blistering, itching, and peeling of the skin may occur, especially if bendamustine hydrochloride is given with other drugs.
- Some people using bendamustine hydrochloride in clinical trials have developed other cancers. It is unclear

what role, if any, bendamustine hydrochloride played in the development of those malignancies.

Pregnant or breastfeeding

Bendamustine hydrochloride is a pregnancy category D drug, meaning that it is known to have adverse effects on a fetus. Women who are pregnant or who might become pregnant should not use bendamustine hydrochloride. It is not known whether the drug is excreted in breast milk. Women taking this drug should not breastfeed, as there is the potential for this drug to cause serious harm to the nursing infant.

Side effects

Bendamustine hydrochloride has many potential side effects, including:

- chest pain
- difficulty breathing
- difficulty swallowing
- fast heartbeat (tachycardia)
- fatigue
- nausea and vomiting
- diarrhea or constipation
- swelling and fluid retention (edema)
- heartburn
- dry mouth or bad taste in mouth
- decreased ability to taste
- loss of appetite and weight loss
- headache
- anxiety
- depression
- insomnia
- bone or joint pain
- sweating or night sweats

Side effects that require immediate medical attention include signs of infection (e.g., chills, fever, cough), or signs of an allergic reaction and anaphylaxis (e.g., difficulty breathing, difficulty swallowing, or swelling of the face, tongue, ears, lips). Patients should report these or other worrisome side effects to their healthcare provider.

Interactions

All interactions with bendamustine hydrochloride are not known. Patients should provide their healthcare provider and pharmacist with a complete list of all prescription and nonprescription drugs, herbs, and dietary supplements that they are taking before starting this drug.

Drugs

Bendamustine hydrochloride is thought to interact with certain drugs, especially a group of antibiotic drugs called fluoroquinolones. Drugs known to interact with bendamustine hydrochloride include:

- **ciprofloxacin** (Cipro)
- gemifloxacin (Factive)
- **levofloxacin** (Levaquin)
- **moxifloxacin** (Avelox)
- norfloxacin (Noroxin)
- ofloxacin (Floxin)
- cimetidine (Tagamet)
- **omeprazole** (Prilosec)
- ticlopidine (Ticid)

Since all drug, herb, and supplement interactions are not yet known, patients should check with their doctor or pharmacist for the most up-to-date information.

Resources

BOOKS

Wilkes, Gail M., and Margaret Barton-Burke. *2013 Oncology Nursing Drug Handbook*. Burlington, MA: Jones & Bartlett Learning, 2013.

PERIODICALS

Eichbaum, M., et al. "Bendamustine Hydrochloride—A Renaissance of Alkylating Strategies in Anticancer Medicine." *Drugs of Today* 45, no. 6 (2009): 431. <http://dx.doi.org/10.1358/dot.2009.45.6.1376696> (accessed February 18, 2015).

WEBSITES

AHFS Consumer Medication Information. "Bendamustine Injection." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a608034.html> (accessed February 18, 2015).

National Cancer Institute. "FDA Approval for Bendamustine Hydrochloride." <http://www.cancer.gov/cancertopics/druginfo/fda-bendamustine-hydrochloride> (accessed February 18, 2015).

ORGANIZATIONS

American Cancer Society, 250 Williams Street NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org/>.
Leukemia & Lymphoma Society, 1311 Mamaroneck Avenue, Suite 310, White Plains, NY 10605, (914) 949-5213, Fax: (914) 949-6691, infocenter@lls.org, <http://www.lls.org/>.
National Cancer Institute, 9609 Medical Center Drive, BG 9609 MSC 9760, Bethesda, MD 20892-9760, (800) 4-CANCER (422-6237), <http://www.cancer.gov/>.

Tish Davidson, AM

REVIEWED BY KEVIN GLAZA, RPH

Benicar see **Olmесartan**

Benzaclin see **Clindamycin/benzoyl peroxide**

Benzoyl peroxide/clindamycin see **Clindamycin/benzoyl peroxide**

Benzotropine

Definition

Benzotropine is classified as an antiparkinsonian agent. It is in the same family of drugs known as anticholinergic drugs.

Purpose

Benzotropine is used to treat a group of side effects (called parkinsonian side effects) that includes tremors, difficulty walking, and slack muscle tone. These side effects may occur in patients who are taking antipsychotic medications used to treat mental disorders such as schizophrenia.

Description

Some medicines used to treat schizophrenia and other mental disorders, called antipsychotic drugs, can cause side effects that are similar to the symptoms of Parkinson's disease. Patients do not have Parkinson's disease but experience symptoms such as shaking in muscles while at rest, difficulty with voluntary movements, and poor muscle tone.

One way to eliminate these undesirable side effects is to stop taking the antipsychotic medicine. However, this can cause the symptoms of the original mental disorder to return, so simply stopping the antipsychotic medication is not a reasonable option in most cases. Some drugs that control the symptoms of Parkinson's disease, such as benztropine, also control the parkinsonian side effects of antipsychotic medicines.

Benzotropine works by restoring the chemical balance between dopamine and acetylcholine, two neurotransmitter chemicals in the brain. Taking benztropine along with the antipsychotic medicine helps to control symptoms of the mental disorder, while reducing parkinsonian side effects.

U.S. brand names

Benzotropine is sold in the United States under the brand name Cogentin and is also available under its generic name.



Benztropine, 1 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Recommended dosage

Benzotropine is available in 0.5, 1, and 2 milligram (mg) tablets and in an injectable form containing 2 mg in each 2 milliliter (mL) glass container. For the treatment of tremors, poor muscle tone, and similar side effects, benztropine should be started at a dose of 1–2 mg orally. In cases of severe side effects, benztropine can be given as an intramuscular injection two to three times daily or as needed. Parkinson-like side effects caused by antipsychotic drugs may come and go, so benztropine may not be needed on a regular basis. Benzotropine may also be prescribed to prevent these side effects before they actually occur. This type of treatment is called a prophylactic (preventative) therapy.

Precautions

Like all anticholinergic drugs, benztropine decreases the body's ability to sweat and cool itself. People who are unaccustomed to being outside in hot weather should take care to stay as cool as possible and drink extra fluids. Individuals who are chronically ill, have a central nervous system impairment, or work outside during hot weather may need to avoid taking benztropine.

Although it is rare, some patients experience euphoria while taking benztropine and may abuse it for this reason. Euphoria can occur at doses only two to four times the normal daily dose. Patients with a history of drug abuse should be observed carefully for benztropine abuse.

KEY TERMS

Acetylcholine—A naturally occurring chemical in the body that transmits nerve impulses from cell to cell. It causes blood vessels to dilate, lowers blood pressure, and slows the heartbeat. Central nervous system well-being is dependent on a balance among the neurotransmitters acetylcholine, dopamine, serotonin, and norepinephrine.

Anticholinergic—Related to the ability of a drug to block the nervous system chemical acetylcholine. When acetylcholine is blocked, patients often experience dry mouth and skin, increased heart rate, blurred vision, and difficulty urinating. In severe cases, blocking acetylcholine may cloud thinking and cause delirium.

Catheterization—Placement of a tube in the bladder so that it can be emptied of urine.

Dopamine—A chemical in brain tissue that serves to transmit nerve impulses (is a neurotransmitter) and helps to regulate movement and emotions.

Neurotransmitter—A chemical in the brain that transmits messages between neurons, or nerve cells.

Parkinsonian—Related to symptoms associated with Parkinson's disease, a nervous system disorder characterized by abnormal muscle movement of the tongue, face, and neck; inability to walk or move quickly; walking in a shuffling manner; restlessness; and tremors.

Pediatric

Benzotropine should never be used in children under age three. It should be used cautiously and with close physician supervision in older children.

Geriatric

Benzotropine should be used with caution in elderly patients. Older patients taking the drug should receive close physician supervision.

Other conditions and allergies

Individuals with the following medical conditions may experience increased negative side effects when taking benztropine. Those who have these problems should discuss their conditions with their healthcare provider before starting the drug:

- glaucoma, especially closed-angle glaucoma
- intestinal obstruction
- prostate enlargement

- urinary bladder obstruction

Side effects

Although benztropine helps to control the side effects of antipsychotic drugs, it can produce side effects of its own. An individual taking benztropine may experience some of the following reactions, which may vary in intensity:

- dry mouth
- dry skin
- blurred vision
- nausea or vomiting
- constipation
- disorientation
- drowsiness
- irritability
- increased heart rate
- urinary retention

Dry mouth, if severe to the point of causing difficulty speaking or swallowing, may be managed by reducing the dosage of or temporarily discontinuing benztropine. Chewing sugarless gum or sucking on sugarless candy may also help to increase the flow of saliva. Some artificial saliva products may give temporary relief.

Men with prostate enlargement may be especially prone to urinary retention. Symptoms of this problem include having difficulty starting a urine flow and more difficulty passing urine than usual. This side effect may be severe and require discontinuation of the drug. Urinary retention may require catheterization. Individuals who think they may be experiencing any side effects from this or any other medication should tell their physicians.

Patients who take an overdose of benztropine are treated with forced vomiting, removal of stomach contents and stomach washing, activated charcoal, and respiratory support if needed. They are also given physostigmine, an antidote for anticholinergic drug poisoning.

Interactions

Drugs such as benztropine decrease the speed with which food moves through the stomach and intestines. Because of this, the absorption of other drugs being taken may be enhanced by benztropine. Patients receiving benztropine should be alerted to unusual responses to other drugs they might be taking and report any changes to their physicians.

Drugs

When drugs such as benztropine are taken with antidepressants, such as **amitriptyline**, **imipramine**, trimipramine, **desipramine**, nortriptyline, protriptyline,

amoxapine, and **doxepin**, or with antihistamines that also have anticholinergic properties, the intended and adverse effects of benzotropine are usually intensified.

Resources

BOOKS

American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda, MD: American Society of Health-System Pharmacists, 2015.

Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger Publications, 2013.

PERIODICALS

Muench, John, and Ann M. Hamer. "Adverse Effects of Antipsychotic Medications." *American Family Physician* 81, no. 5 (2010): 617–22.

Wijegunaratne, H., H. Qazi, and M. M. Koola. "Chronic and Bedtime Use of Benzotropine with Antipsychotics: Is It Necessary?" *Schizophrenia Research* 153, nos. 1–3 (2014): 248–49. <http://dx.doi.org/10.1016/j.schres.2014.01.006> (accessed February 18, 2015).

WEBSITES

AHFS Consumer Medication Information. "Benzotropine Mesylate Oral." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682155.html> (accessed February 18, 2015).

Micromedex. "Benzotropine (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/benzotropine-oral-route/description/drg-20072652> (accessed February 18, 2015).

ORGANIZATIONS

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) 463-6332, <http://www.fda.gov/>.

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Betamethasone/clotrimazole see
Clotrimazole/betamethasone

Betapace see **Sotalol**

Betimol see **Timolol**

Bevacizumab

Definition

Bevacizumab is an anticancer drug. It is in a class of medications known as angiogenesis inhibitors, which block



Avastin (bevacizumab), 100 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

the growth of blood vessels that supply tumors. Blocking the blood vessels can stop a tumor's ability to grow.

Purpose

Bevacizumab was the first drug of its class used in the United States to treat various types of cancer. It is mainly used for metastatic cancer, which is cancer that has traveled from its point of origin to various other parts of the body. The types of metastatic cancer that bevacizumab is used to treat include colon cancer, some types of lung cancer, and certain ovarian cancers, all with varying results. Bevacizumab was granted accelerated approval in 2008 for treating a specific type of breast cancer (HER2-negative breast cancer), but this approval was revoked in 2011.

In May 2009, the U.S. Food and Drug Administration (FDA) granted approval for use of bevacizumab as a single chemotherapeutic agent for treatment of a form of brain cancer known as glioblastoma. Glioblastomas are tumors that originate from brain cells known as glial cells, which provide chemical and physical support for the growth of neurons. In August 2014, the FDA approved bevacizumab for treatment of late-stage, aggressive cervical cancer. Clinical studies are under way to explore its possible use in treating other types of cancer.

There are varying opinions and study results in the medical community regarding the effectiveness of bevacizumab in extending patient survival time. Results also vary regarding how effective the drug is at preventing recurrence of cancer.

KEY TERMS

Acute myelogenous leukemia (AML)—A type of cancer of the blood, characterized by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells.

Angina—Ischemic heart disease that produces chest pain.

Angiogenesis—Physiological process involving the growth of new blood vessels from pre-existing blood vessels; a process used by some cancers to create their own blood supply.

Cerebrovascular accident—Terminology that may be used to describe a stroke.

Cytostatic—Inhibiting or suppressing cellular growth and multiplication.

Cytotoxic—Having a toxic effect on cells.

Encephalopathy—Syndrome of global brain disease or injury.

Fistula—Abnormal connection or passageway between two organs or vessels that normally do not connect.

Glioblastoma—Most aggressive and common type of primary brain tumor.

Humanized monoclonal antibody—Human-like antibodies usually genetically engineered in mice and used in a therapeutic manner.

Median survival time—The time from either diagnosis or treatment at which half of the patients with a given disease are expected to still be alive.

Myocardial infarction—Heart attack.

Pulmonary embolism—Formation in a blood vessel of a clot (thrombus) that breaks loose (forms an embolus), is carried by the bloodstream, and blocks a vessel in the lungs.

Stroke—Medical condition in which blood flow to a part of the brain is compromised due to blockage of the blood vessel or blood vessel hemorrhage.

Thromboembolic event—Formation in a blood vessel of a clot (thrombus) that breaks loose (forms an embolus), is carried by the bloodstream, and blocks another vessel, such as in a stroke.

Transient ischemic attack (TIA)—Changes in the blood supply to a particular area of the brain, resulting in brief neurologic dysfunction that persists for less than 24 hours.

Vascular endothelial growth factor (VEGF)—A chemical compound in the body that contributes to the growth of new blood vessels.

Off-label use

Bevacizumab may be used off label to treat the “wet” type of age-related macular degeneration (AMD), a disorder characterized by vision loss. It may also be used to treat macular edema, another eye condition. Although healthcare providers may prescribe bevacizumab as a treatment for these conditions, the drug is not approved by the FDA for these purposes.

Description

Bevacizumab works by binding to and inhibiting a growth factor known as vascular endothelial growth factor (VEGF), which is responsible for the formation of tumor blood vessels. It specifically binds to the growth factor target secreted by cancer cells to prevent the process of angiogenesis, or tumor blood vessel growth. Once a solid tumor reaches a certain size, it needs blood vessels in order for its cells to remain alive and to continue to grow. Blood vessels that supply tumors also contribute to a cancer’s ability to metastasize, or spread, to other parts of the body.

Bevacizumab has both cytotoxic and cytostatic effects. Cytotoxic drugs are toxic to the cancer cells and can therefore destroy the cells. Cytostatic drugs do not kill the cancer cells directly, but instead stop the cancer cells from multiplying and growing further. Bevacizumab has both of these functions, which reduces tumor growth, increases median survival time, and increases time to tumor progression. Median survival time is the time from either diagnosis or treatment at which half of the patients with a given disease are expected to still be alive. Time to tumor progression describes a period of time from when disease is diagnosed (or treated) until the disease becomes worse.

Bevacizumab is considered a first-line treatment for metastatic colorectal cancer in combination with other chemotherapeutic agents. First-line drug therapy is a term used to describe the drug or combination of drugs that has been evaluated as the most effective treatment for a given disease. Bevacizumab is also used with other drugs as part of treatment for a type of kidney cancer, and as of early 2015, studies were under way to determine its

possible use in treating pancreatic, prostate, kidney, and liver cancers, as well as melanoma and a form of blood cancer called acute myelogenous leukemia. Though bevacizumab is used for colon cancer that has metastasized, a study released in April of 2009 showed that following surgery, bevacizumab was not effective at preventing the recurrence of nonmetastatic colon cancer.

Bevacizumab is an expensive drug. Although it may extend the life span of some cancer patients, it does not significantly treat the disease. For this reason, its cost has been criticized by some in the medical community in light of the perceived value of benefit. Some early studies showed that bevacizumab could increase life span by several months at a cost of approximately \$40,000 to \$50,000, a price that not all cancer patients are able to pay, given that it may not be covered by some medical insurance companies. More recent estimates place the cost at approximately \$50 per cancer treatment. However, treatment with the drug takes some time in order to destroy the blood supply to tumors.

U.S. brand names

Bevacizumab is produced by Roche/Genentech under the trade name Avastin.

Origins

Bevacizumab was the first commercially available drug in its class of anticancer drugs, specifically angiogenesis inhibitors. It is a humanized monoclonal antibody. The drug was first developed as a genetically engineered version of a mouse antibody that contained components originating from both humans and mice. It was first approved for use in metastatic colon cancer in 2004 and later for multiple other types of cancer, including some types of lung and breast cancer.

Recommended dosage

Bevacizumab is given intravenously and may be mixed with other chemotherapeutic agents. It may be given to adults for chemotherapy in doses of 5–15 milligrams (mg) per kilogram (kg, or 2.2 lb.) of body weight, usually administered once every 14 days. The dose used varies with the type of cancer, other drugs used in combination with bevacizumab, and the individual's medical history. It may be given in one 90-minute, one 60-minute, and then multiple 30-minute infusions. The dose used does not need to be modified for patients with mild liver or kidney impairment. While bevacizumab distributes throughout the body and is cleared from the body differently in men and women, studies have shown that doses do not need to be modified based on these factors.

Pediatric

Bevacizumab is not approved for use in children.

Geriatric

Patients older than 65 years of age may experience a higher rate of serious side effects in comparison to younger patients.

Pregnant or breastfeeding

There are no human studies on the effects of bevacizumab in pregnant women, but animal studies have shown fetal toxicity. In the United States, bevacizumab is listed as a category C drug. Category C includes drugs in which animal reproduction studies have shown an adverse effect on the fetus, but there are no adequate studies in humans. However, potential benefits to the patient and medical necessity may sometimes warrant use of the drug in pregnant women despite its potential risks.

It is unknown whether bevacizumab is excreted in breast milk, but similar compounds are known to be excreted in this way. The use of bevacizumab in nursing mothers is a clinical decision based on risk and benefits. If the drug is critical enough for the mother, her healthcare provider may advise ceasing breastfeeding in order to take bevacizumab.

Precautions

Bevacizumab may cause a problem with wound healing after some surgical procedures. The risk of fatal surgical complications is increased in patients taking this drug. For this reason, bevacizumab is discontinued for 28 days before and after surgical procedures and until all surgical wounds are healed. Bleeding problems are also reported with this drug, so patients with a history of hemorrhage are at risk. Bevacizumab may not be suitable for use in any of these cases.

Use of bevacizumab increases the risk of perforation of the nasal septum, the cartilage wall that divides the right and left nostrils of the nose. There have been some cases of bowel perforation, where the wall of the stomach or intestines is broken and its contents leak into the abdominal cavity. Patients who already have a history of bowel perforation may be at risk.

In August 2004, the FDA and the Genentech Inc. company issued a drug warning to healthcare providers that there is evidence of an increased risk of serious arterial thromboembolic events with use of bevacizumab. A thromboembolic event is the formation of a clot (thrombus) in a blood vessel, where the clot breaks loose, is carried by the blood, and blocks another vessel.

elsewhere in the body. The clot may block a vessel in the lungs (pulmonary embolism) or in the brain (stroke), causing death. The types of medical complications associated with thromboemboli and use of bevacizumab include cerebrovascular accident, myocardial infarctions, transient ischemic attacks, and angina.

In September 2006, another drug warning was issued stating that there is an increased risk of a negative clinical side effect known as reversible posterior leukoencephalopathy syndrome (RPLS). RPLS is a rare brain-capillary leaking syndrome associated with high blood pressure, fluid retention, and toxic effects on the lining of blood vessels.

In September 2007, a safety labeling update was issued stating that in patients receiving bevacizumab, fistula formation had been reported in parts of the body outside of the gastrointestinal tract, including the vagina and the bladder. Fistulas are abnormal connections or passageways that form between two organs or blood vessels that would not normally be connected. Most of the bevacizumab-associated fistulas occurred within the first six months of treatment and made discontinuation of the drug necessary.

Further warnings were issued in 2013 about thromboembolic events and surgery and wound healing. Anyone considering use of bevacizumab should discuss these warnings with their doctor and a pharmacist.

Other conditions and allergies

Because bevacizumab interferes with the formation of new blood vessels, it may cause problems for people who have atherosclerosis (blocked blood vessels), coronary artery disease (in blood vessels of the heart), or peripheral artery disease (in blood vessels of the arms or legs). In these disease states, the formation of new blood vessels around the diseased vessels is important to maintain blood flow.

Side effects

Bevacizumab is known to cause high blood pressure (hypertension) and an increased risk of bleeding problems. Headache, nosebleeds, alterations of taste, nausea, vomiting, and dry skin may occur. Infections such as pneumonia, catheter infections, and wound infections may also occur. Other side effects such as myocardial infarction (heart attack), stroke, congestive heart failure, kidney problems, some types of encephalopathy (brain damage), and perforation of the bowel or nasal septum have been reported.

When bevacizumab is used to treat conditions of the eye, most of these side effects are avoided.

Interactions

Patients should make their doctor aware of any and all medications or supplements they are taking before using bevacizumab.

Drugs

Bevacizumab has been combined with multiple other chemotherapeutic agents in clinical trials with no clinical problems. However, bevacizumab is known to interact with one other chemotherapy agent called sunitinib, causing a severe form of anemia known as hemolytic anemia.

Resources

BOOKS

Brunton, Laurence, Bruce Chabner, and Bjorn Knollman. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill Medical Publishing, 2012.

PERIODICALS

- Jin, E., et al. "Comparative Effectiveness of Intravitreal Bevacizumab with or without Triamcinolone Acetonide for Treatment of Diabetic Macular Edema." *Annals of Pharmacotherapy* (January 26, 2015): e-pub ahead of print. <http://dx.doi.org/10.1177/1060028014568006> (accessed February 18, 2015).
- Penson, R. T., et al. "Bevacizumab for Advanced Cervical Cancer: Patient-Reported Outcomes of a Randomised, Phase 3 Trial (NRG Oncology-Gynecologic Oncology Group Protocol 240)." *Lancet Oncology* (January 28, 2015): e-pub ahead of print. [http://dx.doi.org/10.1016/S1470-2045\(15\)70004-5](http://dx.doi.org/10.1016/S1470-2045(15)70004-5) (accessed February 18, 2015).
- Tewari, K. S., et al. "Improved Survival with Bevacizumab in Advanced Cervical Cancer." *New England Journal of Medicine* 370 (February 24, 2014): 734–43. <http://dx.doi.org/10.1056/NEJMoa1309748> (accessed February 18, 2015).

WEBSITES

- AHFS Consumer Medication Information. "Bevacizumab Injection." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a607001.html> (accessed February 18, 2015).
- American Academy of Ophthalmology. "What is Avastin®?" EyeSmart.org. <http://www.geteyesmart.org/eyesmart/diseases/avastin.cfm> (accessed February 18, 2015).
- American Cancer Society. "Bevacizumab." <http://www.cancer.org/treatment/treatmentsandsideeffects/guidetocancerdrugs/bevacizumab> (accessed February 18, 2015).
- National Cancer Institute. "Angiogenesis Inhibitors." <http://www.cancer.gov/cancertopics/factsheet/Therapy/angiogenesis-inhibitors> (accessed February 18, 2015).
- National Cancer Institute. "FDA Approval for Bevacizumab." <http://www.cancer.gov/cancertopics/druginfo/fda-bevacizumab> (accessed February 18, 2015).

U.S. Food and Drug Administration. "FDA Commissioner Removes Breast Cancer Indication from Avastin Label." <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm279485.htm> (accessed February 18, 2015).

ORGANIZATIONS

National Cancer Institute, 9609 Medical Center Drive, BG 9609 MSC 9760, Bethesda, MD 20892-9760, (800) 4-CANCER (422-6237), <http://www.cancer.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) 463-6332, <http://www.fda.gov/>.

Revised by Teresa G. Odle

REVIEWED BY KEVIN GLAZA, RPH

Biaxin see **Clarithromycin**

Binosto see **Alendronate**

Birth control pills see **Oral contraceptives**

Boniva see **Ibandronate**



Budesonide, 3 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Budesonide

Definition

Budesonide is one of the medications in the group called corticosteroids, which are man-made compounds that are similar to a naturally occurring hormone called cortisol. Budesonide is prescribed to treat Crohn's disease and other medical conditions.

Purpose

Budesonide is prescribed for the treatment of Crohn's disease, in which the body mistakenly attacks harmless gut bacteria as well as the beneficial gut bacteria that are important for digestion. This causes inflammation-related damage to the lining of the digestive tract and leads to chronic inflammation and symptoms that may include persistent diarrhea, abdominal cramps and pain, constipation, fever, weight loss, and fatigue. In addition, budesonide is also prescribed for congestion and for symptoms of severe asthma and other lung diseases. These symptoms include wheezing, shortness of breath, and other breathing problems.

Description

Corticosteroids are modeled after the hormone cortisol. Produced by adrenal glands located on top of

the kidneys, naturally occurring cortisol does many things in the body. Cortisol is involved in generating glucose, which increases blood sugar and helps the body to metabolize fats, proteins, and carbohydrates, and in suppressing the immune system so that inflammatory responses are dampened.

With regard to budesonide, the dampening of inflammation is an especially important aspect. When used in the treatment of Crohn's disease, budesonide mimics cortisol and attaches to cortisol docking sites, called receptors, in the ileum (the last section) of the small intestine and in the first and middle sections of the colon. The influx of the drug functions similarly to an influx of cortisol and helps to control the inflammation of Crohn's disease. For respiratory-related conditions, including asthma, budesonide mimics cortisol to reduce inflammation in the lungs.

Budesonide is sold as tablets and capsules and as an oral and nasal inhaler.

U.S. brand names

For treatment of Crohn's disease, budesonide is sold in the United States under the brand name Entocort. An extended-release form of budesonide is sold under the brand name of Uceris. Pulmicort is an inhaled powder marketed for use in asthma, while Rhinocort is a nasal spray marketed for use in allergic rhinitis.

KEY TERMS

Bronchodilator—A medication that dilates, or enlarges, the airways (bronchi and bronchioles) to increase airflow.

Corticosteroids—Man-made compounds that mimic a naturally occurring hormone called cortisol; used to treat such health conditions as asthma and Crohn's disease.

Cortisol—A naturally occurring hormone with numerous functions in the body, including the suppression of the immune system so that inflammatory responses are dampened.

Crohn's disease—A disorder in which the body is overzealous in its attack on gut bacteria, causing inflammation-related damage to the lining of the digestive tract.

International brand names

Internationally, budesonide is sold under a number of brand names. These include:

- Aeronide
- Aerovent
- B-Cort
- Budair
- Budecort
- Budenase
- Budenofalk
- Budesonid
- Budiair
- Eltair
- Entocort
- Giona
- Inflammide
- Miflonide
- Neplit
- Neumocort
- Obucort
- Pulmicort
- Rhinocort
- Rhinocort Aqua
- Tafen

Origins

The U.S. Food and Drug Administration (FDA) approved AstraZeneca Pharmaceutical's application for

Entocort EC budesonide capsules in 2001 for the treatment of mild to moderate Crohn's disease involving the ileum and ascending colon. In 2013, the FDA approved Uceris, which is extended-release budesonide in tablet form, to encourage remission in patients who have mild to moderate ulcerative colitis. Budesonide inhalation powder for asthma received FDA approval in 2006.

Recommended dosage

For oral budesonide, the typical adult dosage for mild to moderate Crohn's disease or ulcerative colitis is 9 milligrams (mg) once each morning for up to eight weeks. For prevention of returning Crohn's disease symptoms, the typical adult dosage is 6 mg once each morning for up to three months. For inhaled budesonide, the typical adult dosage varies from 200 to 400 micrograms (mcg) once or twice a day based on the patient's medical history, including his or her use of bronchodilators or other corticosteroids and his or her response to treatment.

Pediatric

Safety and efficacy of oral budesonide have not been established in children, so it is not recommended for this population. Inhaled budesonide (e.g., the brand Pulmicort Respules) is available for use by children. Pulmicort Respules is used as maintenance and preventive treatment for children aged 12 months to 8 years. The recommended dosage of this brand is 0.25–0.5 mg twice daily, or 0.5–1.0 mg once daily, and the doctor will determine dosage based on treatment history and patient response.

Geriatric

No special dosage recommendations for budesonide are made for older patients, but because this population is more likely to have kidney, liver, or heart conditions, doctors may be more conservative in dosage of budesonide and more vigilant in monitoring patient progress.

Precautions

For all budesonide prescriptions, patients should inform their prescribing doctors about all existing health conditions, including diabetes, high blood pressure (hypertension), thyroid problems, tuberculosis or any other infections, osteoporosis, seizures, liver or kidney disease, intestinal disorders, and heart disease. Patients who are undergoing surgery, including dental surgery, should not only tell their prescribing doctor about the upcoming procedure but should also inform the surgeon

or dentist. Patients should refrain from getting an immunization or vaccination before talking to their doctor about possible side effects while using budesonide. In addition, a budesonide regimen should not be stopped abruptly. Rather, the doctor will recommend a gradual lowering of the dosage.

Doctors should make sure patients know that inhaled budesonide is not an emergency inhaler and that it does not treat acute asthma episodes. Typically, doctors will prescribe a separate emergency inhaler for asthma patients. Individuals using inhaled budesonide should be monitored for mouth and throat infection and should be advised to rinse the mouth following inhalation. Patients who are already fighting a bacterial, viral, or fungal infection, or who have tuberculosis or ocular herpes simplex (a type of eye infection), may experience a worsening of their infections. Chickenpox and measles may also be more severe and potentially fatal, so patients should avoid contact with family members and others who have either illness.

Patients who are new to an inhaled medication should be sure to understand how to administer the drug properly before leaving the prescribing doctor's office. For patients using a bronchodilator (an inhaled medication designed for the rapid relief of breathing difficulties), doctors typically recommend the following procedure: 1) use the bronchodilator, 2) wait a few minutes, then 3) administer the inhaled budesonide. This allows budesonide to penetrate more fully into the lungs.

Pediatric

The potential for growth/development suppression exists with the use of inhaled budesonide for asthma in this population, so these patients should be closely monitored.

Geriatric

Older patients are more likely to have a greater number of health problems than younger adults, so they should discuss all of their health conditions with their doctor and become fully aware of potential side effects before beginning budesonide. They should also be sure to notify their doctors about any health changes they experience while taking the medication.

Pregnant or breastfeeding

Oral budesonide is in the FDA pregnancy category C, which indicates that animal studies have shown a risk to the fetus. As soon as a woman learns she is pregnant, she should immediately consult with her doctor about her

use of budesonide so they can discuss benefits versus risks and make an informed decision.

Other conditions and allergies

Some patients experience hypersensitivity reactions with the use of inhaled budesonide. These may include bronchospasm (sudden muscle constriction in the airways), rash, hives or hive-like swelling (angioedema), or anaphylaxis (a whole-body allergic reaction). If any of these occur, the patient is advised to stop taking the medication and contact their care provider or seek emergency treatment if necessary.

Side effects

Side effects may occur with orally taken and with inhaled budesonide.

Side effects associated with oral budesonide include:

- easy bruising
- cough, sore throat, or hoarseness
- flulike symptoms, which may include fever, coughing or sneezing, sore throat, stuffy nose, and chills
- abdominal, stomach, chest, back, muscle, or joint pain
- unusual feelings in the skin (e.g., tingling, numbness, burning)
- headache
- digestive problems, including indigestion, gas, heartburn, diarrhea, nausea, and vomiting

Side effects associated with inhaled budesonide include:

- dry or sore mouth or throat, possibly accompanied by difficulty speaking
- cough
- dizziness
- sleep problems
- neck pain
- stomach pain
- long-lasting cold or infection
- muscle aches or weakness

Pediatric

Side effects for inhaled budesonide include:

- respiratory infection
- inflammation of the nose (rhinitis) or nosebleed (epistaxis)
- coughing
- ear infection or inflammation
- viral infection

- yeast infection of the mouth or throat (moniliasis)
- inflammation of the stomach and intestines (gastroenteritis)
- vomiting
- abdominal pain
- pink eye (conjunctivitis)
- reduction in bone mineral density (with prolonged use)
- rash

Geriatric

Side effects in this age group are similar to those seen in younger adults. Since older patients generally have more health problems than younger adults, however, doctors will carefully monitor older patients for side effects, making prescription alterations as necessary.

Interactions

Budesonide has some known interactions with drugs and other substances. Patients should provide their doctor with a list of all prescription drugs, as well as over-the-counter medications, that they are taking.

Drugs

The use of budesonide is typically not recommended with a variety of drugs, including but not necessarily limited to:

- boceprevir and telaprevir (used to treat hepatitis)
- **bupropion** (depression and smoke cessation)
- **carbamazepine** and primidone (seizures)
- cobicistat or ritonavir (HIV)
- ceritinib, dabrafenib, idelalisib, mitotane, nilotinib, pixantrone, and siltuximab (cancers)
- eslicarbazepine acetate (epilepsy)
- and piperazine (malaria)

Other medications, such as the antibiotic **erythromycin** or the antifungal agents itraconazole and **ketoconazole**, may increase side effects associated with budesonide.

Herbs and supplements

Patients should alert their doctor about any vitamins or herbal supplements they are taking so they understand potential interactions.

Foods and other substances

Patients should discuss the ingestion of grapefruit and grapefruit juice with their doctor, as this may lead to increased levels of the medication in the patient's blood.

Resources

BOOKS

Adler, Douglas G. "Small Intestine." In *The Little GI Book: An Easily Digestible Guide to Understanding Gastroenterology*. Thorofare, NJ: Slack, 2013.

Farraye, Francis A. "Treatment Options." In *Questions and Answers about Crohn's Disease*. Burlington, MA: Jones & Bartlett Learning, 2012.

PERIODICALS

Hoshino, Makoto. "Effects of Budesonide/Formoterol Combination Therapy Versus Budesonide on Airway Dimensions in Asthma." *European Respiratory Journal* 40, suppl. 56 (2014): P2342.

Suissa, S., et al. "Inhaled Corticosteroids in COPD and the Risk of Serious Pneumonia." *Thorax* 68, no. 11 (2013): 1029–36.

OTHER

AstraZeneca Pharmaceuticals. "Pulmicort Respules." AstraZeneca.com. <http://www1.astrazeneca-us.com/pi/pulmicortrespules.pdf> (accessed January 30, 2015).

U.S. Food and Drug Administration, Center for Drug Evaluation and Research. "Approval Letter (Pulmicort Flexhaler)." http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2006/021949s000ltr.pdf (accessed January 30, 2015).

U.S. Food and Drug Administration, Center for Drug Evaluation and Research. "Approval Letter: Application Number 21-324." http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-324_Entocort_Approv.pdf (accessed January 30, 2015).

WEBSITES

"Budesonide." Drugs.com. <http://www.drugs.com/mtm/budesonide.html> (accessed January 3, 2015).

Cleveland Clinic. "Asthma Treatments." http://my.clevelandclinic.org/health/diseases_conditions/hic_Asthma_An_Overview/hic_Medications_for_Treating_Asthma (accessed January 30, 2015).

Mayo Clinic staff. "Budesonide (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/budesonide-oral-route/description/drg-20073233> (accessed January 30, 2015).

MedlinePlus. "Budesonide Oral." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a608007.html> (accessed January 30, 2015).

MedlinePlus. "Budesonide Oral Inhalation." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699056.html> (accessed January 30, 2015).

MPR Drug News. "Uceris Approved for Active Ulcerative Colitis." January 15, 2013. EMPR.com. <http://www.empr.com/uceris-approved-for-active-ulcerative-colitis/article/276075> (accessed January 30, 2015).

ORGANIZATIONS

Crohn's & Colitis Foundation of America, 733 Third Avenue, Suite 510, New York, NY 10017, (800) 932-2423, info@ccfa.org, <http://www.ccfa.org/>.

National Institute of Diabetes and Digestive and Kidney Diseases, 9000 Rockville Pike, Bethesda, MD 20892, (301) 496-3583, <http://www.niddk.nih.gov/>.

National Heart, Lung, and Blood Institute Health Information Center, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, NHLBIinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov/>.

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Budesonide/formoterol

Definition

Budesonide/formoterol is a combination drug that is administered via an oral inhaler to manage asthma and chronic obstructive pulmonary disease (COPD).

Purpose

Budesonide/formoterol is prescribed for the management of asthma and COPD. Asthma is a chronic disease that causes inflammation and narrows the airways, making breathing difficult. COPD is a progressive illness that also affects the airways and impacts breathing. Budesonide/formoterol opens the airways and reduces inflammation in the respiratory tract, which eases breathing.

Description

Budesonide/formoterol is a combination drug. **Budesonide** is a corticosteroid, a man-made compound that is similar to a naturally occurring hormone called cortisol. This hormone is produced by adrenal glands located at the top of the kidneys, and one of cortisol's roles is to suppress the immune system so that inflammation responses are dampened. By mimicking cortisol and its anti-inflammatory properties, budesonide eases inflammation in the airways of the respiratory system. The airways include air tubes called bronchi and bronchioles, as well as air sacs called alveoli.

Formoterol (also called formoterol fumarate or formoterol fumarate dihydrate) is one of a group of drugs known as long-acting beta-agonists or beta-adrenergic agonists. Beta-agonists work on certain structures, the beta adrenoreceptors, that are located on cell membranes. Beta



Symbicort (budesonide/formoterol, 160 mcg/4.5 mcg).
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adrenoreceptors relax muscles around the airways, specifically the bronchi and bronchioles. When the respiratory system is inflamed or otherwise irritated, as it is in asthma and COPD, bands of muscle tighten around the bronchi and bronchioles, causing these airways to become narrower. As a beta-agonist, formoterol acts to relax these muscles, which dilates the airways and allows the patient to breathe easier.

Budesonide/formoterol is sold as an aerosol. Patients inhale a metered dose that is administered through an inhaler that they insert between their lips.

U.S. brand names

Budesonide/formoterol is sold in the United States under the brand name of Symbicort.

Canadian brand names

Budesonide/formoterol is sold in Canada under the brand names of Symbicort 100 Turbuhaler and Symbicort 200 Turbuhaler.

International brand names

Internationally, budesonide/formoterol is sold under a number of brand names. These include:

- Aerovial
- Alenia

- Assieme
- Budamate
- Combipack
- Edoflo
- Foracort
- Foradil
- Formonide
- Prehistam
- Rilast
- Rilast Forte Turbuhaler
- Sinestic
- Vannair
- Ventofo-Combi

Origins

The U.S. Food and Drug Administration (FDA) approved budesonide/formoterol (Symbicort) for the maintenance treatment of asthma in patients 12 years old and older in 2006. In 2009, the FDA followed with a second approval of budesonide/formoterol for the maintenance treatment of airflow obstruction in patients with COPD, including the types of COPD known as chronic bronchitis (inflammation of the bronchial tubes) and emphysema (damage to the alveoli).

Recommended dosage

Budesonide/formoterol is typically sold in two formulations: 80 micrograms (mcg) of budesonide with 4.5 mcg of formoterol and 160 mcg of budesonide with 4.5 mcg of formoterol. Based on the doctor's prescription, which takes into account the severity of the patient's condition, the dosage may be two inhalations twice daily of the 80/4.5 formulation or two inhalations twice daily of the 160/4.5 formulation for patients with asthma. For maintenance treatment of COPD patients, the recommended dosage is two inhalations twice daily of the 160/4.5 formulation.

Pediatric

Safety and efficacy of budesonide/formoterol have not been established for patients younger than 12, so it is not recommended for this population. For asthma patients 12 years old and older, the dosage is the same as it is for adults.

Precautions

Patients should be made fully aware that budesonide/formoterol is not a fast-acting medication to treat emergency respiratory distress. Doctors will prescribe a

KEY TERMS

Beta-agonists—Also known as long-acting beta-agonists (LABA) or beta-adrenergic agonists, this group of drugs is used to relax muscles around the airways, specifically the bronchi and bronchioles.

Bronchi—Two major divisions of the airways that lead into the right and left lungs.

Bronchioles—Very small, thin-walled air passages in the lungs that branch off from the bronchi.

Bronchodilator—A medication that dilates, or enlarges, the airways (bronchi and bronchioles) to increase airflow.

Chronic obstructive pulmonary disease (COPD)—A progressive illness that also affects the airways and impacts breathing.

Corticosteroids—Man-made compounds that are similar to a naturally occurring hormone, cortisol.

Cortisol—A naturally occurring hormone with numerous functions in the body, including the suppression of the immune system so that inflammation responses are dampened.

separate medication, such as a short-acting beta-agonist, for that purpose.

The use of long-acting beta-agonists, including formoterol, has been associated with a heightened risk of asthma-related death, so the use of budesonide/formoterol is not recommended for asthma patients who are receiving adequate relief from long-term asthma control measures, such as inhaled corticosteroids. Doctors should not prescribe budesonide/formoterol to patients who are undergoing rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. Rapidly deteriorating asthma is signified by an increased need for quick-acting emergency inhalers (so-called “short-acting beta-agonists”).

Patients should follow the doctor's instructions when using budesonide/formoterol. The overuse of long-acting beta-agonists, such as budesonide/formoterol, has been associated with cardiovascular issues and deaths.

Patients using budesonide/formoterol should be monitored for mouth and throat infections and advised to rinse the mouth following inhalation. Patients who are already fighting a bacterial, viral, or fungal infection or who have tuberculosis or ocular herpes simplex (a type of eye infection) may experience a worsening of their infections and should discuss their use of budesonide/formoterol with the doctor. Chickenpox and measles may also be more severe and potentially fatal.

Pediatric

The potential exists for growth development suppression with the use of inhaled budesonide/formoterol, so patients in this population should be closely monitored.

Geriatric

Older patients are more likely to have a greater number of health problems than younger adults, so they should discuss all of their health conditions with the doctor and become fully aware of potential side effects before beginning to use budesonide/formoterol. This is especially important for older patients who have cardiovascular disease that could be impacted by beta-agonists, such as formoterol. In addition, the use of budesonide/formoterol increases the risk of pneumonia, glaucoma, and cataracts, as well as reduced bone mass density.

Pregnant or breastfeeding

Budesonide/formoterol is in the FDA pregnancy category C, which indicates that animal studies have shown a risk to the fetus. Infants born to women who have received corticosteroids during pregnancy may experience hypoadrenalism (inadequate production of cortisol and other steroid hormones). As soon as a woman learns she is pregnant, she should immediately consult with her doctor about her use of this medication so they can discuss benefits versus risks.

Other conditions and allergies

Patients should be aware of the range of severe allergic reactions that may occur with the use of budesonide/formoterol and which reactions warrant discussion with their doctor or the need for emergency medical care. These include such symptoms as worsening asthma or COPD symptoms, tightness in the chest, fainting, rapid heartbeat, seizures, severe or repeated vomiting spells, and others.

Patients should inform their prescribing doctors about all existing health conditions, including diabetes, high blood pressure (hypertension), thyroid problems, tuberculosis or any other infections, osteoporosis, seizures, liver or kidney disease, intestinal disorders, and heart disease.

Patients who have liver (hepatic) disease should be closely monitored while taking budesonide/formoterol. This is because the liver clears medications, including budesonide/formoterol, from the system. Impaired liver function may cause the drug to accumulate in the body and cause health problems. Doctors should also closely monitor patients who are switching from a systemically active corticosteroid (one that works throughout the body) to inhaled budesonide/formoterol, which is

available to a limited region of the body, as deaths have occurred during this transition.

Some patients experience hypersensitivity reactions with the use of budesonide/formoterol. These may include bronchospasm, hives or hive-like swelling (angioedema), or rash. If any of these occur, the patient is advised to stop taking the medication and contact their care provider or seek emergency treatment if necessary.

Side effects

Side effects may occur with budesonide/formoterol. They include:

- common cold
- yeast infection of the mouth or throat (moniliasis)
- respiratory infection, including pneumonia
- inflammation of the airways (bronchitis)
- cough, sore throat, or hoarseness
- flulike symptoms, which may include fever, coughing or sneezing, stuffy nose, or chills
- headache
- digestive problems, including vomiting and stomach upset
- rash
- paradoxical bronchospasms (an increase in breathing difficulties)
- reduction in bone mineral density (with prolonged use)
- heightened risk for glaucoma, increased intraocular (in the eye) pressure, and cataracts (with prolonged use)
- hypokalemia (abnormally low potassium levels), which can cause cardiovascular issues

Pediatric

Side effects are similar to those seen in adults. In addition, inhaled corticosteroids, such as budesonide, may affect growth, so the growth of young patients should be monitored diligently while they are taking budesonide/formoterol.

Geriatric

Side effects in this age group are similar to those seen in younger adults. Since older patients generally have more health problems than younger adults, however, doctors will carefully monitor older patients for side effects, making prescription alterations as necessary.

Interactions

Budesonide/formoterol has some known interactions with drugs and other substances. Patients should provide their doctor with a list of all prescription drugs as well as over-the-counter medications they are taking.

Drugs

The use of budesonide/formoterol should not be combined with use of other long-acting beta-agonists, such as **salmeterol** or another prescription for formoterol fumarate, as this can result in cardiovascular problems and even death. Patients who use or have used monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants should be carefully monitored while using budesonide/formoterol. Budesonide/formoterol interacts with a variety of additional drugs and should not be used in combination with these drugs except with the explicit consent of the prescribing doctor. These include:

- beta-blockers, including eyedrops
- ritonavir or other cytochrome P-450 3A4 (CYP3A4) inhibitors
- loop or thiazide diuretics or other non-potassium-sparing diuretics

Herbs and supplements

Patients should alert their doctor about any vitamins or herbal supplements they are taking so they understand any potential interactions.

Foods and other substances

Patients should discuss the ingestion of grapefruit and grapefruit juice with their doctor, as this may lead to increased levels of the medication in the patient's blood.

Resources

BOOKS

- Farraye, Francis A. "Adrenergic Agonists and Antagonists." In *Goodman and Gilman's Manual of Pharmacology and Therapeutics*. Burlington, MA: Jones & Bartlett Learning, 2012.
- Schachter, Neil. "Hospital Management of COPD Exacerbations." In *Essentials of Hospital Medicine: A Practical Guide for Clinicians*, edited by Andrew Dunn, Navneet Kathuria, and Paul Klotman. Hackensack, NJ: World Scientific Publishing Co., 2013.

PERIODICALS

- Akamatsu, Taisuke, et al. "Switching from Salmeterol/Fluticasone to Formoterol/Budesonide Combinations Improves Peripheral Airway/Alveolar Inflammation in Asthma." *Pulmonary Pharmacology & Therapeutics* 27, no. 1 (2014): 52–56.
- Patel, Mitesh, et al. "Efficacy and Safety of Maintenance and Reliever Combination Budesonide–Formoterol Inhaler in Patients with Asthma at Risk of Severe Exacerbations: A Randomised Controlled Trial." *Lancet* 1, no. 1 (2013): 32–42.
- Suissa, S., et al. "Inhaled Corticosteroids in COPD and the Risk of Serious Pneumonia." *Thorax* 68, no. 11 (2013): 1029–36.

OTHER

- AstraZeneca Pharmaceuticals. "Symbicort." AstraZeneca.com. <http://www1.astrazeneca-us.com/pi/symbicort.pdf> (accessed January 30, 2015).
- University of Michigan Health System staff. "How to Use Your Symbicort Inhaler (Budesonide/Formoterol)." Care Guides from Your UMHS Clinician. <http://www.med.umich.edu/1libr/COPD/Inhalers/Symbicort.pdf> (accessed January 30, 2015).

WEBSITES

- American Thoracic Society. "What Are Beta-Agonists?" <http://www.thoracic.org/clinical/copd-guidelines/for-patients/what-kind-of-medications-are-there-for-copd/what-are-beta-agonists.php> (accessed January 30, 2015).
- "Budesonide." Drugs.com. <http://www.drugs.com/mtm/budesonide.html> (accessed January 30, 2015).
- Cleveland Clinic staff. "Asthma Treatments." http://my.clevelandclinic.org/health/diseases/conditions/hic_Asthma_An_Overview/hic_Medications_for_Treating_Asthma (accessed January 30, 2015).
- Mayo Clinic staff. "Budesonide and Formoterol (Inhalation Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/budesonide-and-formoterol-inhalation-route/description/drg-20068949> (accessed January 30, 2015).
- MedlinePlus. "Budesonide Oral Inhalation." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699056.html> (accessed January 30, 2015).

ORGANIZATIONS

- American Lung Association, 55 W. Wacker Drive, Suite 1150, Chicago, IL 60601, (312) 801-7630, (800) LUNGUSA (586-4872), Fax: (202) 452-1805, <http://www.lung.org/>.
- American Thoracic Society, 25 Broadway, New York, NY 10004, (212) 315-8600, Fax: (212) 315-6498, atsinfo@thoracic.org, <http://www.thoracic.org/>.
- National Heart, Lung, and Blood Institute Health Information Center, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, NHLBIinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov/>.

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Buprenorphine/naloxone

Definition

Buprenorphine/naloxone is a prescription-only medication that combines buprenorphine, a pain reliever (analgesic) that belongs to the family of drugs called opioid analgesics, and naloxone, a drug that blocks some of the effects of opioid drugs (opioid partial agonist).



Suboxone (buprenorphine/naloxone, 8 mg/2 mg). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Buprenorphine/naloxone is used to treat dependence on opioid drugs. Buprenorphine helps ease the symptoms of withdrawal from addiction, and naloxone prevents the buprenorphine from being abused.

Description

Buprenorphine/naloxone is classified by the U.S. Drug Enforcement Administration (DEA) as a Schedule III drug. This means that buprenorphine/naloxone:

- carries a low to moderate potential for abuse (less than drugs categorized as Schedule II)
- is medically accepted as a therapeutic agent
- carries a high potential of initiating psychological or physical dependence if abused

Buprenorphine/naloxone is available in a variety of formulations, all of which are placed under the tongue (sublingual) or in the cheek (buccal), allowing the medication to be absorbed as the tablet or film melts.

Available combinations of the sublingual tablets include:

- 2 milligrams (mg) buprenorphine and 0.5 mg naloxone
- 8 mg buprenorphine and 2 mg naloxone
- 1.4 mg buprenorphine and 0.36 mg naloxone
- 5.7 mg buprenorphine and 1.4 mg naloxone
- 8.6 mg buprenorphine and 2.1 mg naloxone
- 11.4 mg buprenorphine and 2.9 mg naloxone

Available formulations of the buccal film combine:

- 2 mg buprenorphine and 0.5 mg naloxone
- 2.1 mg buprenorphine and 0.3 mg naloxone
- 4.2 mg buprenorphine and 0.7 mg naloxone
- 6.3 mg buprenorphine and 1 mg naloxone

Available formulations of sublingual films combine:

- 2 mg buprenorphine and 0.5 mg naloxone
- 4 mg buprenorphine and 1 mg naloxone
- 8 mg buprenorphine and 2 mg naloxone
- 12 mg buprenorphine and 3 mg naloxone

U.S. brand names

Buprenorphine/naloxone is sold in the United States under the brand names Bunavail, Suboxone, and Zubsolv.

Canadian brand names

In Canada, buprenorphine/naloxone is sold under the brand name Suboxone.

Recommended dosage

Dosing of buprenorphine/naloxone depends on the specific formulation/delivery system to be used, whether the individual is addicted to long- or short-acting narcotics, when narcotics were last used, and the degree of addiction. Additionally, the regimen will be determined based on whether the treatment is for induction of withdrawal from a drug or maintenance of abstinence from the drug, and whether the individual will be taking the medication unsupervised. The goal is to prevent drug cravings and the uncomfortable side effects of withdrawal. The dosage format chosen (tablet versus film, sublingual site versus buccal) will also affect the dosage chosen. Care must be taken when switching between delivery systems and sites, as dosages may need to be adjusted.

The dosage formats below are examples of possible dosing but do not completely cover the full range of possibilities for safe dosing:

- buccal film: 2.1–12.6 mg buprenorphine/0.3–2.1 mg naloxone, once daily
- sublingual film and sublingual tablet: 4–24 mg buprenorphine/1–6 mg naloxone, once daily

Other conditions and allergies

Individuals with moderate liver impairment should not use buprenorphine/naloxone during the induction phase of withdrawal and should use the drug with caution for maintenance therapy. Individuals with severe liver impairment should not use buprenorphine/naloxone. Mild liver impairment does not require dosage changes.

KEY TERMS

Analgesic—A drug used to control pain.

Buccal—The lining of the inside of the cheek.

Narcotic—A class of chemical that contains opium or opium derivatives. These drugs decrease pain, often cause drowsiness, may induce a sense of euphoria or well-being, and have profound side effects that include respiratory depression in overdoses and addictive potential.

Opioid—A substance that resembles opium and binds to the same types of receptors in the body, producing similar effects in pain relief, pleasure, and addictiveness. It does not actually contain opium but is synthetically produced to mimic its therapeutic benefits.

Pregnancy class—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk but no human studies exist, or adverse effects have been seen in animals but not in well-controlled human studies. Category C: No adequate human or animal studies exist, or adverse fetal effects have occurred in animal studies but there is no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk, and risks outweigh any benefits.

Sublingual—Under the tongue.

Precautions

The following precautions apply to all individuals.

- Buprenorphine/naloxone should be used with caution in individuals who have had previous reactions to narcotic drugs.
- Buprenorphine/naloxone can cause drowsiness and impair physical abilities as well as mental processing and alertness.
- Sudden discontinuation of the drug can lead to symptoms of withdrawal, including nausea, vomiting, diarrhea, teary eyes, runny nose, severe sweating, itchy skin, twitchy muscles, uncontrollable yawning.
- Sublingual tablets and films and buccal films should not be chewed or swallowed whole. The drug should be left undisturbed under the tongue or in the cheek until completely dissolved and absorbed. Food and drink

should not be consumed until the entire tablet or film has dissolved.

Geriatric

Elderly and debilitated patients are at particular risk of complications from buprenorphine/naloxone use, especially adverse effects on the central nervous system, respiratory system, and digestive system (constipation). Buprenorphine/naloxone should be used with extreme caution and close monitoring in this population.

Pregnant or breastfeeding

Buprenorphine/naloxone is a pregnancy category C drug. Pregnancy category C means that risk to the fetus cannot be ruled out in pregnant individuals, so use of this drug should be avoided whenever possible. Babies with short-term exposure to buprenorphine/naloxone before birth may be born with decreased respiratory drive and a weak suck. Babies who have been exposed to buprenorphine/naloxone for a longer period may experience withdrawal syndrome (neonatal abstinence syndrome) after birth when no longer receiving buprenorphine/naloxone through the placenta. These babies may require treatment to avoid severe symptoms of withdrawal.

Buprenorphine/naloxone is known to pass into breast milk. Caution should be exercised if the drug is utilized by breastfeeding women.

Other conditions and allergies

Buprenorphine/naloxone should not be used in individuals with the following conditions:

- increased pressure in the skull (intracranial pressure)
- respiratory depression (as with chronic obstructive pulmonary disease, emphysema, a severe spinal abnormality or an enlarged heart that puts pressure on the lungs, severe states of asthma)
- a known sensitivity to buprenorphine or naloxone, or to other ingredients within a specific delivery formulation

Buprenorphine/naloxone use needs to be carefully monitored if used in individuals with the following conditions:

- adrenal problems
- gallbladder problems
- thyroid disease
- prostate disease
- psychoses
- narrowing or obstruction of the gastrointestinal tract
- history of alcoholism or delirium tremens
- head or brain injury

Side effects

The most common side effects of buprenorphine/naloxone treatment include:

- headache
- drowsiness
- confusion or unclear thinking
- depression
- sweating or itching
- runny nose or tearing
- dry mouth
- flushing
- chills
- pain
- sore mouth, tongue, or cheek where medication is placed
- stiff, weak, or achy muscles
- upset stomach, nausea, or vomiting
- diarrhea or constipation
- problems sleeping

Rare but serious signs of a significant allergic reaction to buprenorphine/naloxone should prompt the user to seek immediate medical care. These include:

- difficulty breathing or swallowing
- hoarse voice
- wheezing, shortness of breath, or cough
- fever
- pain in the abdomen
- blue skin or lips
- yellow cast to the skin or the whites of the eyes
- headache
- stiff neck
- confusion
- seizures
- swollen face, lips, tongue, or throat
- rash, hives, blisters, or peeling skin
- dizziness

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients should tell the prescribing physician about all the medications that they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamins.

Drugs

The following drugs and substances may increase the possibility of side effects from buprenorphine/naloxone treatment:

- amphetamines
- anticholinergic agents
- dronabinol
- brimonidine
- cannabis
- droperidol
- magnesium sulfate
- methylnaltrexone
- nabilone
- naltrexone
- perampanel
- rufinamide
- sodium oxybate
- succinylcholine
- tapentadol

Buprenorphine/naloxone treatment may increase the side effects of the following drugs:

- alvimopan
- azelastine
- desmopressin
- diuretics
- hydrocodone
- monoamine oxidase inhibitors (MAOIs)
- methotrimeprazine
- metyrosine
- naloxegol
- orphenadrine
- paraldehyde
- **pramipexole**
- ropinirole
- rotigotine
- selective serotonin reuptake inhibitors (SSRIs)
- suvorexant
- thalidomide
- **zolpidem**

Buprenorphine/naloxone treatment may decrease the effectiveness of the following drugs:

- atazanavir
- boceprevir
- bosentan
- pegvisomant

Herbs and supplements

Use of the herb kava kava may increase the risk of side effects from buprenorphine/naloxone.

Food and other substances

Alcohol use may increase the risk of side effects from buprenorphine/naloxone.

Resources

BOOKS

- Aronson, J. K. *Meyler's Side Effects of Analgesics and Anti-inflammatory Drugs*. Oxford: Elsevier, 2010.
- Benzon, Honorio T. *Essentials of Pain Medicine*. 3rd ed. Philadelphia: Saunders, 2011.
- Smith, Howard S. *Current Therapy in Pain*. Philadelphia: Saunders, 2009.
- Waldman, Steven D. *Pain Management*. 2nd ed. Philadelphia: Saunders, 2011.

WEBSITES

- AHFS Consumer Medication Information. "Buprenorphine Sublingual." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a605002.html> (accessed February 19, 2015).
- U.S. Food and Drug Administration. "Subutex (Buprenorphine Hydrochloride) and Suboxone Tablets (Buprenorphine Hydrochloride and Naloxone Hydrochloride)." <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm191520.htm> (accessed February 19, 2015).
- U.S. National Library of Medicine. *Drugs and Lactation Database (LactMed)*. <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm> (accessed February 19, 2015).

ORGANIZATIONS

- National Alliance of Advocates for Buprenorphine Treatment (NAABT), PO Box 333, Farmington, CT 06034, Fax: (860) 269-4391, <http://www.naabt.org/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Bupropion

Definition

Bupropion (bupropion hydrochloride) is an antidepressant drug used to elevate and stabilize mood and to restore a normal range of emotions in patients with depressive disorders such as major depressive disorder



Bupropion XL (extended release), 150 mg. (U.S. National Library of Medicine, Pillbox)

and seasonal affective disorder. In addition, bupropion is used as an aid in smoking cessation treatment.

Purpose

Bupropion is approved by the U.S. Food and Drug Administration (FDA) to treat depression and seasonal affective disorder and to aid in smoking cessation.

Off-label use

Bupropion has been found to have therapeutic uses in panic disorder, attention deficit hyperactivity disorder (ADHD), and bipolar depression, but these are not FDA-approved indications. Use of bupropion for bipolar depressive patients is not only for its efficacy in treating depression but also because it has a lower risk of inducing hypomania or mania in bipolar disorders.

Description

Bupropion is a nontricyclic antidepressant drug. Tricyclic antidepressants that were used for many years to treat depression were noted for unwanted side effects, including sedation, dizziness, fainting, and weight gain. Bupropion was one of the first antidepressants to be developed by pharmaceutical researchers seeking drugs effective in treating depression but without the unwanted actions of the tricyclic antidepressants.

The exact way bupropion works in the brain is not understood. Its mechanism of action appears to be different from that of most other antidepressant drugs, although bupropion does act on some of the same neurotransmitters and neurotransmission pathways. Neurotransmitters are naturally occurring chemicals that regulate the transmission of nerve impulses from one

KEY TERMS

Anxiety—An emotion that can be experienced as a troubled feeling, sense of dread, fear of the future, or distress over a perceived threat to a person's physical or mental well-being.

Attention deficit hyperactivity disorder (ADHD)—A developmental disorder characterized by distractibility, hyperactivity, impulsive behaviors, and the inability to remain focused on tasks or activities.

Bipolar disorder—A mental disorder characterized by alternating feelings of elation and depression.

Depression—A mental state characterized by feelings of sadness, despair, discouragement, and low energy, sometimes accompanied by oversleeping and/or overeating.

Insomnia—Having difficulty falling asleep and/or staying asleep.

Neurotransmitter—A naturally occurring chemical in the body that carries chemical messages to nerve cells, often by transmitting nerve impulses. Central nervous system well-being is dependent on a balance among the neurotransmitters acetylcholine, dopamine, serotonin, and norepinephrine.

Seizure—A convulsion or uncontrolled discharge of nerve cells that may spread to other cells throughout the brain.

cell to another. Mental well-being is partially dependent on maintaining the proper balance among the various neurotransmitters in the brain. Bupropion may stabilize emotional feelings by counteracting abnormalities of neurotransmission that occur in depressive disorders.

Bupropion is less likely to cause weight gain and adverse effects on blood pressure and the heart than other antidepressants. However, it is more likely to trigger epileptic seizures and may also raise blood pressure (hypertension).

U.S. brand names

In the United States, bupropion is sold as an antidepressant under the brand name Wellbutrin. Other trade names worldwide include Aplenzin, Budeprion, Buproban, and Forfivo. As a smoking cessation treatment, the drug is marketed in the United States under the brand name Zyban.

Recommended dosage

Bupropion is formulated as a film-coated tablet. The usual adult dose of bupropion (Wellbutrin) is 100 milligrams (mg), taken three times per day, with at least six hours between doses. The sustained-release form of the drug (Wellbutrin SR) is taken as 150 mg twice a day with at least eight hours between doses. An extended-release, once-daily dose (Wellbutrin XL) is also available and is usually taken in the morning. The extended-release formulations should never be split or crushed before taking. They should always be swallowed whole. For smoking cessation, bupropion (Zyban) is taken as 150 mg sustained-release tablets twice a day, with at least eight hours between doses. Bupropion treatment is typically started at a lower dose, then gradually increased to a therapeutic dosage as directed by the physician. A 450 mg once-daily extended-release formulation is also available for major depressive disorder. Generally, the total dosage should not exceed 300 mg per day, except as directed by the physician.

The therapeutic effects of bupropion, like other antidepressants, appear slowly. Maximum benefit is often not evident for several weeks after starting the drug. People taking bupropion should be aware of this and continue taking the drug as directed even if they do not see immediate improvement in mood.

Since higher doses of bupropion increase the risk of seizures, no more than 150 mg of a regular-release formulation should be given at any one time, and the total daily dosage should not be increased by more than 100 mg every three days. Increasing the dosage gradually also minimizes any agitation, restlessness, and insomnia that may occur.

Pediatric

Although bupropion has been taken by children and adolescents under age 18, no systematic studies have been conducted in these age groups.

Geriatric

Healthy adults over age 65 do not appear to be more sensitive to side effects of bupropion than younger adults and do not require reduced doses.

Other conditions and allergies

Certain medical conditions, especially liver and kidney disease, may require dose reduction.

Precautions

Bupropion is more likely to trigger epileptic seizures than other antidepressants. The drug should

not be given to patients who have a history of epilepsy, take other medication to help control seizures, or have some other condition associated with seizures, such as head trauma or alcoholism. Nevertheless, less than 1% of healthy people taking bupropion at the recommended dose have seizures. The possibility of seizures is increased at higher doses and following a sudden increase in dose. Patients should minimize alcohol intake while taking bupropion, since alcohol consumption increases the chance of seizures. The treatment of bipolar disorders with mood-stabilizing agents such as bupropion is associated with the same risks and cautions as other antidepressants.

Antidepressants increase the risk of suicidal thoughts and behavior in children, adolescents, and young adults, but this is less likely in patients over age 24. Nevertheless, patients of all ages who are taking bupropion should be watched closely by families and caregivers for worsening of depression and for emergence of suicidal thoughts and behavior. Because of the possibility of overdose, potentially suicidal patients should be given only small quantities of bupropion at one time. Increases in blood pressure have occurred in patients taking bupropion along with nicotine-based treatments for smoking cessation. Monitoring blood pressure is recommended in such cases. Excessive stimulation, agitation, insomnia, and anxiety have been troublesome side effects for some patients, especially when treatment is first begun or when the dose is increased. Such adverse effects may be less intense and less frequent when the dose is increased gradually.

When bupropion is taken for smoking cessation, some patients have developed severe neuropsychiatric symptoms, including aggression, depression, mania, panic attacks, and suicidal thoughts and actions. This may occur during bupropion treatment or while discontinuing the drug. Patients are advised to consult with their doctors and read the medication guide before starting treatment with bupropion.

Pediatric

It is generally not advised for children under the age of 18 to take bupropion for any reason, but depending on the diagnosis, it may be the best treatment available.

Pregnant or breastfeeding

It has not been determined whether bupropion is safe to take during pregnancy. Pregnant women should take bupropion only if necessary. The drug is secreted

in breast milk. Women taking bupropion should consult their physicians about risks associated with breastfeeding.

Side effects

Bupropion is a mild stimulant and may cause insomnia, agitation, confusion, restlessness, and anxiety. These effects may be more pronounced at the beginning of therapy and after dose increases and are less likely to occur with gradual increases in dosage. Headache, dizziness, and tremor may occur. Blood pressure may increase (hypertension), especially in smokers and those undergoing nicotine-based treatment for smoking cessation. Despite its stimulating effects, bupropion may also cause sedation.

Weight loss is more common with bupropion than weight gain, but both have been reported. Other adverse effects may include:

- excessive sweating
- dry mouth
- sore throat
- nausea
- vomiting
- decreased appetite
- constipation
- blurred vision
- rapid heart rate

Interactions

Patients should inform their healthcare providers of all medications they are currently taking, including over-the-counter drugs, herbs, and dietary supplements.

Drugs

Bupropion should not be administered while taking other medications that lower the seizure threshold, such as steroids and the asthma medication theophylline. Many psychiatric medications also lower the seizure threshold. Monoamine oxidase inhibitors (MAOIs), another type of antidepressant medication, should not be taken with bupropion or for two weeks before starting the drug. MAOI drugs include isocarboxazid, **linezolid**, methylene blue injection, phenelzine, rasagiline, selegiline, and tranylcypromine, among others. Adverse effects may increase in patients taking levodopa and other medications for Parkinson's disease along with bupropion.

Nicotine patch therapy may be administered concurrently with bupropion in smoking cessation treatment. Nicotine-based smoking cessation treatment is associated

PATIENT PROFILE

A 40-year-old man who had been smoking cigarettes for about 15 years was beginning to experience shortness of breath when lifting packages during his work as a delivery service driver. Besides being concerned about compromising his own health, he wanted to quit smoking to protect the health of his wife and young children. Since he was unsure about trying nicotine-based products available without prescription, a visit to his doctor's office was the first step in his plan to stop smoking. The doctor commended him on his decision and prescribed bupropion (Zyban), a drug that is used as an aid in smoking cessation treatment. Bupropion is a nontricyclic antidepressant drug that is used for treating various depressive or mood disorders (sold under the trade name Wellbutrin), but it is also approved by the FDA as an aid in smoking cessation. Bupropion works by balancing the activity of various neurotransmitters in the brain. When taking the drug to reduce smoking, the proper balance achieved among the neurotransmitters helps to reduce dependence on nicotine by reducing symptoms of nicotine withdrawal.

The starting dose of bupropion (Zyban) was established as one 150 mg sustained-release tablet a day. Treatment would start while the patient was still smoking, exactly one week before the patient's scheduled quit date. Starting the drug prior to quitting usually primes the body to deal with the stress of quitting. The patient was advised that the dose would be increased to the recommended 300 mg per day (150 mg twice a day with at least eight hours between doses)

after the first week and that treatment would continue for 12 weeks. He was also advised to maintain the dosage schedule carefully and to report any unusual symptoms that might develop as the body adjusted to the medication.

Two weeks after the dose of bupropion had been doubled from 150 mg a day to 300 mg per day, the patient reported being nervous, jittery, and easily agitated, as well as being unable to stay asleep the whole night (insomnia). As a smoker and prior to deciding to quit, he had always thought that smoking cigarettes was calming. Consequently, when he encountered treatment-related symptoms of nervousness and agitation, he had begun to smoke again intermittently. Although he had reduced his smoking habit, he seemed unable to quit entirely. However, rather than discontinuing treatment, the doctor recommended returning to the lower dose of 150 mg per day and adding a simple form of nicotine replacement therapy. The patient opted for the nicotine patch (one 21 mg patch per day), an intradermal system that slowly and continuously releases nicotine into the bloodstream while the patch is being worn. After the first week's trial of the combination, the patient experienced gradual diminishing of nervousness and insomnia, and his urge to smoke was also reduced. The combined treatment was continued for the remaining eight weeks, during which the patient quit smoking successfully.

with increases in blood pressure, requiring regular monitoring of blood pressure if the nicotine patch is used.

Certain drugs, especially those cleared by the liver, may interfere with the elimination of bupropion from the body, resulting in higher blood levels of the drug and increased side effects. Conversely, bupropion may delay the elimination of other medicines, including many antidepressants, antipsychotic drugs, and heart medications, resulting in higher blood levels of these drugs and potentially increased side effects.

Food and other substances

Alcohol should be avoided while taking bupropion.

Resources

BOOKS

Albers, Lawrence J., Rhoda K. Hahn, and Christopher Reist. *Handbook of Psychiatric Drugs, 2011 Edition*. Laguna Hills: Current Clinical Strategies, 2010.

American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda: American Society Health-System Pharmacists, 2015.

Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland: New Harbinger, 2013.

PERIODICALS

Englisch, S., et al. "Risks and Benefits of Bupropion Treatment in Schizophrenia: A Systematic Review of the Current Literature." *Clinical Neuropharmacology* 36, no. 6 (2013): 203–15.

Espanol, E., G. Kelsberg, and S. Safranek. "Clinical Inquiry: Does Any Antidepressant Besides Bupropion Help Smokers Quit?" *Journal of Family Practice* 63, no. 11 (2014): 680–88.

Lader, M. "Foreword. A Comprehensive Review of Bupropion." *Clinical Drug Investigation* 31, suppl. 1 (2011): 1–3.

WEBSITES

AHFS Consumer Medication Information. "Bupropion." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/>

druginfo/meds/a695033.html (accessed February 21, 2015).

Micromedex. "Bupropion (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/bupropion-oral-route/description/drg-20062478> (accessed February 21, 2015).

U.S. Food and Drug Administration. "Bupropion Hydrochloride (Marketed as Wellbutrin, Zyban, and Generics) Information." <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103318.htm> (accessed February 21, 2015).

ORGANIZATIONS

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.

National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

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Buspar see **Buspirone**

Buspirone

Definition

Buspirone is an antianxiety (anxiolytic) drug.

Purpose

Buspirone is used for the treatment of generalized anxiety disorders and for short-term relief of symptoms of anxiety.

Description

Buspirone's mechanism of action is unclear, but it likely acts upon central nervous system chemicals such as dopamine, serotonin, acetylcholine, and norepinephrine. These chemicals are called neurotransmitters and are involved in the transmission of nerve impulses from cell to cell. Mental well-being is partially dependent on maintaining a balance among different neurotransmitters.

Buspirone's actions are different from another group of anxiolytics called benzodiazepines. The primary actions of benzodiazepines are to reduce anxiety, relax



Buspirone, 15 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

skeletal muscles, and induce sleep. The earliest drugs in this class were **chlordiazepoxide** (Librium) and **diazepam** (Valium). The mechanism of buspirone's action is also different from barbiturates such as phenobarbital. Unlike benzodiazepines, buspirone has no anticonvulsant or muscle-relaxant properties, and unlike benzodiazepines or barbiturates, it does not have strong sedative properties. If insomnia is a component of the patient's anxiety disorder, a sedative/hypnotic drug may be taken along with buspirone at bedtime. Buspirone also diminishes feelings of anger and hostility in most people. Unlike benzodiazepines, which may aggravate anger and hostility in some patients (especially older patients), buspirone may help patients with anxiety who also have a history of aggression.

The benefits of buspirone take a long time to become evident. Unlike benzodiazepines, with which the onset of action and time to maximum benefit are short, patients must take buspirone for three to four weeks before feeling the maximum benefit of the drug. In some cases, effects may not be felt for up to six weeks. Patients should be aware of this and continue to take the drug as prescribed even if they think they are not seeing any improvement.

U.S. brand names

Buspirone is sold in the United States under the brand name BuSpar. It is also available under its generic name.

KEY TERMS

Anxiety—An emotion that can be experienced as a troubled feeling, sense of dread, fear of the future, or distress over a possible threat to a person's physical or mental well-being.

Anxiolytic—Any of a group of medications prescribed to relieve anxiety. Also called tranquilizers, anxiolytics include benzodiazepines, some of the selective serotonin reuptake inhibitors (SSRIs), barbiturates, and buspirone.

Depression—A mental state characterized by feelings of sadness, despair, and discouragement.

Generalized anxiety disorder—An anxiety disorder characterized by daily irrational worry that is often excessive and uncontrolled.

Insomnia—Having difficulty falling asleep or remaining asleep.

Neurotransmitter—A chemical that aids or alters the transmission of impulses between the points that connect nerves.

Serotonin—A chemical messenger in the brain thought to play a role in mood regulation.

Recommended dosage

Buspirone is available in 5, 10, 15, and 30 milligram (mg) tablets. The usual starting dose of this drug is 10–15 mg per day. This total amount is divided into two or three doses throughout the day—for example, a dose of 5 mg may be given two or three times per day to make a total dose of 10 to 15 mg per day. The dose may be increased in increments of 5 mg daily every two to four days. Most patients respond to a dose of 15 to 30 mg daily. Patients should not take a total dose of more than 60 mg daily. When patients are receiving certain other drugs in addition to buspirone, starting doses of buspirone may need to be lowered (e.g., 2.5 mg twice daily), and any dosage increase should be done with caution and under close physician supervision.

Other conditions and allergies

Dosages may need to be reduced in patients with kidney or liver problems.

Precautions

Buspirone is less sedating (it causes less drowsiness and mental sluggishness) than other antianxiety drugs. However, some patients may still experience drowsiness and mental impairment. Because it is impossible to predict

which patients may experience sedation with buspirone, those starting this drug should not drive or operate machinery until they know how the drug will affect them.

Patients who have been taking benzodiazepines for a long time should be gradually withdrawn from them while they are being switched over to buspirone. They should also be observed for symptoms of benzodiazepine withdrawal.

Other conditions and allergies

Patients with kidney damage should take buspirone with caution in close consultation with their physician. They may require a lower dosage of buspirone to prevent buildup of the drug in the body. Patients with severe kidney disease should not take buspirone. Patients with liver damage should likewise be monitored for a buildup of buspirone and have their doses lowered if necessary.

Side effects

The most common side effects associated with buspirone involve the nervous system. Ten percent of patients may experience dizziness, drowsiness, and headache, and another 5% may experience fatigue, nervousness, insomnia, and light-headedness. Patients may also experience:

- excitement
- depression
- anger
- hostility
- confusion
- nightmares or other sleep disorders
- lack of coordination
- tremor
- numbness of the extremities

Although buspirone is considered nonsedating, some patients experience drowsiness and lack of mental alertness at higher doses, especially early in therapy. In most patients, these side effects decrease with time.

The following side effects have also been associated with buspirone:

- nausea
- dry mouth, abdominal distress, gastric distress, diarrhea, and constipation
- rapid heart rate and palpitations
- blurred vision
- increased or decreased appetite
- flatulence
- nonspecific chest pain
- rash
- irregular menstrual periods or breakthrough bleeding

Interactions

Individuals should inform their healthcare provider about all drugs they are currently taking, including supplements, before starting treatment with buspirone.

Drugs

Dangerously high blood pressure has resulted from the combination of buspirone and members of another class of antidepressants known as monoamine oxidase inhibitors (MAOIs). Because of this, buspirone should never be taken in combination with MAOIs. Patients taking any MAOIs, such as phenelzine sulfate (Nardil) or tranylcypromine sulfate (Parnate), should stop the MAOIs and wait at least 14 days before starting buspirone. The same holds true when discontinuing buspirone and starting any MAOIs.

Certain drugs that affect the liver may alter the metabolism of buspirone. Examples of such drugs are **erythromycin**, a broad-spectrum antibiotic; itraconazole, an oral antifungal agent; and nefazodone, an antidepressant. When these drugs are combined with buspirone, buspirone concentrations may increase to the point of toxicity (poisoning). These combinations either should be avoided or doses of buspirone should be decreased to compensate for this interaction.

Food and other substances

Patients should avoid drinking grapefruit juice while on buspirone, as it inhibits the metabolism of the drug, resulting in potentially toxic amounts of the substance in the bloodstream.

Resources

BOOKS

- Albers, Lawrence J., Rhoda K. Hahn, and Christopher Reist. *Handbook of Psychiatric Drugs*. Laguna Hills, CA: Current Clinical Strategies, 2011.
- American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda, MD: ASHP, 2015.
- Graham, George. *The Disordered Mind: An Introduction to Philosophy of Mind and Mental Illness*. 2nd ed. New York: Routledge, 2013.
- Holland, Leland Norman, and Michael Patrick Adams. *Core Concepts in Pharmacology*. 4th ed. New York: Prentice Hall, 2014.
- North, Carol, and Sean Yutzy. *Goodwin and Guze's Psychiatric Diagnosis*. 6th ed. New York: Oxford University Press, 2010.
- Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger, 2013.

PERIODICALS

- Baldwin, David S., and Claire Polkinghorn. "Evidence-Based Pharmacotherapy of Generalized Anxiety Disorder." *International Journal of Neuropsychopharmacology* 8, no. 2 (June 2005): 293–302.
- Loane, C., and M. Politis. "Buspirone: What Is It All About?" *Brain Research* 1461 (June 21, 2012): 111–18.
- Verster, Joris C., Dieuwke S. Veldhuijzen, and Edmund R. Volkerts. "Is It Safe to Drive a Car When Treated with Anxiolytics? Evidence from On-the-Road Driving Studies During Normal Traffic." *Current Psychiatry Reviews* 1, no. 2 (June 2005): 215–25.

WEBSITES

- AHFS Consumer Medication Information. "Buspirone." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a688005.html> (accessed February 23, 2015).
- Micromedex. "Buspirone (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/buspirone-oral-route/description/drg-20062457> (accessed February 23, 2015).
- National Alliance on Mental Illness. "Buspirone (BuSpar)." [http://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Buspirone-\(BuSpar\)](http://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Buspirone-(BuSpar)) (accessed February 23, 2015).

ORGANIZATIONS

- American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.
- Anxiety Disorders Association of America, 8701 Georgia Avenue, Suite 412, Silver Spring, MD 20910, (240) 485-1001, Fax: (240) 485-1035, <http://www.adaa.org/>.
- National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.
- National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

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Butalbital/acetaminophen/cafeine

Definition

Butalbital/acetaminophen/cafeine is a prescription-only medication that combines butalbital, a barbiturate;



Butalbital/acetaminophen/caffeine, 50 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

acetaminophen, a nonprescription pain reliever (analgesic); and caffeine, a stimulant.

Purpose

Butalbital/acetaminophen/caffeine is used to treat moderate pain from tension headaches.

Description

Butalbital/acetaminophen/caffeine is available as oval or round tablets in blue and white, scored or non-scored, and as white or blue-and-white capsules. Imprints on tablets or printing on capsules varies depending on manufacturer.

Tablets are available in the following combinations:

- 50 milligrams (mg) of butalbital combined with 325 mg of acetaminophen and 40 mg caffeine
- 50 mg of butalbital combined with 500 mg of acetaminophen and 40 mg caffeine

Capsules are available in the following combinations:

- 50 mg of butalbital combined with 300 mg of acetaminophen and 40 mg caffeine
- 50 mg of butalbital combined with 325 mg of acetaminophen and 40 mg caffeine
- 50 mg of butalbital combined with 500 mg of acetaminophen and 40 mg caffeine

Liquid formulations provide 50 mg butalbital, 325 mg acetaminophen, and 40 mg caffeine for every 15 milliliters (mL) volume of medication.

Butalbital (Fiorinal) is classified by the U.S. Drug Enforcement Administration (DEA) as a Schedule III drug, which means that it has some potential for abuse. However, combination butalbital/acetaminophen/caffeine does not fall within any of the DEA drug schedules.

U.S. brand names

Butalbital/acetaminophen/caffeine is sold in the United States under the brand names Alagesic LQ, Dolgic Plus, Esgic, Esgic-Plus, Fioricet, Margesic[DSC], and Zebutal.

Recommended dosage

Adults may take one to two tablets or capsules or 15–30 mL of liquid every four hours. The maximum dose per day is six tablets or capsules or 90 mL of liquid.

Geriatric

This drug is not recommended for use in the elderly.

Precautions

A boxed warning is included with this product regarding acetaminophen, which has the potential to damage the liver, usually due to acetaminophen overdose. Overdose sometimes occurs unintentionally, when more than one acetaminophen-containing product is taken concurrently. Acute liver failure may result in the need for a liver transplant or in death. It is critical that patients know to keep their acetaminophen intake from all sources to less than 4 grams (g) per day. In addition, individuals who ingest more than three alcohol drinks daily have an increased risk of liver complications with the use of acetaminophen and acetaminophen-containing products.

The following precautions apply to all individuals:

- Butalbital/acetaminophen/caffeine can cause drowsiness and can impair physical abilities as well as mental processing and alertness.
- Butalbital/acetaminophen/caffeine has been associated with severe skin reactions, including pustules, blistering, and peeling. The development of a rash should prompt discontinuation of the drug.
- Because of the addictive potential of butalbital/acetaminophen/caffeine, sudden discontinuation after long-term use of the drug may lead to symptoms of withdrawal, including nausea, vomiting, diarrhea, teary eyes, runny nose, severe sweating, itchy skin, twitchy muscles, or uncontrollable yawning.

KEY TERMS

Analgesic—A drug used to control pain.

Barbiturates—Drugs that cause sedation and relax muscles.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Pregnancy category—A system of classifying drugs for their use during pregnancy. Category A: Controlled human studies have identified no fetal risk. Category B: Animal studies indicate no fetal risk, but no human studies exist, or adverse effects have been seen in animals but not in well-controlled human studies. Category C: No adequate animal or human data available, or adverse effects have been seen in animal studies but no human data available. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk and risks outweigh any benefits.

Tension headache—A type of headache that has sometimes been theorized to be caused by contraction of muscles in the head. The sensation of a tension headache is often described as the feeling of a painfully tight band squeezing the head.

- Caffeine has stimulating and irritating effects on the central nervous system, heart, and gastrointestinal tract. Butalbital/acetaminophen/caffeine should be used with extreme caution and close monitoring in individuals with peptic ulcer disease or gastroesophageal reflux (GERD), and it should not be used in individuals with symptoms due to abnormal heart rhythms.

Pregnant or breastfeeding

Butalbital/acetaminophen/caffeine is classified as a pregnancy category C drug. Pregnancy category C means that risk cannot be ruled out in pregnant individuals. If at all possible, use of this drug should be avoided during pregnancy. The combination is also known to pass into breast milk and should be avoided by breastfeeding women.

Other conditions and allergies

Butalbital/acetaminophen/caffeine should not be given to individuals with a known sensitivity or who

have had previous reactions to butalbital, acetaminophen, barbiturate drugs, caffeine, or other ingredients within a specific delivery formulation. The combination should not be used in patients who are acutely intoxicated with ethanol, hypnotics, centrally acting analgesics, opioids, or psychotropic drugs.

In addition, butalbital/acetaminophen/caffeine should be avoided or carefully monitored in people with specific conditions, such as:

- Abdominal conditions. Butalbital/acetaminophen/caffeine can mask symptoms of abdominal conditions, so care should be used in prescribing it to patients with potential intra-abdominal pathological conditions.
- History of substance abuse or alcoholism. Because of butalbital/acetaminophen/caffeine's abuse potential, individuals with a history of addiction may have an increased risk of becoming addicted to this drug combination.
- G6PD deficiency. Low levels of this enzyme may hamper metabolism of butalbital/acetaminophen/caffeine.
- Respiratory disorders. Exercise caution when using this drug in individuals with any form of respiratory compromise, which may be due to lung disorders or cardiac or skeletal conditions that result in low lung volumes.

Side effects

The most common side effects of butalbital/acetaminophen/caffeine treatment include:

- dizziness, drowsiness, or feeling sedated
- upset stomach, nausea, or vomiting
- shortness of breath or respiratory depression
- headache
- agitation or confusion
- sweating
- itching
- shakiness
- dehydration
- constipation
- dry mouth
- nasal congestion
- increased urine output
- weak muscles
- euphoria
- blurred vision
- ringing in the ears
- laboratory evidence of liver damage

Rare but serious signs of a significant allergic reaction to butalbital/acetaminophen/caffeine should prompt the individual to seek immediate medical care. These include:

- difficulty breathing or swallowing
- hoarse voice
- wheezing, shortness of breath, cough
- fever
- pain in the abdomen
- blue skin or lips
- yellow cast to the skin or the whites of the eyes
- headache
- stiff neck
- confusion
- seizures
- swollen face, lips, tongue, or throat
- rash, hives, blisters, or peeling skin
- dizziness

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Use of the following drugs and substances may increase the possibility of side effects from butalbital/acetaminophen/caffeine treatment:

- busulfan
- cannabis
- **carbamazepine**
- dronabinol
- droperidol
- chloramphenicol
- felbamate
- fosphenytoin-phenytoin
- hydrocodone
- **hydroxyzine**
- isoniazid
- magnesium sulfate
- metyrapone
- nabilone

- norfloxacin
- primidone
- probenecid
- rufinamide
- sodium oxybate
- somatostatin acetate
- tapentadol
- **valproic acid**

Butalbital/acetaminophen/caffeine treatment may increase the side effects of the following drugs:

- **aripiprazole**
 - **atomoxetine**
 - azelastine
 - buprenorphine
 - dasatinib
 - formoterol
 - hypotensive agents
 - **imatinib**
 - indacaterol
 - **linezolid**
 - lomitapide
 - meperidine
 - methotrimeprazine
 - mipomersen
 - **mirtazapine**
 - olodaterol
 - orphenadrine
 - paraldehyde
 - phenylephrine
 - pimozide
 - **pramipexole**
 - prilocaine
 - rotigotine
 - selective serotonin reuptake inhibitors (SSRIs)
 - sodium nitrite
 - sorafenib
 - suvorexant
 - thalidomide
 - thiazide diuretics
 - **zolpidem**
- Butalbital/acetaminophen/caffeine treatment may decrease the effectiveness of the following drugs:
- adenosine
 - beta-blockers
 - calcium channel blockers
 - **doxycycline**

- etoposide
- griseofulvin
- iogenguane
- lamotrigine
- lithium
- propafenone
- theophylline
- tricyclic antidepressants
- vitamin K antagonists

Herbs and supplements

Use of the herb kava kava may increase the risk of side effects from butalbital/acetaminophen/caffeine.

Food and other substances

Alcohol may increase the risk of side effects from butalbital/acetaminophen/caffeine, especially liver damage and drowsiness.

Resources

BOOKS

- Aronson, J. K. *Meyler's Side Effects of Analgesics and Anti-inflammatory Drugs*. Oxford: Elsevier, 2010.
- Benzon, Honorio T. *Essentials of Pain Medicine*. 3rd ed. Philadelphia: Saunders, 2011.
- Smith, Howard S. *Current Therapy in Pain*. Philadelphia: Saunders, 2009.
- Waldman, Steven D. *Pain Management*. 2nd ed. Philadelphia: Saunders, 2011.

WEBSITES

- AHFS Consumer Medication Information. "Acetaminophen, Butalbital, and Caffeine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601009.html> (accessed February 19, 2015).
- Brigham and Women's Hospital. "Butalbital, Acetaminophen, Caffeine Oral Tablet." <http://healthlibrary.brighamand-womens.org/RelatedItems/121,4> (accessed February 19, 2015).
- U.S. Department of Justice, Drug Enforcement Administration. "Controlled Substance Schedules." <http://www.deadiversion.usdoj.gov/schedules/index.html> (accessed February 19, 2015).
- U.S. National Library of Medicine. *Drugs and Lactation Database (LactMed)*. <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm> (accessed February 19, 2015).

ORGANIZATIONS

- American Headache Society, 19 Mantua Road, Mount Royal, NJ 08061, (856) 423-0043, Fax: (856) 423-0082, ahshq@talley.com, <http://www.americanheadachesociety.org/>.
- National Pain Foundation, 14828 West 6 Avenue, Suite 16-B, Room 1, Golden, CO 80401-5000, (720) 541-6808, Fax: (720) 541-6809, <http://www.thenationalpainfoundation.org/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Bystolic see **Nebivolol**



Caffeine/acetaminophen/butalbital see
Butalbital/acetaminophen/caffeine
Calan SR see **Verapamil SR**

Calcitriol

Definition

Calcitriol is a synthetic compound similar to a form of vitamin D. It is used to treat low calcium levels in patients with kidney or parathyroid problems.

Purpose

Calcitriol is prescribed for the treatment of hypocalcemia, which is an abnormally low level of calcium in the blood. Patients with hypocalcemia may sometimes experience severe muscle cramps and spasms (tetany) in the hands and feet; a bothersome tingling feeling in the hands, feet, and around the mouth; general tiredness; headache; problems sleeping; and bone and abdominal pain. One of the causes of hypocalcemia is hypoparathyroidism, a condition in which the parathyroid glands—glands located in the neck—do not secrete enough parathyroid hormone. This hormone increases the concentration of calcium in the blood, and without enough of the hormone, calcium levels can drop too low. Another cause of hypocalcemia is vitamin D deficiency (sometimes called hypovitaminosis D), because vitamin D helps the body absorb and use calcium. Vitamin D deficiency can result from a combination of insufficient vitamin D in the diet and inadequate exposure to sunlight or from a number of health conditions and disorders, notably chronic kidney disease, that limit the absorption or usage of vitamin D.

As a topical ointment, calcitriol is also sometimes recommended for the treatment of mild to moderate plaque psoriasis.

Description

Calcitriol is a synthetic analog of the active form of vitamin D, also known as 1,25-dihydroxycholecalciferol or 1,25-dihydroxyvitamin D₃. 1,25-Dihydroxycholecalciferol is the active form of vitamin D, which is the form that takes up calcium from the gut and increases calcium levels in the blood. Calcium is not only a major mineral in the body but also one of the most important minerals. It is involved in numerous aspects of human body function, including building bone, maintaining a normal heart rhythm, transmitting and receiving signals in the nervous system, clotting blood, and releasing hormones, which themselves have many roles in health and development. As a synthetic analog, calcitriol works like 1,25-dihydroxycholecalciferol and therefore helps to increase blood calcium levels.

Calcitriol is available as an ointment for the treatment of mild to moderate psoriasis, a chronic inflammatory condition in which raised, red patches can appear anywhere on the body. These patches are layered over with a whitish, flaky buildup of dead skin cells. For this use, the calcitriol-containing ointment is rubbed into the patches. The mechanism of action for calcitriol in the treatment of psoriasis is not known. A study published in 2014, however, suggested that calcitriol “inhibits critical pathological events associated with the inflammatory-proliferative cascades of psoriasis.” Specifically, the study noted the calcitriol-induced apoptosis (cell death) in psoriasis-related cells (T lymphocytes and normal human epidermal keratinocytes, or NHEKs), as well as inhibited gene expression of certain psoriasis-related proteins (epidermal proteins and chemokines).

Calcitriol is also available as orally taken capsules and as an intravenous injection.

U.S. brand names

Calcitriol is sold in the United States under the brand names Rolcaltrol, Vectical, and Calcijex. Calcijex is an injectable form of calcitriol.



Calcitriol, 0.25 mcg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Canadian brand names

Calcitriol is sold in Canada under the brand names of Rolcaltrol, Silkis, and Calcijex.

International brand names

Internationally, calcitriol is sold under a number of brand names. These include:

- Bonky
- Calcijex
- Decostriol
- Meditriol
- Osteod
- OsteoD
- Osteotriol
- Otanol
- Rocaltrol
- Silkis
- Ticocarol
- Tirocal

Origins

American endocrinologist Michael F. Holick conducted research that in 1971 identified the active form of vitamin D, which is 1,25-dihydroxyvitamin D₃. The active form, also known as calcitriol, is responsible for increasing calcium levels in the blood. Holick went on to make many contributions to the understanding of vitamin D, including

its involvement in disease, which led to new therapies and prevention strategies for a variety of diseases. Calcitriol (Rolcaltrol) received initial U.S. Food and Drug Administration approval in 1978 for “the treatment of hypocalcemia and the resultant metabolic bone disease in patients undergoing chronic renal dialysis.”

Recommended dosage

The recommended initial adult dosage of orally taken calcitriol for the treatment of hypocalcemia is 0.25 micrograms (mcg) once a day. The initial dosage for hypoparathyroidism is the same, and patients are usually advised to take the dose in the morning. In both cases, the dosage may be increased slowly to meet objectives. In adults with rickets (the softening and weakening of bones due to insufficient vitamin D, calcium, or phosphate), the typical dosage is 1 mcg once a day.

The initial dosage of the intravenously injected form of calcitriol is typically 0.5–2 mcg (although it may be as high as 4 mcg) three times per week. The dosage will vary from patient to patient depending on their condition. Upon careful patient monitoring, including checking the levels of calcium and phosphorus in the blood, the doctor will then adjust the dosage over time to provide optimal care for the patient.

Pediatric

The typical dosage for treating hypoparathyroidism ranges from 0.04–0.08 mcg per kilogram (kg, or 2.2 lb.) of body weight orally once a day for infants to 0.5–2 mcg orally for those aged six and older. The doctor will adjust the dosage to match the patient’s response to the medication. As with adults, dosage increases are made slowly over time. In children with rickets, the typical dosage is based on the type of rickets and patient response and varies to up to 2 mcg once a day.

For children with chronic kidney disease, the dosage depends on the severity of the disease and the patient’s levels of vitamin D, parathyroid hormone, total calcium, and phosphorus.

Precautions

As a vitamin D analog that boosts calcium levels, calcitriol requires the presence of calcium to provide benefit to the patient. For this reason, patients will be advised to maintain the proper level of calcium through diet and supplements. Too much calcium can cause health problems, some of which can be dangerous, so patients should follow the doctor’s guidelines carefully to ensure they receive the benefits from calcitriol and do not experience any adverse side effects associated with excessive calcium. Patients who will be undergoing

KEY TERMS

Hypocalcemia—An abnormally low level of calcium in the blood.

Hypoparathyroidism—A condition in which parathyroid glands, which are glands located in the neck, do not secrete enough parathyroid hormone.

Parathyroid hormone—A hormone that controls the concentration of calcium, vitamin D, and phosphorus in the blood.

Psoriasis—A chronic inflammatory condition that includes the presence of raised, red patches that are layered over with a whitish, flaky buildup of dead skin cells.

Vitamin D deficiency—Also known as hypovitaminosis D, it is an abnormally low level of vitamin D in the body that can cause bone, cardiovascular, and other problems.

surgery should notify the prescribing doctor and the surgeon about their use of calcitriol, and patients who are bedridden or otherwise immobilized should also check with their doctor about their use of calcitriol, as they have an increased risk of experiencing abnormally high levels of calcium (hypercalcemia).

Patients who are undergoing dialysis require diligent monitoring while using calcitriol, as it can cause a dangerous deposition of calcium salts in tissues (ectopic calcification). They should also follow the doctor's instructions for a low-phosphate diet and for avoiding antacids and other preparations that contain magnesium.

Patients who are undergoing cholesterol or other laboratory tests should notify the laboratory technicians of their use of calcitriol, as the medication can affect lab results.

Geriatric

No specific precautions are noted. Since older patients are more likely to have a greater number of health problems than younger adults, however, they should discuss all of their health conditions with the doctor and become fully aware of potential side effects before beginning to take calcitriol.

Pregnant or breastfeeding

Calcitriol is in the U.S. Food and Drug Administration (FDA) pregnancy category C, which indicates that animal studies have shown a risk to the fetus. As soon as a woman learns she is pregnant, she should immediately

consult with her healthcare provider about her use of this medication so she and her doctor can discuss benefits versus risks. Women who are nursing should not take calcitriol, as the drug is released in breast milk and increases the risk that newborns will face hypercalcemia.

Side effects

Side effects are not common with calcitriol. When they do occur, however, they may include:

- headache
- constipation
- nausea
- pain at the injection site (with injectable calcitriol)
- weakness
- muscle, bone, or abdominal pain
- loss of appetite or weight loss
- a metallic taste in the mouth
- cardiac arrhythmia
- inflammation of the pancreas (pancreatitis)
- high blood pressure (hypertension)

Some of these side effects can be serious. Patients who experience side effects should contact the doctor immediately, or seek emergency medical help if necessary.

Geriatric

Side effects in this age group are similar to those seen in younger adults. Since older patients generally have more health problems than younger adults, however, doctors will carefully monitor older patients for side effects and make prescription alterations as necessary.

Interactions

Calcitriol has known interactions with some compounds. Patients should provide the doctor with a list of all prescription drugs as well as over-the-counter medications, vitamins, and supplements they are taking before beginning a new prescription for calcitriol. Before beginning any new prescriptions, vitamins, or supplements, patients should also consult with the prescribing physician about potential interactions with calcitriol.

Drugs

Calcitriol may interact with other medications that contain calcium, magnesium (e.g., antacids), phosphates, or vitamin D. While these can sometimes be used safely in combination with calcitriol, patients should be sure to discuss possible interactions with the prescribing

physician or the pharmacist. Other drugs that may interact with calcitriol include:

- digitalis, **digoxin**, and other cardiac glycosides
- corticosteroids
- diuretics, also known as “water pills”

Herbs and supplements

Patients should not take any supplements containing vitamin D or calcium without the express recommendation of their doctor. Excessive calcium can lead to dangerous health problems.

Foods and other substances

While taking calcitriol, patients must take in enough calcium, but not too much. The doctor will provide dietary guidelines to maintain a proper amount of calcium in the diet. Patients should also avoid dehydration and drink plenty of fluids while using calcitriol.

Resources

BOOKS

Conigrave, Arthur D. “Regulation of Calcium and Phosphate Metabolism.” In *Diseases of the Parathyroid Glands*, edited by Angelo A. Licata and Edgar V. Lerma. New York: Springer, 2012.

Gropper, Sareen S., and Jack L. Smith. “Major Minerals.” In *Advanced Nutrition and Human Metabolism*. 6th ed. Independence, KY: Wadsworth Cengage Learning, 2012.

PERIODICALS

DeDea, Larissa. “Understanding Vitamin D Formulations.” *Journal of the American Academy of Physician Assistants* 26, no. 10 (2013): 10–12.

Fong, J., and A. Khan. “Hypocalcemia: Updates in Diagnosis and Management for Primary Care.” *Canada Family Physician & Therapeutics* 58, no. 2 (2012): 158–62.

Raychaudhuri, Suravi, Anupam Mitra, and Ananya Datta-Mitra. “Immunomodulatory Mechanisms of Action of Calcitriol in Psoriasis.” *Indian Journal of Dermatology* 59, no. 2 (2014): 116–22.

WEBSITES

Boston Children’s Hospital. “Hypocalcemia.” <http://www.childrenshospital.org/health-topics/conditions/hypocalcemia> (accessed January 30, 2015).

“Calcitriol.” Drugs.com. <http://www.drugs.com/international/calcitriol.html> (accessed January 30, 2015).

HypoPARAthyroidism Association. “What Is Hypocalcemia?” <https://www.hypopara.org/support-services/newly-diagnosed/what-is-hypocalcemia.html> (accessed January 30, 2015).

MedlinePlus. “Calcitriol.” U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/>

medlineplus/druginfo/meds/a682335.html (accessed January 30, 2015).

Skugor, Mario. “Hypocalcemia.” Cleveland Clinic. <http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/endocrinology/hypocalcemia> (accessed January 30, 2015).

ORGANIZATIONS

American Thyroid Association, 6066 Leesburg Pike, Suite 550, Falls Church, VA 22041, (703) 998-8890, thyroid@thyroid.org, <http://www.thyroid.org/>.

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), 31 Center Drive, Building 31, Room 2A32, Bethesda, MD 20892-2425, (800) 370-2943, NICHDInformationResourceCenter@mail.nih.gov, <http://www.nichd.nih.gov/>.

HypoPARAthyroidism (HPTH) Association, PO Box 2258, Idaho Falls, ID 83403, (208) 524-3857, (866) 213-0394, jsanders@hypopara.org, <https://www.hypopara.org/>.

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Canasa see **Mesalamine**

Candesartan

Definition

Candesartan cilexetil is a type of medication known as an angiotensin II receptor blocker. It is prescribed for the treatment of high blood pressure (hypertension) and heart failure.

Purpose

Candesartan is used for the treatment of hypertension in adults as well as children aged one year and older. In addition, candesartan cilexetil is prescribed for the treatment of heart failure occurring in individuals who have left ventricular systolic dysfunction, which is the most common cause of heart failure. Left ventricular systolic dysfunction is the improper functioning of the left ventricle, one of the heart’s large chambers that pumps blood to the body. In this condition, the left ventricle pumps only 40% or less of the blood volume that it should. Candesartan cilexetil is prescribed to reduce deaths and hospitalizations related to heart failure.

Description

Candesartan cilexetil is part of the class of medicines called angiotensin II receptor blockers



Candesartan cilexetil/hydrochlorothiazide, 16 mg/12.5 mg.
(U.S. National Library of Medicine, Pillbox)

(ARBs), sometimes called angiotensin II receptor antagonists. These drugs block the action of a certain peptide hormone (a type of protein) known as angiotensin II. Angiotensin II stimulates muscles in the blood vessels, causing them to constrict, and also increases the volume of fluid in the blood. As a result, more blood is moving through narrowed vessels, which causes blood pressure to increase and make the heart work harder to pump blood through the body. Candesartan curtails the activity of angiotensin II and therefore lowers blood pressure.

Candesartan cilexetil is often prescribed with an angiotensin-converting enzyme (ACE) inhibitor, as this combination may be more beneficial in the treatment of heart failure than candesartan cilexetil alone. An ACE inhibitor is a drug that regulates blood pressure by blocking an enzyme called angiotensin-converting enzyme. Candesartan cilexetil is also frequently prescribed with other drugs, such as **hydrochlorothiazide**, for the treatment of hypertension.

U.S. brand names

Candesartan cilexetil is sold in the United States under the brand name of Atacand. It is also available in generic form.

Canadian brand names

Candesartan cilexetil is sold in Canada under the brand name of Atacand.

International brand names

Internationally, candesartan cilexetil is sold under a number of brand names. These include:

- Amias
- Atacand
- Bilaten
- Blopress
- Blox
- Candelong
- Candex
- Di Zhi Ya
- Kairasec
- Kenzen
- Minart
- Omegacand
- Parapres
- Pemzek
- Ratacand

Recommended dosage

To treat hypertension, doctors typically prescribe a starting dose for adults of 16 milligrams (mg) once a day when this medication is used alone and when the patient's blood volume is not abnormally low (the patient is not "volume depleted"). The exact dosage a patient receives will vary from one to two daily doses for a total of 8–32 mg per day, and this individualized dosage will be based on patient response and other factors. For instance, the doctor may prescribe a starting dose of 8 mg for those patients who have moderate liver function issues, known as hepatic insufficiency. The drug is not recommended for patients who have severe hepatic insufficiency.

To treat heart failure, the recommended starting dosage is 4 mg of candesartan cilexetil once a day. That dosage is increased slowly, usually to 8 mg, then to 16 mg, and finally to 32 mg once daily as necessary.

Pediatric

Children younger than one year old should not use candesartan cilexetil. This medication can affect kidney development. For children ages one to five, the recommended initial dosage for hypertension is 0.20 mg per kilogram (kg, or 2.2 lb.) of body weight in an oral suspension (a solution made by crushing the tablets and adding them to a liquid). As warranted, the dosage may be adjusted to 0.05 to 0.4 mg/kg. For children aged 6–17, the recommended initial dosage is 4–8 mg (in tablet form) per day for those weighing less than 110 lb. (50 kg) and 8–16 mg for those 110 lb. (50 kg) or more. Dosages may be adjusted to 2–16 mg daily for those weighing less than 110 lb. (50 kg) and to 4–32 mg daily for those weighing more than 110 lb (50 kg). For children who are

KEY TERMS

ACE inhibitor—A drug that disrupts the ability of angiotensin-converting enzyme (ACE) to produce the hormone angiotensin II, which raises blood pressure.

Angiotensin II—A hormone that causes blood vessels to constrict and increases the volume of fluid in the blood, which together cause blood pressure to increase.

Angiotensin II receptor blockers—Sometimes called angiotensin II receptor antagonists, these are drugs that block the action of a certain peptide hormone (a type of protein) known as angiotensin II.

Angiotensin-converting enzyme—Often abbreviated to ACE, this enzyme is a hormone that is part of the renin-angiotensin system, which regulates both blood pressure and the balance of fluid in the body.

Hypertension—High blood pressure.

unable to swallow tablets, doctors may recommend the oral suspension instead.

Geriatric

No special dosage recommendations are made for older patients, but older patients are more likely to have other health conditions, notably heart failure, that may increase the risk for abnormal kidney function. Doctors will take such health conditions into account when prescribing candesartan and will carefully monitor these patients for adverse effects.

Precautions

An increased risk of impaired renal function, which may be life threatening, exists for patients with heart failure or a history of kidney (renal) problems. For this reason, doctors will carefully monitor these patients, especially when patients start a new prescription of candesartan.

Pediatric

Children less than a year old should not take candesartan cilexetil. In addition, all children up to 17 years old should not take the drug if they have kidney problems, signified by a glomerular filtration rate of less than 30 milliliters per minute per square meter of body surface area (mL/min/1.73 m²). Glomerular filtration rate

is a measure of kidney function that focuses on the amount of blood that passes through the kidney's filters, which are called glomeruli.

Geriatric

Older patients who are taking diuretics (sometimes called “water pills”), are volume depleted, or have kidney function issues should use nonsteroidal anti-inflammatory drugs (NSAIDs) with candesartan cilexetil only under the consent and guidance of their physician.

Pregnant or breastfeeding

Candesartan cilexetil is in the U.S. Food and Drug Administration's (FDA) pregnancy category D during the second and third trimesters, which indicates a risk to the fetus. Specifically, candesartan cilexetil may affect kidney function, may cause damage including skeletal deformities and underdevelopment of the lungs (lung hypoplasia), and may lead to death of the developing fetus. As soon as a woman learns she is pregnant, she should immediately consult with the doctor about stopping her prescription and perhaps beginning an alternate treatment.

Candesartan is excreted in rat milk, but it is unknown whether this is also true for humans. Women who are nursing should discuss the potential risks to the baby in determining whether to use the medication or to switch to another treatment option.

Other conditions and allergies

Patients who are sensitive to candesartan cilexetil should not take this drug. In addition, patients who are undergoing surgery or other care involving the use of anesthetics should inform their prescribing doctor and the doctor performing the surgery or care, as there is a heightened risk of hypotension (abnormally low blood pressure) occurring during surgery and while under anesthesia.

Side effects

This medication is generally well tolerated, but some patients do experience side effects. When used to treat hypertension, side effects include headache and dizziness. When used for heart failure, side effects include:

- abnormal kidney function
- hyperkalemia (increased potassium levels in the blood)
- symptomatic hypotension, which is abnormally low blood pressure accompanied by such symptoms as dizziness or fainting

Symptomatic hypotension is mainly associated with patients who are undergoing prolonged diuretic therapy,

on a salt-restrictive diet or dialysis, or experiencing diarrhea or vomiting, and among patients who have congestive heart failure.

Pediatric

Adverse effects in children taking candesartan cilexetil for hypertension are similar to those in adults and include headache and dizziness.

Interactions

Candesartan cilexetil has some known interactions with drugs and other substances.

Drugs

Patients who are diabetic and take the hypertension-fighting drug aliskiren should not take candesartan cilexetil. For nondiabetic patients who use aliskiren and certain other drugs, including angiotensin receptor blockers and ACE inhibitors, doctors will diligently monitor blood pressure, kidney function, and electrolytes (minerals in the blood and other body fluids that carry an electric charge).

There is a potential for an interaction between candesartan cilexetil and lithium, so patients who are taking both should have their serum lithium levels monitored. Lithium therapy is used to treat a number of illnesses, including bipolar disorder, depression, eating disorders, and anemia.

In addition, elderly patients should consult with their doctor about using NSAIDs with candesartan cilexetil if they are also taking diuretics, if they are volume depleted, or if they have kidney-function issues. If the doctor does consent to the use of NSAIDs, patients should receive periodic monitoring of kidney function.

Herbs and supplements

Due to the increased risk of hyperkalemia, patients should discuss the use of potassium supplements or potassium-containing salt substitutes with their doctor. They should also alert the doctor about any other vitamins or supplements they are taking so they understand any potential interactions.

Foods and other substances

Patients should not use potassium-containing salt substitutes while taking candesartan cilexetil without the consent and advice of the doctor. The use of these salt substitutes can lead to high potassium levels in the blood, and this can cause irregular heartbeat, confusion, weakness, or other issues.

Resources

BOOKS

- Kaplan, Norman M., and Ronald G. Victor. *Kaplan's Clinical Hypertension*. 11th ed. Philadelphia: Wolters Kluwer, 2015.
- Mann, Samuel J. *Hypertension and You: Old Drugs, New Drugs, and the Right Drugs for Your High Blood Pressure*. Plymouth, UK: Rowman & Littlefield Publishers, 2012.

PERIODICALS

- Elgendy, Islam Y., et al. "Efficacy and Safety of Angiotensin Receptor Blockers in Older Patients: A Meta-Analysis of Randomized Trials." *American Journal of Hypertension* (November 11, 2014): e-pub ahead of print. <http://dx.doi.org/10.1093/ajh/hpu209> (accessed February 28, 2015).
- Zaiken, K., T. R. Hudd, and J. W. Cheng. "A Review of the Use of Angiotensin Receptor Blockers for the Prevention of Cardiovascular Events in Patients with Essential Hypertension Without Compelling Indications." *Annals of Pharmacotherapy* 47, no. 5 (2013): 686–93.

WEBSITES

- American College of Cardiology. "Candesartan." CardioSmart.org. <https://www.cardiosmart.org/Healthwise/d043/22/d04322> (accessed February 16, 2015).
- AstraZeneca. "FDA Approves AstraZeneca's Atacand (Candesartan Cilexetil) for the Treatment of Heart Failure." <http://www.astrazeneca.com/Media/Press-releases/Article/20050223-FDA-APPROVES-ASTRAZENECAS-ATACAND-CANDESARTAN-CILE> (accessed February 16, 2015).
- Drugs.com. "Candesartan." <http://www.drugs.com/interactional/candesartan.html> (accessed February 16, 2015).
- Healthwise. "Candesartan." University of Michigan Health System. <http://www.uofmhealth.org/health-library/d04322a1> (accessed February 16, 2015).
- Mayo Clinic. "Candesartan (Oral Route)." <http://www.mayoclinic.org/drugs-supplements/candesartan-oral-route/description/drg-20068192> (accessed February 16, 2015).
- U.S. National Library of Medicine. "Candesartan." MedlinePlus. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601033.html> (accessed February 16, 2015).
- U.S. National Library of Medicine. "Label: Atacand—Candesartan Cilexetil Tablet." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a73e1339-9643-4eea-2cbe-e879c88fb50e> (accessed February 16, 2015).

ORGANIZATIONS

- American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org/>.
- American Society of Hypertension, 45 Main Street, Suite 712, Brooklyn, NY 11201, (212) 696-9099, Fax: (347) 916-0267, <http://www.ash-us.org/>.

National Heart, Lung, and Blood Institute Health Information Center, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, NHLBIinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov/>.

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Capoten see **Captopril**

Captopril

Definition

Captopril is a type of medication that inhibits a certain type of enzyme called angiotensin-converting enzyme (ACE). One of captopril's primary uses is for the treatment of high blood pressure.

Purpose

Captopril is prescribed for the treatment of high blood pressure (hypertension). Doctors may also recommend it for other uses, including the treatment of heart failure, the improvement of survival for patients who have had a heart attack, and the treatment of certain kidney problems (diabetic nephropathy) due to type 1 diabetes mellitus (once known as juvenile diabetes).



Captopril, 25 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Description

Captopril is one of a group of compounds known as ACE inhibitors. These compounds hinder angiotensin-converting enzyme, which has an important role in the system that regulates blood pressure (renin-angiotensin system). Within this system, ACE transforms one type of hormone into another, specifically angiotensin I into angiotensin II. Angiotensin II stimulates muscles in the blood vessels and causes the vessels to constrict, also increasing the volume of fluid in the blood. As a consequence, more blood is moving through narrower vessels, causing the pressure within the blood vessels—the blood pressure—to increase. As an ACE inhibitor, captopril curbs the hormone conversion, reduces the production of angiotensin II, and thereby reduces blood pressure. The decrease in blood pressure eases the work that the heart has to do, which has benefits for treating heart failure and for increasing the survival of patients after a heart attack. For diabetic neuropathy, captopril helps to lower the amount of protein that is excreted in the urine. An abnormally high protein level (proteinuria) is a sign of kidney disease.

Captopril is also particularly beneficial for overweight and obese patients with hypertension, as it not only lowers blood pressure but also reduces body weight and serum glucose concentration (a measure of sugar in the blood). It can also improve a patient's lipid profiles, which are blood tests that check for levels of cholesterol, triglycerides, and other lipids.

U.S. brand names

Captopril is sold in the United States under the brand name of Capoten.

International brand names

Internationally, captopril is sold under a number of brand names. These include:

- Acenorm
- Aceomel
- Alkadil
- Apo-Capto
- Apuzin
- Capotec
- Capril
- Captogamma
- Captopril
- Kapril
- Lopril
- Ropril

KEY TERMS

ACE inhibitor—A drug that disrupts the ability of angiotensin-converting enzyme (ACE) to produce the hormone angiotensin II, which raises blood pressure.

Angioedema—A condition signified by pronounced rapid, below-the-skin swelling; somewhat similar to hives.

Angiotensin II—A hormone that causes blood vessels to constrict and increases the volume of fluid in the blood, which together cause blood pressure to increase.

Angiotensin-converting enzyme—Often abbreviated to ACE, this enzyme is a hormone that is part of the renin-angiotensin system, which regulates both blood pressure and the balance of fluid in the body.

Dialysis—A blood-filtration therapy that replaces the function of the kidneys, filtering fluids and waste products out of the bloodstream.

Hypertension—High blood pressure.

Renal—Relating to the kidney.

- Tensiomin
- Zapto

Recommended dosage

For hypertension in adults, doctors typically prescribe a starting dose of 25 milligrams (mg) two or three times a day. This dosage may be adjusted up to 150 mg two to three times a day until the optimal effects are attained. For congestive heart failure, the typical starting dosage is up to 25 mg three times a day depending on patient condition. As warranted, the dosage may be increased (usually to 50–100 mg three times daily). Following a heart attack, the dosage usually starts at least three days later with one 6.25 mg administration, followed by 12.5 mg three times a day and then increased to as much as 50 mg three times a day as warranted. For diabetic neuropathy, the dosage is typically 25 mg three times a day. Regardless of treatment target, the prescriptions will be adjusted based on the patient's condition (e.g., a lower dosage for patients who have kidney problems) and response.

In some patients, particularly those of African descent, the doctor may prescribe captopril along with a diuretic (“water pill”) to achieve blood pressure goals.

Pediatric

For hypertension, heart failure, and diabetic neuropathy, the typical dosages are:

- newborns up to 7 days old and preterm babies: 0.01 mg (in solution) per kilogram (kg, or 2.2 lb.) of body weight two to three times a day, adjusted as necessary
- term babies from 1–4 weeks old: initial dose of 0.05–0.1 mg/kg one to three times a day, adjusted as necessary up to a maximum of 0.5 mg/kg per day divided into one to four doses
- infants from 4 weeks to 1 year: initial dose of 0.15–0.3 mg/kg, adjusted as necessary over time up to a maximum of 6 mg/kg per day divided into one to four doses
- children: initial dose depending on age, adjusted as necessary over time up to a maximum of 6 mg/kg per day divided into two to four doses
- adolescents: initial dose of 12.5–25 mg two to three times a day, adjusted slowly over time to a maximum of 450 mg per day

Geriatric

No special dosage recommendations are made for older patients. Among those older patients who have kidney or other health issues, which are more prevalent in this population, doctors typically use a reduced starting dose and a lower overall maintenance dosage to achieve the desired effects.

Precautions

Patients should inform their doctors about all existing health conditions when beginning a prescription of captopril, as well as new health issues that arise while using the drug. Patients with severe congestive heart failure or a history of kidney (renal) problems and those using diuretics should be carefully monitored, especially when they begin a new prescription of captopril. In addition, patients who have signs of infection, such as a sore throat or fever, should tell their prescribing physician, who then may order tests to check the patient's level of white blood cells.

Pediatric

Doctors are especially cautious about prescribing captopril in children and will closely monitor young patients for adverse side effects.

Geriatric

Older patients are more likely to have a greater number of health problems than younger adults and therefore have a greater tendency for adverse side effects.

This population should learn the signs that may accompany life-threatening side effects and be sure to report any other concerns to their doctors.

Pregnant or breastfeeding

Captopril is in the U.S. Food and Drug Administration (FDA) pregnancy category D during the second and third trimesters, which indicates a risk to the fetus. Specifically, captopril may affect kidney function, can cause damage including skeletal deformities, and may lead to death of the developing fetus. As soon as a woman learns she is pregnant, she should consult with the doctor about immediately stopping her prescription and perhaps beginning alternative antihypertensive treatment.

Other conditions and allergies

Patients who are sensitive to captopril or any other ACE inhibitors should not take captopril. They should also inform the prescribing doctor of any allergies they may have as well as their medical history, including occurrences of angioedema. Patients who have experienced angioedema with another ACE inhibitor and patients with hereditary angioedema or idiopathic angioedema (angioedema from an unknown cause) should not take captopril.

Patients who are undergoing dialysis with high-flux membranes sometimes have adverse reactions when using captopril, so doctors will be cautious in prescribing the drug, and when they do, they will be diligent in monitoring patients for side effects. In addition, patients who are undergoing surgery or other care (including dental surgery) involving the use of anesthetics should inform their prescribing doctor and the doctor performing the surgery or care. Captopril carries a heightened risk of hypotension (abnormally low blood pressure) in conjunction with this care.

Side effects

Captopril is generally well tolerated, but some patients do experience side effects. These may include:

- chest pain
- pounding heartbeat
- irregular heartbeat
- angioedema of the arms and legs; the face, including the lips and tongue; the intestines; and the voice box (larynx) as well as the glottis, which is the opening to the upper larynx
- symptomatic hypotension, which is abnormally low blood pressure accompanied by such symptoms as dizziness or fainting

- low levels of the infection-fighting blood cells called neutrophils (a condition called neutropenia), accompanied by fever or other symptoms of an infection
- jaundice (yellowing of the skin), which in rare instances may progress to a serious health threat
- hyperkalemia (increased potassium levels in the blood)

Pediatric

Side effects in children are similar to those in adults.

Geriatric

Side effects in this age group are similar to those seen in younger adults, but because this population is more likely to have concurrent health problems, doctors are typically especially vigilant in monitoring these patients for adverse side effects.

Interactions

Captopril has some known interactions with drugs and other substances.

Drugs

Doctors will closely monitor patients who take thiazide diuretics (a type of “water pill”), as captopril and thiazide diuretics taken together have additive effects in lowering blood pressure.

Doctors should assess the potential benefits and the risks before prescribing captopril to patients who have collagen vascular disease (which affects connective tissue), who are undergoing therapy involving bee/wasp (hymenopteran) venom, or who have taken or are taking other drugs that affect the immune system. Patients who have diabetes should not take the hypertension medication aliskiren with captopril.

Herbs and supplements

Patients should not use potassium supplements while taking captopril without the consent and advice of the doctor. They should also alert the doctor about any vitamins or herbal supplements they are taking, so they understand any potential interactions.

Foods and other substances

Patients should not use salt substitutes while taking captopril without the consent and advice of the doctor. In addition, alcohol can reduce blood pressure, which may intensify side effects, so alcohol consumption should be discussed with the doctor before beginning to take captopril.

PATIENT PROFILE

A 70-year-old man with high blood pressure and atrial fibrillation began taking captopril (Capoten), an angiotensin-converting enzyme (ACE) inhibitor that is used to manage high blood pressure (hypertension). ACE inhibitors slow or stop the specific tightening action of angiotensin on blood vessel walls, relaxing the blood vessels and lowering blood pressure. Controlling blood pressure levels is especially important to reduce the risk of stroke or heart attack in someone with atrial fibrillation, an irregular heartbeat known to produce blood clots that travel via the bloodstream. Shortly after starting to take captopril, the patient developed a dry cough and wheezing. He reported the cough to his doctor, describing that it felt like tightness in the chest but without actual congestion. The doctor ordered tests to measure the patient's lung function (pulmonary function tests), but no significant lung problem was found except for a slightly reduced capacity to inhale and exhale. The doctor explained that this was probably more related to aging lungs than to overt lung disease.

Respiratory side effects of captopril are reported to include a dry, persistent cough in a small percentage of patients (about 4%), especially in those with a history of asthma or an asthmatic tendency. However, this patient did not recall ever having asthma or a family history of asthma, although he did report that he had various allergies as a child and had been a smoker when he was in his 20s and 30s. The doctor suggested that the cough was most likely an underlying tendency toward bronchial hyperreactivity, a type of allergic reaction.

Most people who take captopril are of advanced age and take higher doses. Because the patient's high blood pressure had been essentially uncontrolled prior to visiting the doctor, he was started on an initial dose of 150 mg per day, which the doctor increased to 200 mg per day (a 100 mg tablet twice a day) after one month to provide further blood-pressure reduction. A few weeks later, the patient reported having the persistent cough and wheezing. Although the doctor did not believe that discontinuing the drug was necessary, she thought it was prudent, at least temporarily, to reduce the dosage of captopril to the initial dosage of a 50 mg tablet taken three times a day with meals (total 150 mg per day). It was important to see if the cough could be corrected without substantially reducing the effect of lowering the patient's blood pressure.

Taking 50 mg captopril three times daily with meals effectively reduced the patient's coughing and wheezing, but it did not control his blood pressure sufficiently. Since increasing captopril was not an option for this patient, the doctor recommended adding a low dose of a thiazide-type diuretic—25 mg of hydrochlorothiazide (Microzide)—daily, to reduce the amount of fluid in the circulatory system. Removing extra fluid reduces total blood volume and helps to further reduce blood pressure. The combination of an ACE inhibitor and a diuretic worked well to manage the patient's blood pressure without causing bronchial sensitivity and the resulting cough.

Resources

BOOKS

Filardi, Pasquale Perrone, ed. *ACEi and ARBS in Hypertension and Heart Failure*. New York: Springer, 2015.

Kaplan, Norman M., and Ronald G. Victor. *Kaplan's Clinical Hypertension*. 11th ed. Philadelphia: Wolters Kluwer, 2015.

Mann, Samuel J. *Hypertension and You: Old Drugs, New Drugs, and the Right Drugs for Your High Blood Pressure*. Plymouth, UK: Rowman & Littlefield Publishers, 2012.

PERIODICALS

"Captopril Approved for Hypertension." *FDA Drug Bulletin* 11, no. 2 (1981): 10–11.

Mahmood, Isam Hamo, and Nada Sati Al-Rawi. "Effects of Captopril vs. Amlodipine on Blood Pressure, Serum Glucose, and Lipid Profile in Overweight and Obese Hypertensive Patients." *Rawal Medical Journal* 38, no. 2 (2013): 104–108.

Smith, Charles G., and John R. Vane. "The Discovery of Captopril." *FASEB Journal* 17, no. 8 (2003): 788–89.

WEBSITES

U.S. Food and Drug Administration. "Capoten (Captopril Tablets)." http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/018343s085lbl.pdf (accessed February 28, 2015).

WEBSITES

Drugs.com. "Captopril Tablets." <http://www.drugs.com/pro/captopril-tablets.html> (accessed February 26, 2015).

Johns Hopkins Medicine. "ACE Inhibitors." http://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_Diabetes_Guide/547002/all/ACE_inhibitors (accessed February 26, 2015).

Micromedex. "Captopril (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/captopril-oral-route/description/drg-20069213> (accessed February 26, 2015).

U.S. National Library of Medicine. "Captopril." MedlinePlus. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682823.html> (accessed February 26, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org/>.

American Society of Hypertension, 45 Main Street, Suite 712, Brooklyn, NY 11201, (212) 696-9099, Fax: (347) 916-0267, <http://www.ash-us.org/>.

National Heart, Lung, and Blood Institute Health Information Center, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, NHLBIinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov/>.

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Carbamazepine

Definition

Carbamazepine is an anticonvulsant drug that is indicated for use in treating epileptic seizures and nerve pain, including trigeminal neuralgia.

Purpose

Carbamazepine is used in the treatment of psychomotor and grand mal seizures and a type of facial nerve pain called trigeminal neuralgia.

Off-label use

Carbamazepine is sometimes combined with other drugs to treat psychiatric conditions such as bipolar disorder, manic episodes, and extreme aggression. Carbamazepine is also occasionally used to control pain in patients with cancer.

Description

Carbamazepine was first marketed as an antiseizure medication and as first-line treatment for trigeminal neuralgia. It is structurally similar to tricyclic antidepressants such as **amitriptyline** and **imipramine**, and it was later noted to be effective in patients with certain psychiatric disorders. Psychiatrists began combining it with other drugs such as lithium and major tranquilizers in severe cases of bipolar disorder and aggressive behavior that could not be managed with single-drug therapy.

U.S. brand names

In the United States, carbamazepine is marketed under the trade names Tegretol and Carbatrol. Other trade names for this drug include Eptol and Equetro.



Carbamazepine, 200 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Recommended dosage

Carbamazepine is formulated in 100 milligram (mg) chewable tablets, 200 mg capsules, and an oral suspension of 100 mg per 5 milliliters (mL) of liquid. When used to treat seizure disorders or psychiatric diseases, the recommended initial dosage of carbamazepine is 200 mg two times each day. The effectiveness of carbamazepine may decline with time, so, if needed, the daily dosage may be increased by 200 mg once each week as determined by the physician. Total daily dosages for adults should not exceed 1,200 mg. Carbamazepine doses should be taken with meals. Dosage changes should be made only by the physician and not by patients themselves.

Pediatric

Total daily dosages should not exceed 1,000 mg in children between the ages of 12 and 15 years.

Precautions

Carbamazepine may affect mental alertness, especially early in therapy, and patients receiving this drug are advised not to operate dangerous machinery or drive a car until the drug's effects can be fully evaluated.

Carbamazepine should be used with caution in persons who also experience other types of seizure disorders such as atypical absence seizures. Among such individuals, carbamazepine usage has been associated with an increased risk of initiating, rather than

KEY TERMS

Agranulocytosis—A type of blood disorder in which infection-fighting white blood cells called granulocytes are markedly reduced.

Analgesic—Pain reliever.

Aplastic anemia—A type of blood disorder in which bone marrow activity is suppressed and not enough immature red cells, white cells, and platelets are produced to maintain sufficient numbers of these cells in the blood circulation. This may be the result of a toxic reaction to therapy with specific drugs.

Bipolar disorder—A mental disorder characterized by alternating feelings of elation and depression.

Platelets—Tiny blood cells that are components of the blood-coagulation process in the body. Platelets are formed in the bone marrow and then circulate in the bloodstream.

Seizure—A convulsion or uncontrolled discharge of nerve cells that may spread to other cells throughout the brain.

Thrombocytopenia—A severely reduced platelet count, which may result in coagulation problems and bleeding.

Trigeminal neuralgia—A disorder of the trigeminal nerve that causes severe facial pain.

controlling, generalized convulsions. Carbamazepine should never be discontinued abruptly unless another treatment for seizures is initiated at the same time, since sudden discontinuance of carbamazepine may result in seizures. Discontinuing the drug should be done only with physician guidance and not by the patient.

People taking carbamazepine may experience sudden, wide mood swings, a sense of detachment from self or body, and thoughts of suicide. Family members and caretakers should be advised that these adverse effects are possible, and the person should be watched closely for any changes in mood or behavior.

Carbamazepine has been reported to cause aplastic anemia, a form of anemia in which the bone marrow does not produce adequate amounts of immature red blood cells, white blood cells, and platelets. Another hematologic effect can be mild, transient, or severe deficiency of platelets in the blood (thrombocytopenia), which can result in blood coagulation problems or bleeding. Agranulocytosis, a severe reduction in infection-fighting white blood cells called granulocytes, may also develop

in individuals taking carbamazepine. Although the incidence of these blood conditions is low, baseline blood cell counts should be obtained prior to starting the drug, and then cell counts should be monitored regularly. Some people with previously diagnosed suppression of bone marrow activity should not take carbamazepine. Patients and caretakers should also be alert for signs and symptoms of bone marrow toxicity such as fever, sore throat, infection, mouth sores, easy bruising, or signs of bleeding just under the skin (hematoma). Rarely, carbamazepine can cause dangerous, sometimes fatal skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) in patients who are positive for the human leukocyte antigen HLB-2, which is found exclusively in persons of ancestry from certain areas of Asia. However, if carbamazepine has been taken for a month or more without skin reactions, risks of this reaction are low.

Although carbamazepine is used for treating nerve pain, it is not a simple analgesic and should not be used for any other aches or pains.

Pregnant or breastfeeding

Carbamazepine may cause birth defects and should not be taken by pregnant women. An effective contraceptive method should be used by sexually active women who are taking carbamazepine. It is important to note that this medication may decrease the effectiveness of **oral contraceptives**. The drug can cross into breast milk and should be avoided by women who are breastfeeding.

Side effects

The most commonly reported adverse reactions to carbamazepine are dizziness, drowsiness, shakiness and unsteady or shuffling walk, nausea, and vomiting. These are more common when therapy is just beginning. Carbamazepine may also cause aching joints and muscles, muscle trembling or stiffness, and other problems with muscle coordination. A red pinpoint skin rash, hives, or sensitivity to the sun (photosensitivity) may occur. Other dermatologic symptoms may be noted, such as constant itching (pruritus), changes in skin pigmentation, exfoliative dermatitis, and hair loss (alopecia).

Interactions

Due to the potential of many interactions with other drugs, individuals should consult with a physician or pharmacist prior to starting any new medications purchased over the counter or prescribed by another physician.

PATIENT PROFILE

Trigeminal neuralgia is a painful nerve condition originating in the trigeminal nerve of the face that carries facial sensations to the brain. A 52-year-old woman first noticed twinges of facial pain across her right jaw and cheek when she was brushing her teeth and sometimes when eating foods that required considerable chewing. When nonprescription pain relievers did not reduce her pain and her symptoms increased to severe shooting pain from her jaw to her forehead, she consulted her dentist and was referred to a neurologist. After undergoing scans to make sure the cause of pain was not pressure on the nerve from a tumor or nearby blood vessel, she was diagnosed with trigeminal neuralgia of unknown cause. The neurologist prescribed carbamazepine (Tegretol), an anticonvulsant drug used to treat seizures, epilepsy, and nerve pain. The doctor told her that if the anticonvulsant medication did not reduce the occurrence of nerve pain successfully, they could then consider gamma knife radiosurgery, a type of radiation treatment of the nerve, or surgical removal of the blood vessels pressing on the nerve or part of the nerve itself (neurectomy). However, anticonvulsant medication was the preferred first-line treatment rather than risk destruction of nerve fibers, which can sometimes result in some degree of facial paralysis.

Although the typical starting dose of carbamazepine is 200 mg twice daily for seizures, this patient was started on a relatively low dose of a 100 mg chewable tablet twice daily to treat her trigeminal neuralgia. Carbamazepine provided relief fairly quickly, taking the edge off of the patient's pain, but it did not reduce pain spasms completely. When the patient reported to her doctor after two weeks' treatment that she was still experiencing pain, her dosage was increased to a 200 mg tablet twice a day. This controlled the pain effectively, but the patient reported feeling sleepy and unable to focus in her daily work as a

financial analyst. Her neurologist confirmed that this effect sometimes occurs in early therapy with carbamazepine and that it would likely subside with continued use of the drug. She agreed to continue with treatment and to take time off from work if necessary until her body adjusted to the drug. However, within the next two weeks, the drowsiness continued and she also developed a feeling of shakiness and unsteady walking. Even when she was seated, she felt that her whole body was shaking. The neurologist explained that drowsiness, dizziness, unsteady movement, and muscle trembling were indeed common side effects of carbamazepine and that other options could be explored. However, since sudden discontinuance can result in seizures, the doctor cautioned the patient against discontinuing the drug abruptly.

When she returned to the doctor's office for consultation, the patient was tested for current drug levels of carbamazepine and was advised to return for repeat testing in one week to help determine the minimum effective level that would relieve her facial pain. The doctor explained that different formulations produced different peak levels of the drug, and since carbamazepine had effectively treated her trigeminal neuralgia, it made sense to change the formulation rather than to change the drug. Therefore, until the minimum effective level was determined, the patient was switched to a sustained-release tablet of 100 mg to be taken twice daily. This was equal to the original dosage, which had not produced symptoms of dizziness, unsteadiness, or muscle trembling. However, the sustained-release version of the medication maintained steady blood levels of the drug rather than a higher peak level. The change in dosage and formulation was effective without causing symptoms, and a 200 mg sustained-release tablet was ultimately shown to be the minimum effective dose for the patient.

Drugs

Blood levels of carbamazepine may be reduced when it is used in combination with other drugs such as phenobarbital, **phenytoin**, or primidone. This means that inadequate amounts of carbamazepine are available to the body, limiting the ability of the drug to control seizure activity or treat psychiatric disorders. Carbamazepine also reduces the blood levels of the following drugs when they are used simultaneously: phenytoin, **warfarin**, **doxycycline**, **haloperidol**, **valproic acid**, and theophylline.

The simultaneous administration of carbamazepine with erythromycin, cimetidine, propoxyphene, isoniazid, **fluoxetine**, and calcium channel blockers such as

nifedipine and verapamil may increase the blood level of carbamazepine to a toxic range.

The simultaneous use of carbamazepine and oral contraceptives may increase the possibility that the oral contraceptive will not effectively prevent pregnancy. Some physicians recommend that a different method of contraception be used while taking carbamazepine.

Food and other substances

People taking carbamazepine should not drink grapefruit juice. Grapefruit juice slows the breakdown of carbamazepine, increasing the concentration of carbamazepine in the bloodstream.

Resources

BOOKS

- Albers, Lawrence J., Rhoda K. Hahn, and Christopher Reist. *Handbook of Psychiatric Drugs, 2011 Edition*. Laguna Hills: Current Clinical Strategies, 2010.
- American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda: American Society of Health-System Pharmacists, 2015.
- Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland: New Harbinger, 2013.

PERIODICALS

- Chbili, C., et al. "Relationships Between Pharmacokinetic Parameters of Carbamazepine and Therapeutic Response in Patients with Bipolar Disease." *Annales de Biologie Clinique (Paris)* 72, no. 4 (2014): 453–59.
- Di Stefano, G., et al. "Natural History and Outcome of 200 Outpatients with Classical Trigeminal Neuralgia Treated with Carbamazepine or Oxcarbazepine in a Tertiary Centre for Neuropathic Pain." *Journal of Headache Pain* 15 (June 2014): 34.
- Findling, R. L. and L. D. Ginsberg. "The Safety and Effectiveness of Open-Label Extended-Release Carbamazepine in the Treatment of Children and Adolescents with Bipolar Disorder Suffering from a Manic or Mixed Episode." *Neuropsychiatric Disease and Treatment* 10 (August 2014): 1589–97.
- Kenyon, K., S. Mintzer, and M. Nei. "Carbamazepine Treatment of Generalized Tonic-Clonic Seizures in Idiopathic Generalized Epilepsy." *Seizure* 23, no. 3 (2014): 234–36.
- Powell, G., M. Saunders, and A. G. Marson. "Immediate-Release Versus Controlled-Release Carbamazepine in the Treatment of Epilepsy." *Cochrane Database System Reviews* 2, art. no. CD007124 (February 2014). <http://dx.doi.org/10.1002/14651858.CD007124.pub4> (accessed March 1, 2015).

OTHER

- U.S. Food and Drug Administration. "Tegretol [prescribing information]." http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/016608s101,018281s0481bl.pdf (accessed March 1, 2015).

WEBSITES

- AHFS Consumer Medication Information. "Carbamazepine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682237.html> (accessed March 1, 2015).
- U.S. Food and Drug Administration. "Information on Carbamazepine (Marketed as Carbatrol, Equetro, Tegretol, and Generics)." <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107834.htm> (accessed March 1, 2015).

ORGANIZATIONS

- Epilepsy Foundation, 8301 Professional Place East, Suite 200, Landover, MD 20785-2353, (800) 332-1000, ContactUs@efa.org, <http://www.epilepsy.com/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Carbidopa/levodopa

Definition

Carbidopa/levodopa is a combination drug that is considered the treatment of choice for people who have Parkinson's disease, an ongoing and progressive movement disorder. The levodopa portion is a central nervous system agent that is converted to a neurotransmitter called dopamine in the brain. Carbidopa is a decarboxylase inhibitor that inhibits, or controls, the levodopa so that it is not broken down by the body before reaching the brain.

Purpose

People who have Parkinson's disease experience progressively worse symptoms such as tremors, or slight



Carbidopa/levodopa, 25 mg/100 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

shakiness, while the person is at rest; rigid limbs; slow movements; and problems with balance and walking. They also may have pain, fatigue, and other physical and neuropsychiatric symptoms. Carbidopa/levodopa can help the patient move and ease other symptoms related to Parkinson's disease. The medication is also used for people who have Parkinson's-like symptoms from other causes, such as some antipsychotic drugs.

Description

The active ingredients of carbidopa and levodopa are combined in a single tablet. Levodopa converts to dopamine in the body, which helps to ease symptoms. The levodopa can become active immediately, affecting all of the body's nerves, if not inhibited before it reaches the brain. The ability of carbidopa to inhibit levodopa eases some side effects and the amount of levodopa required for effectiveness.

U.S. brand names

In the United States, carbidopa/levodopa is sold under the following brand names:

- Parcopa
- Sinemet

A drug called Stalevo contains carbidopa, levodopa, and entacapone, which allows more of the levodopa to reach the brain and better ease symptoms.

Canadian brand names

In Canada, carbidopa is sold as Sinemet. The combined carbidopa, levodopa, and entacapone formula is available as Stalevo.

Origins

This combination drug was first approved by the U.S. Food and Drug Administration (FDA) in 1988 and has remained the primary medical treatment for Parkinson's disease since that time.

Recommended dosage

Each drug is designed with varying ratios of carbidopa to levodopa. For example, Sinemet comes in tablets with carbidopa-to-levodopa ratios of 1:4 and 1:10. This means that there are 25 milligrams (mg) of carbidopa for every 100 mg of levodopa in the 1:4 ratio formula and 25 mg of carbidopa for every 250 mg of levodopa in the 1:10 ratio tablets.

The drug is taken by mouth three times a day, and dosage is titrated, meaning that patients start at a lower dose and doctors slowly and methodically increase the

KEY TERMS

Dopamine—A neurotransmitter in the brain that influences many of the brain's functions, including movement, areas of thinking, pleasure, and control of hormones.

Dyskinesia—Difficulty in performing voluntary muscular movements.

Neuropsychiatric—Referring to disorders that affect the mind and nervous system.

Neurotransmitter—A chemical in the brain that can affect the activity of neurons, or nerve cells.

Parkinson's disease—A disease of the nervous system most common in people over age 60, characterized by a shuffling gait, muscle stiffness, and tremors.

dose depending on how well the medicine is working and how well the patient tolerates the drug's side effects. Eventually, the dose is leveled off at a daily amount that works well for the patient. When the FDA approved the combination formula, the agency set the maximum daily limit at 800 mg, or eight tablets of 25/100 mg a day.

Precautions

Patients taking levodopa or combined carbidopa/levodopa should have their liver, kidney, heart, blood vessel, and blood cell functions checked regularly for possible serious side effects of the drug. Patients taking levodopa may experience dyskinesias, which are jerky motions. Reducing the dosage can sometimes lessen the effect. Some people who take the drug have reported hallucinations, problems with impulse control, and other psychological symptoms. In 2010, the FDA issued a notification about Stalevo, which combines entacapone with carbidopa and levodopa. The FDA reported that people who take Stalevo may be at higher risk for heart attack, stroke, and death from cardiovascular events.

It is important to take carbidopa/levodopa tablets regularly, according to the schedule the doctor and pharmacist provide, to ensure that the medicine works as it should.

Pediatric

Carbidopa/levodopa is not recommended for use in anyone younger than 18 years old.

Geriatric

Older patients may be more sensitive to the drug's side effects.

Pregnant or breastfeeding

Carbidopa/levodopa is in the FDA pregnancy category C, meaning that adverse fetal effects have been found in animal studies, but there are no comparable human studies. Women who are pregnant should take the medication only if the potential benefits outweigh possible risks. Levodopa can be passed to an infant through breast milk, so any woman who is breastfeeding should use caution if taking carbidopa/levodopa.

Other conditions and allergies

Anyone who has glaucoma must be carefully monitored while using carbidopa/levodopa. The medicine can change pressures in the eyes.

Side effects

One of the most common and concerning side effects of carbidopa/levodopa is dyskinesias, or jerky twitching and twisting motions. Other side effects include:

- dizziness
- vomiting, nausea, and loss of appetite
- constipation or diarrhea
- dry mouth and change in taste
- confusion and forgetfulness
- headache
- nervousness
- sleep disturbances

Some side effects of carbidopa/levodopa can be serious and should be reported to a doctor immediately. These include:

- uncontrollable and unusual movement, especially of the mouth, face, tongue, neck, and limbs
- pounding, rapid, or irregular heartbeat
- hallucinations
- depression or suicidal thoughts
- blood in vomit or stools
- problems with swallowing or breathing

Interactions

Carbidopa/levodopa can interact with other drugs and substances. Anyone taking the drug should tell their doctor about all herbal supplements, vitamins, and other medications taken. They should also discuss dietary concerns.

Drugs

More than 70 generic and brand-name drugs can have major interactions with carbidopa/levodopa. When a drug interaction occurs, the effectiveness of one drug or another can be lessened or side effects may be made worse. Several of the drugs that interact with carbidopa/levodopa are also combination drugs. Anyone who takes carbidopa/levodopa should fill the prescription at the same pharmacy as other medications so that the pharmacist is aware of all medications taken and can watch for possible drug interactions.

In particular, people who take antihypertensive drugs, which are used to treat high blood pressure, may experience postural hypotension, which is a drop in blood pressure when standing after sitting or lying down that can lead to dizziness or even falling. Drugs called dopamine D₂ antagonists (**risperidone**, phenothiazine) can reduce the effectiveness of levodopa.

Herbs and supplements

Some multivitamins contain high levels of iron salts, which can reduce the amount of levodopa that is available in the body. Anyone taking multivitamins should discuss their use with a doctor or pharmacist when taking carbidopa/levodopa.

Food and other substances

Eating high levels of protein or foods with high acid content can interfere with how well carbidopa/levodopa is absorbed and cause problems with the drug's effectiveness.

Resources

PERIODICALS

Brodell, David W., et al. "Carbidopa/Levodopa Dose Elevation and Safety Concerns in Parkinson's Patients: A Cross-sectional and Cohort Design." *BMJ Open* 2, no. 6 (2012). <http://dx.doi.org/10.1136/bmjopen-2012-001971> (accessed January 31, 2015).

Fernandez, Hubert H. "Updates in the Medical Management of Parkinson Disease." *Cleveland Clinic Journal of Medicine* 79, no. 1 (2012): 28–35.

Patel, Tejal, and Feng Chang. "Parkinson's Disease Guidelines for Pharmacists." *Canadian Pharmacy Journal* 147 (May/June 2014): 161–70.

WEBSITES

"Carbidopa/Levodopa." Drugs.com. <http://www.drugs.com/cdi/carbidopa-levodopa.html> (accessed January 31, 2015).

MedlinePlus. "Levodopa and Carbidopa." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601068.html> (accessed January 31, 2015).

Merck & Co., Inc. "Sinemet." Merck.com. https://www.merck.com/product/usa/pi_circulars/s/sinemet/sinemet_pi.pdf (accessed January 31, 2015).

ORGANIZATIONS

Parkinson's Disease Foundation, 1359 Broadway, Suite 1509, New York, NY 10018, (212) 923-4700, Fax: (212) 923-4778, <http://www.pdf.org/en/index>.

The Michael J. Fox Foundation for Parkinson's Research, Grand Central Station, PO Box 4777, New York, NY 10163-4777, (800) 708-7644, <https://www.michaeljfox.org/>.

Teresa G. Odle, BA, ELS

REVIEWED BY KEVIN GLAZA, RPH

Cardizem see **Diltiazem**

Carisoprodol

Definition

Carisoprodol is a muscle relaxant that is used to treat painful conditions, such as strains and sprains.

Purpose

Carisoprodol is prescribed as a short-term treatment to relieve the pain and discomfort associated with various musculoskeletal (muscle- and bone-related) injuries, including common sports injuries such as



Carisoprodol, 350 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

sprains and strains. It is also sometimes used to treat muscle spasms.

Description

Carisoprodol is a centrally acting skeletal muscle relaxant. Most of the muscle in the human body is skeletal muscle, which is the type of muscle a person uses to control the movement of the skeleton (e.g., lifting arms, walking, typing, nodding the head). Upon taking the medication by mouth, the gastrointestinal system absorbs it and distributes it throughout the central nervous system. Its mode of action is uncertain, but studies suggest that it may interfere with the transmission of pain sensations from the nerves at the pain site to the brain. This drug is meant to be used on a short-term basis and is frequently combined with other therapies, which may include rest, an exercise program, physical therapy, massage, or other measures to treat pain and discomfort and to relax muscles. Combination drugs are also available; these combine carisoprodol with other medications such as **aspirin** or codeine.

U.S. brand names

Carisoprodol is sold in the United States under the brand name SOMA, as well as many generic versions.

International brand names

Although carisoprodol has been removed from the market in some countries, it is still available in others under brand names including:

- Gencari
- Genesafe
- Hiranin
- Listaflex
- Tensaprin

Recommended dosage

Adult dosage varies by condition and patient response and is determined by the patient's doctor. Typically, patients take the carisoprodol tablets four times a day for a short duration, usually no longer than three weeks. Patients should follow the doctor's instructions to the letter and should not take more than the recommended dosage.

Pediatric

Safety and effectiveness have not been established in patients less than 16 years old, so it is not recommended for this population.

KEY TERMS

Central nervous system—The brain and the spinal cord.

Meprobamate—A metabolite of carisoprodol.

Metabolite—In terms of drugs, a metabolite is a modified form of a drug that is produced when the body processes that drug.

Musculoskeletal—Related to muscle and bone.

Skeletal muscle—The muscle that a person controls to power the movement of the skeleton, such as when lifting the arms, walking, typing, nodding the head, etc.

Geriatric

Carisoprodol is not recommended for use in elderly patients due to the risk of severe side effects.

Precautions

Carisoprodol causes sedative effects, so it can impair both physical and mental abilities and compromise the patient's ability to drive, operate machinery, or perform various tasks. The sedative effects can increase if the patient is concomitantly taking another drug that also depresses the central nervous system.

Before beginning a prescription of carisoprodol, patients should inform the doctor of their medical history, including incidence of kidney or liver disease, seizures, and acute intermittent porphyria (a blood disease that can affect the nervous system, skin, or other organs). The doctor also should ask the patient about a history of the regular use or the abuse of alcohol or drugs, as carisoprodol carries a risk for abuse.

Some patients may experience withdrawal reactions when ending a prescription of carisoprodol. Symptoms include stomach cramps, headache, nausea, sleeping problems, or other issues. Patients should report these to the doctor, who may decide to wean the patient off the drug, decreasing the dosage over time to alleviate withdrawal issues. Patients should be sure to take only the dosage recommended and only for the time period recommended. Failure to follow the recommendations can result in increased side effects.

Geriatric

Carisoprodol and other skeletal muscle relaxants can cause sedation and confusion in older adults, which may lead to falls and injury.

Pregnant or breastfeeding

Carisoprodol is in the U.S. Food and Drug Administration (FDA) pregnancy category C, which indicates that animal studies have shown a risk to the fetus, including postnatal death. As soon as a woman learns she is pregnant, she should immediately consult with the doctor about her use of this medication so she and her doctor can discuss benefits versus risks. Caution should be used when prescribing this drug to women who are nursing, as the drug is excreted in breast milk. In addition, animal studies suggest that use of this drug by the mother may affect milk production.

Other conditions and allergies

Patients should inform their doctors of any allergies they may have, especially allergies involving carisoprodol, meprobamate, or the related drugs tybamate and mebutamate.

Side effects

The most common side effects associated with carisoprodol use include:

- sedative effects, including drowsiness and impaired physical and mental abilities
- headache
- dizziness

Less common side effects may include:

- vertigo or fainting
- dizzy spell upon standing (postural hypotension)
- rapid heartbeat (tachycardia)
- tremor
- agitation or irritability
- seizures
- sleeping problems
- nausea, vomiting, or digestive discomfort
- a reduced number of blood cells

Geriatric

Carisoprodol is not recommended for use in elderly patients due to the risk of severe side effects.

Interactions

Carisoprodol has known interactions with many compounds. Patients should provide the doctor with a list of all prescription drugs as well as over-the-counter medications, vitamins, and supplements they are taking before beginning a new prescription for carisoprodol. Patients should also inform the doctor about any new medications or supplements they wish to begin while

taking carisoprodol so that they are aware of potential interactions with carisoprodol.

Drugs

A few of the many drugs that interact with carisoprodol include:

- barbiturates (used to treat anxiety, insomnia, and seizures)
- benzodiazepines (used in the treatment of many conditions, including insomnia and depression)
- buprenorphine (used to treat opioid dependence)
- opiates (painkillers)
- propoxyphene (a painkiller)
- sodium oxybate (used for the treatment of narcolepsy)

Herbs and supplements

No herbs or supplements are specifically noted as interacting with carisoprodol. Patients should still, however, inform their doctors about all herbs and supplements they are using.

Foods and other substances

While taking carisoprodol, patients should discontinue or limit the use of alcohol as advised by the doctor. The combination of carisoprodol and alcohol can cause dizziness, drowsiness, sleeping problems, and impaired judgement and mental alertness.

Resources

BOOKS

- Clark, Glenn T., and Raymond A. Dionne, eds. *Orofacial Pain: A Guide to Medications and Management*. Oxford, UK: Wiley-Blackwell, 2012.
- Deer, Timothy R., et al, eds. *Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches*. New York: Springer, 2013.

PERIODICALS

- Nebhinani, Naresh, et al. "Carisoprodol: An Underrecognized Drug of Abuse in North India." *General Hospital Psychiatry* 35, no. 1 (2013): 89–92.
- Spence, M. M., P. J. Shin, and N. E. Gibbs. "Risk of Injury Associated with Skeletal Muscle Relaxant Use in Older Adults." *Annals of Pharmacotherapy* 47, no. 7 (2013): 993–98.

OTHER

- U.S. Food and Drug Administration. "SOMA (Carisoprodol) Tablets for Oral Use." http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/011792s0431bl.pdf (accessed February 27, 2015).

WEBSITES

- "Carisoprodol." Drugs.com. <http://www.drugs.com/carisoprodol.html> (accessed February 27, 2015).
- Micromedex. "Carisoprodol (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/carisoprodol-oral-route/description/drg-20071941> (accessed February 27, 2015).
- National Highway Traffic and Safety Administration. "Carisoprodol (and Meprobamate)." Drugs and Human Performance Fact Sheets. <http://www.nhtsa.gov/people/injury/research/job185drugs/carisoprodol.htm> (accessed February 27, 2015).
- U.S. Department of Justice, Office of Diversion Control. "Information Regarding Carisoprodol Prescriptions." http://www.deadiversion.usdoj.gov/drug_chem_info/carisoprodol/ (accessed February 27, 2015).
- U.S. National Library of Medicine. "Carisoprodol." Medline-Plus. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682578.html> (accessed February 27, 2015).

ORGANIZATIONS

- American Academy of Pain Management, 975 Morning Star Drive, Suite A, Sonoma, CA 95370, (209) 533-9744, info@aapainmanage.org, <http://www.aapainmanage.org/>.
- American Academy of Pain Medicine, 8735 W. Higgins Road, Suite 300, Chicago, IL 60631-2738, (847) 375-4731, Fax: (847) 375-6477, info@painmed.org, <http://www.painmed.org/>.
- National Institute on Drug Abuse, 6001 Executive Boulevard, Room 5213, MSC 9561, Bethesda, MD 20892-9561, (301) 443-1124, <http://www.drugabuse.gov/>.

Leslie A Mertz, PhD

REVIEWED BY JAMES E. WAUN, MD, RPH

Carvedilol

Definition

Carvedilol is a cardiovascular drug known as a beta-blocker. This drug both dilates blood vessels and lowers blood pressure.

Purpose

Patients take carvedilol as directed by their doctors to treat high blood pressure (hypertension), angina pectoris (chest pain due to reduced blood flow to the heart), and heart failure, including left ventricular dysfunction (a lowered blood-pumping capability of one of the four chambers of the heart) following a heart attack.



Carvedilol, 25 mg. (© Cengage Learning®)

Description

Beta-blockers are a class of commonly used medications that have an effect on chemicals known as catecholamines, which are produced by the adrenal glands. The adrenal glands are located on top of the kidneys. Two major catecholamines are the hormones **epinephrine** (also called adrenaline) and norepinephrine. When a person is under stress, such as watching a scary scene in a movie, running from danger, or facing deadlines at work, nerves in the adrenal glands trigger the release of epinephrine and norepinephrine. Both hormones quickly spread and bind at certain sites, called the alpha-1 adrenergic receptors and the beta-adrenergic receptors, throughout the body. Once bound to these receptors, a number of stress responses follow, including an increased heart rate and elevated blood pressure.

In situations where a real bodily threat is present, such as when a person is confronted with a dangerous situation, this response is short-lived and readies the person for battle or to run away. This is the so-called “fight-or-flight” response, and it dissipates as the danger passes. Day-in and day-out job stress, however, can cause a more continuous stress response that can be unhealthy. Drugs such as carvedilol are designed to prevent binding to these receptors, thereby lowering blood pressure and slowing the heart rate. This is

beneficial in patients who have high blood pressure and in those who have congestive heart failure (a condition in which the heart is not keeping up with the body’s demands). In addition, carvedilol reduces the chest pain of angina pectoris and improves survival in patients with left ventricular dysfunction following myocardial infarction. Carvedilol is recommended to be taken with food.

Prescription carvedilol is sold as tablets, which are taken by mouth. Depending on the formulation, it may be available as 3.125, 6.25, 12.5, or 25 milligram (mg) tablets. Both immediate-release and extended-release formulations are available.

U.S. brand names

Carvedilol is available in the United States under the brand name of Coreg. It is also available in generic form.

International brand names

Carvedilol is also available internationally as Coreg, under many labels as a generic drug, and under a variety of brand names, including:

- Atram
- Avedol
- Carca
- Cardiostad
- Carloc
- Carvedigamma
- Carvedil
- Carvetrend
- Carvipress
- Coryol
- Dilatrend
- Eucardic
- Kredex
- Vedilol
- Zhuo Yi

Origins

One of the earliest beta-blockers with significant medical effects was discovered by Scottish pharmacologist Sir James Whyte Black in 1962. Called **propranolol**, this drug was used to treat angina pectoris. Other beta-blockers, including carvedilol, followed. The U.S. Food and Drug Administration (FDA) initially approved carvedilol (Coreg) in 1995, and it became the first beta-blocker to receive a U.S. indication for the treatment of congestive heart failure.

KEY TERMS

Adrenergic receptors—Certain hormone-binding sites throughout the body.

Angina—Chest pain due to reduced blood flow to the heart.

Beta-blockers—Members of a class of commonly used medications that have an effect on chemicals known as catecholamines, which include epinephrine.

Bradycardia—Abnormally slow heart rate.

Catecholamines—Family of neurotransmitters containing dopamine, norepinephrine, and epinephrine, produced and secreted by cells of the adrenal medulla and the brain.

Congestive heart failure—A condition in which the heart is not keeping up with the body's demands.

Diuretics—Drugs designed to encourage excretion of urine in people who accumulate excess fluid, such as individuals with high blood pressure or heart conditions.

Epinephrine—Also called adrenaline, epinephrine is a stress-triggered hormone that causes such responses as increased heart rate and muscle strength, elevated blood pressure, and heightened sugar metabolism.

Hypertension—High blood pressure.

Hypotension—Abnormally low blood pressure.

Myocardial infarction—Heart attack.

Recommended dosage

Dosages are based on several factors, including patient response and drug tolerance. The typical adult dosages for immediate-release carvedilol (taken with food as recommended by the doctor) follow:

- Hypertension and angina pectoris: An initial dosage of 6.25 mg twice a day, and a maintenance dosage of 6.25–25 mg orally twice a day, with a maximum daily dosage of 50 mg.
- Congestive heart failure: An initial dosage of 3.125 mg twice a day, and a maintenance dosage that is increased gradually to a maximum of 25 mg twice a day in patients weighing 185 lb. (85 kg) or less, or 50 mg twice a day in those weighing more.
- Left ventricular dysfunction following myocardial infarction (heart attack): An initial dosage of 3.25–

6.25 mg twice a day, and a maintenance dosage that is increased gradually to a maximum dosage of 25 mg twice a day.

The typical adult dosages for extended-release carvedilol are:

- Hypertension: An initial dosage of 20 mg once a day, and a maintenance dosage that is increased slowly to a maximum once-a-day dosage of 80 mg.
- Congestive heart failure: An initial dosage of 10 mg once a day, and a maintenance dosage that is increased gradually to as much as 80 mg once a day.
- Left ventricular dysfunction following myocardial infarction: An initial dosage of 20 mg once a day, and a maintenance dosage that is increased slowly to a maximum once-a-day dosage of 80 mg.

Pediatric

Safety and efficacy have not been established for children (persons less than 18 years old), so it is not prescribed for this age group.

Geriatric

Dosage recommendations are the same for older adults as they are for younger adults. Doctors may, however, be more conservative in dosage.

Precautions

Some patients experience a lowered heart rate (bradycardia) while taking carvedilol. The dosage should be reduced if the pulse rate falls below 55 beats per minute. Worsening heart failure or fluid retention is possible when a dosage is increased; if this occurs, diuretics (“water pills”) are recommended at the appropriate dosage. Patients who have scheduled major surgery should discuss their use of carvedilol with the prescribing physician and with the surgeon to determine the best course of action.

Geriatric

When patients are switched from immediate-release carvedilol to an extended-release version of carvedilol, a lower starting dose of the drug is often considered to reduce the risk of hypotension (abnormally low blood pressure) and fainting (syncope).

Pregnant or breastfeeding

Carvedilol carries the FDA pregnancy category C, which indicates that animal studies have shown a risk to the fetus. As soon as a woman learns she is pregnant, she should immediately consult with her doctor about her use of this medication so they can discuss benefits versus risks.

Carvedilol should be used with caution by nursing mothers, as animal studies indicate that it is excreted in breast milk and may increase the risk of death in newborns.

Other conditions and allergies

Doctors should use caution in prescribing carvedilol to patients who have diabetes, impaired kidney function, overactive thyroid, and pheochromocytoma (a rare adrenal gland tumor). Patients with diabetes and congestive heart failure should have their blood glucose monitored when starting carvedilol or changing/stopping the dosage, as these patients may experience worsening hyperglycemia. In addition, kidney function should be carefully monitored in patients who have low blood pressure (systolic blood pressure less than 100 mm Hg), cardiovascular disease, or kidney insufficiency.

Individuals who have bronchospastic disease (e.g., asthma or chronic obstructive pulmonary disease that causes spasms in the bronchi, which are airways in the lungs) should not use carvedilol. Other patients who should not use carvedilol include those with atrioventricular block (an interruption of impulse transmission between heart chambers), sick sinus syndrome (a type of heart-rhythm problem), severe bradycardia (unless the patient has a permanent pacemaker in place), cardiogenic shock (insufficient pumping of blood by the heart), or so-called decompensated heart failure requiring the use of intravenous inotropic therapy.

Persons with allergic reactions to carvedilol or any of the compounds used in making the tablets should not take this medication. Those patients who have a history of severe allergic reaction (anaphylaxis) to an array of allergens may not respond as usual to epinephrine when using carvedilol and should discuss this potentiality with their doctor before beginning carvedilol.

Patients with liver failure or cirrhosis (scarring of the liver) should not take carvedilol. Patients with kidney problems (renal failure) should be carefully monitored while taking carvedilol, especially when their dosage has been increased.

Side effects

Many of the side effects associated with carvedilol occur when the patient first begins taking the drug or when the dosage is changed. Some side effects associated with carvedilol are:

- bradycardia
- diarrhea or nausea
- fainting
- fatigue or weakness

- headache
- hypotension or postural hypotension (occurring when the patient stands)
- lessened tear production/dry eyes, which may be noticeable, especially in patients who wear contact lenses

Interactions

Patients should discuss with their doctor possible interactions between carvedilol and any other medications, vitamins, or supplements they are taking.

Drugs

Interactions may occur with numerous drugs. These include:

- catecholamine-depleting drugs (e.g., reserpine and monoamine oxidase inhibitors)
- **cyclosporine** (a medication used to prevent organ rejection in patients who have had transplants)
- digitalis glycosides (cardiovascular drugs)
- **rifampin** (used to treat tuberculosis and other infections)
- insulin and oral hypoglycemics (diabetes medications)

Herbs and supplements

No specific interactions are noted, but patients should still inform their doctor about any herbs or supplements they are taking.

Foods and other substances

No specific interactions are noted.

Resources

BOOKS

Joshi, Pranav, Mukesh Patel, and Natacarlal Patel. *Design and Development of Carvedilol Phosphate Floating Microsphere: Formulation and In Vitro Evaluation of Carvedilol Phosphate Floating Microsphere*. Saarbrücken, Germany: LAMBERT Academic Publishing, 2013.

Kaplan, Norman M., and Ronald G. Victor. "Treatment of Hypertension: Drug Therapy." In *Kaplan's Clinical Hypertension*. 11th ed. Philadelphia: Wolters Kluwer, 2015.

Mann, Samuel J. *Hypertension and You: Old Drugs, New Drugs, and the Right Drugs for Your High Blood Pressure*. Plymouth, UK: Rowman & Littlefield Publishers, 2012.

PERIODICALS

Armario, Pedro, and Bernard Waeber. "Therapeutic Strategies to Improve Control of Hypertension." *Journal of Hypertension* 31, suppl. 1 (2013): S9–S12.

Bosch, Jaime. "Carvedilol: The β -Blocker of Choice for Portal Hypertension?" *Gut* 62, no. 11 (2013): 1528–30.

Grinnan, Daniel, et al. "Treatment of Group I Pulmonary Arterial Hypertension with Carvedilol Is Safe." *American Journal of Respiratory and Critical Care Medicine* 189, no. 12 (2014): 1562–64.

OTHER

U.S. Food and Drug Administration. "Highlights of Prescribing Information: Coreg." http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020297s029lbl.pdf (accessed March 1, 2015).

WEBSITES

Bristol Laboratories Ltd. "Carvedilol." [Bristol-labs.co.uk](http://www.bristol-labs.co.uk/pages/pharmaceutical-product-details.aspx?BL=0&n=Carvedilol). <http://www.bristol-labs.co.uk/pages/pharmaceutical-product-details.aspx?BL=0&n=Carvedilol> (accessed February 4, 2015).

Buck, Marcia L. "Use of Carvedilol in Children with Cardiac Failure." *Medscape.com*. <http://www.medscape.com/viewarticle/500749> (accessed February 4, 2015).

"Carvedilol." *Drugs.com*. <http://www.drugs.com/carvedilol.html> (accessed February 4, 2015).

Mayo Clinic staff. "Carvedilol (Oral Route)." *MayoClinic.org*. <http://www.mayoclinic.org/drugs-supplements/carvedilol-oral-route/description/drg-20067565> (accessed February 4, 2015).

MedlinePlus. "Carvedilol." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a697042.html> (accessed February 4, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org/>.

American Society of Hypertension, 45 Main Street, Suite 712, Brooklyn, NY 11201, (212) 696-9099, Fax: (347) 916-0267, <http://www.ash-us.org/>.

National Heart, Lung, and Blood Institute Health Information Center, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, Fax: (301) 592-8563, nhlbiinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov/>.

Leslie A. Mertz, PhD

REVIEWED BY JAMES E. WAUN, MD, RPH

Catapres see **Clonidine**

Ceclor see **Cefaclor**

Cefaclor

Definition

Cefaclor is an antibiotic drug in the family of cephalosporin drugs, used mainly to treat bacterial infections.

Purpose

Cefaclor is used to treat bacterial infections—primarily of the ears, lungs, sinuses, skin, and urinary tract—that are sensitive to cephalosporin drugs. Cefaclor fights bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Streptococcus pyogenes*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella*-type bacteria, *Staphylococcus aureus*, and *Streptococcus pyogenes*.

Description

Cefaclor is available in tablet, capsule, and liquid-suspension forms. The medication is taken by mouth and must be prescribed by a physician. Cefaclor is used internationally and is also frequently used in veterinary medicine.

Cefaclor is available in the following forms and strengths:

- capsules, various colors: 250 or 500 milligrams (mg)
- extended-release tablets: 500 mg
- liquid suspension: 125 mg, 250 mg, or 375 mg of active drug per 5 milliliters (mL); reconstitutes to a pink, strawberry-flavored suspension

U.S. brand names

Cefaclor is sold under the brand name Ceclor. It is also manufactured as a generic by many different companies.



Cefaclor, 250 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Canadian brand names

Cefaclor is sold as Apo-Cefaclor, Ceclor, Novo-Cefaclor, Nu-Cefaclor, and PMS-Cefaclor in Canada.

International brand names

Cefaclor is sold under several hundred brand names internationally, including:

- Acef (Pakistan)
- Alfatil (France)
- Articlор (India)
- Camirox (Greece)
- Ceclomek (Peru)
- Keftid (Ireland)
- Losefar (Turkey)
- Vercef (South Africa)

In some countries, cefaclor is only one component of the medication, and there are other medications included in the formulation. In some locations, it is available only for veterinary, not human, use.

Recommended dosage

Recommended dosages are based on the amount of cefaclor needed to treat the infection. In general, recommended adult dosages are 250–500 mg every 8 hours. Other dosing formats may be followed for specific infections or circumstances.

Pediatric

- Children over one month in age are usually dosed 20–40 mg per kilogram (kg, or 2.2 lb.) of body weight per day, divided into two doses given every 12 hours or three doses given every 8 hours. The maximum dose for this age range should not exceed 1 gram per day.
- For ear infections, the dosage should be 40 mg/kg/day, divided into two doses given 12 hours apart.
- For throat infections, the dosage should be 20 mg/kg/day, divided into two doses given 12 hours apart.

Adolescents usually follow adult dosing. However, children under the age of 16 should not be given the extended-release tablets. Other dosing formats may be followed for specific infections or circumstances.

Other conditions and allergies

Patients with impaired kidney function may require a smaller dose of cefaclor. Kidney function is measured by something called creatinine clearance, which measures the amount of creatinine in urine. Creatinine is a waste product excreted by the kidneys. Creatinine clearance is normally 97–137 mL/minute in men and

KEY TERMS

Anaphylaxis—A severe, systemic allergic reaction that can be potentially life threatening.

Creatinine clearance—A test of kidney function that compares the amount of creatinine in the blood to the amount of creatinine in the urine.

Pregnancy category—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk, but no human studies exist, or adverse effects have been seen in animals but not in well-controlled human studies. Category C: No adequate human or animal studies exist, or adverse fetal effects have been seen in animal studies but there is no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk, and risks outweigh any benefits.

88–128 mL/minute in women. If creatinine clearance is 10–50 mL/minute, 50%–100% of the dose of cefaclor should be administered. If creatinine clearance is less than 10 mL/minute, only half of the normal dose should be given.

Precautions

The following precautions apply to all individuals:

- This drug should be taken for the entire length of the prescription, even if symptoms subside. Failure to take a complete course of the medication can result in return of symptoms.
- Cefaclor can be taken with or without food.
- Individuals with a history of kidney problems or on dialysis should tell their doctor before taking this drug. A dosage reduction may be necessary.
- Use of cefaclor over an extended period of time can increase the risk of developing another fungal or bacterial infection (secondary infection).
- Women using **oral contraceptives** should discuss alternative forms of birth control with their doctors, as this drug can interfere with the effectiveness of birth control pills.
- Cefaclor may make the skin more sensitive to sun exposure and tanning lights, resulting in more easily (and potentially severely) burned skin.
- *C. difficile*—associated diarrhea and pseudomembranous colitis have both been associated with long-term use of

cefaclor, even months after the drug has been discontinued.

Pregnant or breastfeeding

Cefaclor is in the U.S. Food and Drug Administration (FDA) pregnancy category B classification, meaning that animal studies have not demonstrated a risk to a fetus, but the drug has not been adequately studied in pregnant women. Women who are pregnant or breastfeeding should tell their doctor before taking cefaclor. This drug can pass into breast milk, and there has not been adequate study of its effects on nursing infants.

Other conditions and allergies

Individuals who are allergic to cefaclor or any cephalosporin drugs—such as cefuroxime (Ceftin), **cefprozil** (Cefzil), cephalexin (Keflex), and **cefdinir** (Omnicef)—should not take cefaclor. Cefaclor should be prescribed cautiously to individuals who have had significant allergic reactions (e.g., hives, anaphylaxis) to penicillin-type drugs.

Individuals with a history of severe allergies, asthma, and prior drug reactions involving anaphylaxis, hives, or severe swelling (angioedema) are at higher risk for serious reactions to cefaclor.

Side effects

Serious and sometimes fatal reactions can occur in individuals who are allergic to penicillin and penicillin-like drugs. Anyone who has had a severe reaction to any drug should alert their physician before taking cefaclor. Symptoms of a severe allergic reaction include difficult breathing or swallowing or a severe skin rash or hives. Any troubling symptoms should be reported to a physician.

The most common adverse side effects of cefaclor for all age groups tend to be mild. They include:

- upset stomach
- loose stools or diarrhea
- nausea and vomiting

These side effects should be brought to the doctor's attention if they do not go away within a few days.

Whitish vaginal discharge or white coating of the tongue and inside of the mouth should also be reported to the doctor.

Interactions

Pharmaceutical drugs may interact with other drugs, herbal and dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness

of the drug or increase the risk of serious side effects. Patients should tell the prescribing doctor about any medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Cefaclor is known to interact with the following pharmaceutical drugs. Other interactions are possible. Patients who develop any unusual or unexpected symptoms should contact a physician.

- Cephalosporins may increase the blood levels or toxic effects of aminoglycoside antibiotics and vitamin K antagonists (such as warfarin).
- Cephalosporins may decrease the blood levels or effectiveness of the bacillus Calmette–Guérin (BCG) vaccine, sodium picosulfate, and the typhoid vaccine.
- Blood levels and toxic effects of cephalosporins may be increased by probenecid (a drug typically used for the treatment of conditions caused by excess uric acid in the body).

Resources

BOOKS

- Bennett, John E., Raphael Dolin, and Martin J. Blaser. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia: Saunders, 2014.
- Cherry, James, et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Saunders, 2014.
- Drug Information Handbook*. 23rd ed. Hudson, OH: Lexicomp, 2014.
- Magill, Alan, et al. *Hunter's Tropical Medicine and Emerging Infectious Diseases*. Philadelphia: Saunders, 2013.
- Rang, Humphrey, et al. *Rang and Dale's Pharmacology*. 7th ed. London: Churchill Livingstone, 2012.

WEBSITES

- AHFS Consumer Medication Information. "Cefaclor." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682729.html> (accessed February 4, 2015).
- "Cefaclor." Drugs.com. <http://www.drugs.com/mtm/cefaclor.html> (accessed February 4, 2015).
- U.S. Food and Drug Administration. "Cefaclor." <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=CEFACTOR> (accessed February 4, 2015).
- U.S. National Library of Medicine. "Cefaclor." DailyMed.gov. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=447da05c-c90f-40eb-a8d9-3e8c69e19c00> (accessed February 4, 2015).
- U.S. National Library of Medicine. Drugs and Lactation Database (LactMed). <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm> (accessed February 9, 2015).

ORGANIZATIONS

American Society of Health-System Pharmacists, 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rosalyn S. Carson-DeWitt, MD

REVIEWED BY JAMES E. WAUN, MD, RPh

Cefalexin see **Cephalexin**

Cefdinir

Definition

Cefdinir is an antibiotic drug in the family of cephalosporin drugs. It belongs to the group referred to as third-generation cephalosporins.

Purpose

Cefdinir is used to treat bacterial infections such as ear infections, chronic bronchitis, throat infections/tonsillitis, sinus infections, community-

acquired pneumonia, and skin infections. Cefdinir is active against bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Streptococcus pyogenes*.

Description

Cefdinir is available in tablet, capsule, and liquid-suspension forms. The medication is taken by mouth and must be prescribed by a physician. Cefdinir is used internationally and is also frequently used in veterinary medicine.

Cefdinir is available in the following forms and strengths:

- Capsules, various colors: 300-milligram (mg) strength available. The printing on the capsule varies with the manufacturer.
- Liquid suspension: When mixed with water, the formula reconstitutes to a pink, strawberry-flavored suspension. The dosage strength per 5 milliliters (mL) of liquid includes either 125 mg or 250 mg of the active drug.

U.S. brand names

Cefdinir is currently sold as a generic by a variety of companies. It was previously sold under the brand name Omnicef.

International brand names

Cefdinir is sold under a number of different brand names internationally. In many countries, the drug is still sold under the name Omnicef. In some countries, cefdinir is only one component of the medication, and there are other medications included in the formulation. In some locations, it is available only for veterinary, not human, use.

Recommended dosage

Recommended dosages are based on the amount of cefdinir needed to treat the infection. In general, recommended adult dosages are 300 mg taken twice a day for 5 to 10 days, or 600 mg taken once a day for 10 days. Other dosing formats may be followed for specific infections or circumstances.

Pediatric

Children older than six months in age are usually dosed with 7 mg per kilogram (kg, or 2.2 lb.) of body weight, given twice a day for 5 to 10 days, or 14 mg/kg, given once a day for 10 days, with a maximum dosage of 600 mg/day. Adolescents (approximately 12–17 years)



Cefdinir, 300 mg. (© Cengage Learning®)

KEY TERMS

Anaphylaxis—A severe, systemic allergic reaction that can be potentially life threatening.

Antibiotic—A drug used to treat infections caused by bacteria and other microorganisms.

Creatinine clearance—A test of kidney function that compares the amount of creatinine in the blood to the amount of creatinine in the urine.

Penicillin—An antibiotic that is used to treat bacterial infections.

usually follow adult dosing. Other dosing formats may be followed for specific infections or circumstances.

Other conditions and allergies

Kidney functioning is measured by a test called creatinine clearance. Creatinine is a waste product excreted by the kidneys in the urine; if levels are low, the kidneys are not functioning properly. The normal range for creatinine clearance is 97–137 mL/minute in men and 88–128 mL/minute in women. If creatinine clearance is greater than or equal to 30 mL/minute, a normal dose of cefdinir may be administered. If creatinine clearance is less than 30 mL/minute, the maximum dose taken per day should be reduced to 300 mg for both adults and children. This reduction is necessary because the kidneys are not flushing the drug from the system as quickly as usual, which can lead to toxic buildup if the normal dose is continued.

Precautions

The following precautions apply to all individuals:

- This drug should be taken for the entire length of the prescription. Failure to take a complete course of the medication can result in return of symptoms.
- Cefdinir can be taken with or without food.
- Individuals with a history of kidney problems or on dialysis should tell their doctor before taking this drug. Dosage reduction may be necessary.
- Use over a long period of time can increase the risk of developing another fungal or bacterial infection.
- *C. difficile*—associated diarrhea and pseudomembranous colitis have both been associated with long-term use of cefdinir, even months after the drug has been discontinued.
- Women using oral birth control should discuss alternative forms of contraception with their doctors, as this

drug can interfere with the effectiveness of the birth control pill.

- Cefdinir may make the skin more sensitive to sun exposure and tanning lights, resulting in more easily (and potentially severely) burned skin.

Pregnant or breastfeeding

Cefdinir is in the U.S. Food and Drug Administration (FDA) pregnancy category B, meaning that animal studies have not demonstrated a risk to the fetus, but the drug has not been adequately studied in pregnant women. Women who are pregnant or breastfeeding should tell their doctor before taking cefdinir. This drug can pass into breast milk, and there has not been adequate study of the effects on nursing infants.

Other conditions and allergies

Individuals who are allergic to cefdinir or any other cephalosporin drugs, including cefuroxime (Ceftin), **cefprozil** (Cefzil), cephalexin (Keflex), and **cefactor** (Ceclor), should not take cefdinir, and cefdinir should be prescribed cautiously to individuals who have had significant allergic reactions (e.g., hives, anaphylaxis) to penicillin-type drugs. Serious and sometimes fatal reactions can occur in individuals who are allergic to penicillin and penicillin-like drugs.

Individuals with a history of severe allergies, asthma, and prior drug reactions involving anaphylaxis, hives, or severe swelling (angioedema) are at higher risk for serious reactions to cefdinir. Anyone who has had a severe reaction to any drug should alert their physician before taking this drug.

Side effects

The most common adverse side effects of cefdinir for all age groups tend to be mild. They include:

- upset stomach
- loose stools or diarrhea
- nausea and vomiting
- headache

These side effects should be brought to the doctor's attention if they do not go away within a few days. Whitish vaginal discharge or white coating of the tongue and inside of the mouth should also be reported to the doctor.

A doctor should be notified immediately if any of these less common but more serious side effects occur:

- wheezing, difficulty breathing, or swallowing—may indicate a severe allergic reaction and require immediate medical attention

- severe skin rash, itching, blistering, peeling, or hives
- swelling
- yellowing of the skin or the whites of the eyes
- vaginal inflammation, itching, or discharge
- seizures
- abdominal pain with fever
- dizziness, fainting
- severe watery or bloody diarrhea, even if it occurs two months after ending treatment
- easy bruising or bleeding
- very dark urine
- numbness, tingling
- confusion, hallucinations

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients should tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Cefdinir is known to interact with the following pharmaceutical drugs. Other interactions are possible. Patients who develop any unusual or unexpected symptoms should contact a physician.

- Cephalosporins may increase the blood levels and toxic effects of aminoglycoside antibiotics and vitamin K antagonists (such as warfarin).
- Cephalosporins may decrease the blood levels and effectiveness of the bacillus Calmette–Guérin (BCG) vaccine, sodium picosulfate, and the typhoid vaccine.
- Blood levels and toxic effects of cephalosporins may be increased by probenecid (a drug typically used for the treatment of conditions caused by excess uric acid in the body).

Herbs and supplements

Blood levels and the effectiveness of cefdinir may be reduced by administering the drug with iron salts or multivitamin/mineral supplements. In the presence of iron-containing supplements, patients may notice red-colored stool; while this causes the stool to appear bloody, it is actually an insoluble complex formed by cefdinir and iron.

Resources

BOOKS

- Bennett, John E., Raphael Dolin, and Martin J. Blaser. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia: Saunders, 2014.
- Cherry, James, et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Saunders, 2014.
- Lexicomp. *Drug Information Handbook*. 23rd ed. Hudson, OH: Lexicomp Inc., 2014.
- Magill, Alan, et al. *Hunter's Tropical Medicine and Emerging Infectious Diseases*. Philadelphia: Saunders, 2013.
- Rang, Humphrey, et al. *Rang and Dale's Pharmacology*. 7th ed. London: Churchill Livingstone, 2012.

WEBSITES

- MedlinePlus. "Cefdinir." <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a698001.html> (accessed February 5, 2015).
- U.S. Food and Drug Administration. "Cefdinir." <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=CEFIDINIR> (accessed February 5, 2015).
- U.S. National Library of Medicine. "Cefdinir—Cefdinir Capsule." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=df26edb0-9bd6-449c-a187-0be0c9e2600c> (accessed February 5, 2015).
- U.S. National Library of Medicine. "LactMed: Cefdinir." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+44> (accessed March 1, 2015).

ORGANIZATIONS

- American Society of Health-System Pharmacists, 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rosalyn Carson-DeWitt, MD

REVIEWED BY JAMES WAUN, RPH

Cefixime

Definition

Cefixime is a semisynthetic antibiotic of the cephalosporin class; it is considered a third-generation cephalosporin. It is a bactericidal, which means that it kills bacteria.

Purpose

Cefixime is used to treat infections caused by susceptible bacteria, including:



Suprax (cefixime), 400 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

- acute bronchitis and acute exacerbations of chronic bronchitis
- otitis media
- tonsillitis and pharyngitis
- uncomplicated gonorrhea
- sexually transmitted diseases (STDs)
- urinary tract infections (UTIs)

Cefixime was previously used as a first-line treatment for gonorrhea and other STDs but has become increasingly less effective in treating these conditions. It is now used primarily when another antibiotic, ceftriaxone, is unavailable or cannot be used by the patient. Cefixime may still be used as part of a multidrug preventative (prophylactic) regimen in victims of sexual assault.

Description

Cefixime is administered orally (by mouth).

U.S. brand names

In the United States, cefixime is sold under the brand name Suprax. It is available in the following formulations:

- chewable tablets, 100 and 200 milligrams (mg)
- capsules, 400 mg
- oral suspension for reconstitution, 100 mg/5 milliliters (mL), 200 mg/5 mL, 500 mg/5 mL

Canadian brand names

Cefixime is readily available in its generic formulation in Canada.

International brand names

Cefixime is readily available in its generic formulation internationally.

Origins

Cefixime was originally marketed by Wyeth Laboratories under the brand name Suprax. The product was discontinued after the patent expired. Lupin Pharmaceuticals is the sole supplier of cefixime in the United States.

Recommended dosage

For treatment of uncomplicated gonorrhea or uncomplicated urinary tract infections, the U.S. Centers for Disease Control and Prevention (CDC) provides guidelines for treating sexually transmitted and related infections. For other approved indications, the normal dose is 400 mg by mouth once per day or 200 mg twice per day at 12-hour intervals.

Pediatric

Cefixime is not approved for use in children under the age of six months. Although there have been reports of use of the drug in children as young as two months, there is no proven benefit for administering the drug to children in place of others that have been studied more extensively and may be available at lower cost.

In children 6 months to 12 years weighing up to 50 kilograms (kg, or 2.2 lb.), a typical dose is 8 mg/kg/day given orally in a single dose or in two divided doses at 12-hour intervals. Over the age of 12, 400 mg/day is given in a single dose or in two divided doses at 12-hour intervals.

Geriatric

There is no other age-specific dosing schedule; geriatric dosages follow those of adults, although adjustments may be needed based on overall health status and the use of other medications.

Other conditions and allergies

Cefixime dosage should be reduced in patients with kidney disease or other sources of renal (kidney) impairment. The revised dose depends on the amount of creatinine passed in the patient's urine (CrCl, or creatinine clearance). Creatinine is a waste material that

KEY TERMS

Antibiotic—A substance that is toxic to bacterial cells but not to cells of higher animals.

Cephalosporin—Any of a group of broad-spectrum, penicillinase-resistant antibiotics derived from the natural antibiotic cephalosporin C. They are usually divided into generations based on their activity against different types of bacteria.

Penicillin—An antibiotic that is used to treat bacterial infections.

Prothrombin—A type of protein (called a glycoprotein) that is involved in the blood-clotting process.

Sexually transmitted disease (STD)—A disease that is passed from one person to another through sexual intercourse or other intimate sexual contact; also referred to as a sexually transmitted infection (STI).

is filtered out of the body by the kidneys. Measuring the amount of creatinine in a patient's urine helps determine kidney function.

- CrCl > 60 mL/min: dosage adjustment not necessary
- CrCl 21–60 mL/min: 260 mg/day as one dose or as two divided doses at 12-hour intervals
- CrCl < 20 mL/min: 200 mg/day as one dose or as two divided doses at 12-hour intervals

Precautions

Bacterial or fungal overgrowth of nonsusceptible organisms may occur with prolonged or repeated therapy. This includes the risk of *Clostridium difficile*-associated diarrhea, which has been known to be fatal, especially in children.

Cephalosporins have been associated with a drop in prothrombin activity, which means that it takes longer for blood to clot. Patients most at risk include individuals with liver or kidney problems, people with inadequate nutrition, and people taking anticoagulant drugs (blood thinners) such as **warfarin**. Vitamin K may be administered to help support blood clotting.

Because cefixime can cause stomach upset, it should normally be taken with food or milk. This will delay the absorption of the drug by about an hour but will not reduce its effectiveness.

Pregnant or breastfeeding

Cefixime has been assigned to pregnancy category B by the U.S. Food and Drug Administration (FDA). This means that although there have been no adequate studies in pregnant women, studies in animals suggest that the drug does not adversely affect a fetus.

According to the U. S. National Library of Medicine, there have been some reports of diarrhea and thrush in infants whose mothers are breastfeeding while taking cefixime; however, it is considered safe to use when nursing.

Other conditions and allergies

Cefixime should not be used in patients who are allergic to cefixime or other cephalosporins. Both cephalosporins and penicillins have a common structural feature, so it is recommended that cephalosporins also be avoided in patients with a penicillin allergy. However, a 2014 paper published in the *Journal of Investigational Allergology and Clinical Immunology* reported that the risk of reaction is lower for second- and third-generation cephalosporins than for first-generation drugs. Even so, care should be exercised when dealing with patients with penicillin allergies.

High doses or drug accumulation through use in patients with renal insufficiency may cause toxicity to the central nervous system (CNS). If seizures appear, use should be discontinued, and anticonvulsant medications may be given if appropriate.

Side effects

Side effects are primarily related to gastrointestinal discomfort and may include:

- gastrointestinal adverse reactions
- diarrhea
- loose or frequent stools
- abdominal pain
- nausea
- upset stomach
- excess gas

Other side effects have been reported but are rare and are not always clearly caused by taking cefixime. Dizziness, headaches, and seizures have been observed and are associated with high blood levels of the drug. Severe allergic reactions have been reported, including anaphylactic shock and fatalities. Milder allergic reactions include skin rash and itching. Acute kidney failure and other kidney problems have been reported.

Interactions

Individuals should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs or supplements, before starting treatment with cefixime.

Drugs

Cefixime may reduce the effectiveness of live vaccines, notably bacillus Calmette–Guérin (BCG) and typhoid vaccines.

Cefixime reduces the effectiveness of the estrogen and estrogenic hormones (such as those used in **oral contraceptives**).

The drug probenecid, used to treat gout, may increase the blood levels of cefixime and increases the risk of adverse reactions.

There are a number of other reported interactions, but they appear to be minor and of no clinical significance.

Herbs and supplements

There have been reported interactions with rose hip and willow bark, but these have been minor and are not considered to hold clinical significance.

Resources

BOOKS

Drug Facts and Comparisons 2013. Philadelphia: Wolters Kluwer Health, 2013.

PERIODICALS

Callero, A., et al. "Tolerance to Cephalosporins in Nonimmediate Hypersensitivity to Penicillins in Pediatric Patients." *Journal of Investigational Allergology and Clinical Immunology* 24, no. 2 (2014): 122–41.

Ison, C. A., C. Deal, and M. Unemo. "Current and Future Treatment Options for Gonorrhoea." *Sexually Transmitted Infections* 89, suppl. 4 (December 2013): 52–56.

Lewis, D. A. "Global Resistance of *Neisseria Gonorrhoeae*: When Theory Becomes Reality." *Current Opinion in Infectious Diseases* 27, no. 1 (February 2014): 62–67.

OTHER

Centers for Disease Control and Prevention. *Gonorrhea Treatment Guidelines*. <http://www.cdc.gov/nchhstp/newsroom/docs/2012/GonorrheaTreatmentGuidelinesFactSheet8-9-2012.pdf> (accessed November 24, 2014).

U.S. Food and Drug Administration. *Highlights of Prescribing Information (Suprax)*. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203195s000lbl.pdf (accessed November 24, 2014).

WEBSITES

AHFS Consumer Medication Information. "Fluoxymesterone." American Society of Health-System Pharmacists.

Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a690007.html> (accessed November 24, 2014).

Centers for Disease Control and Prevention. "Sexually Transmitted Diseases (STDs)." <http://www.cdc.gov/std/treatment/default.htm> (accessed November 24, 2014).

ORGANIZATIONS

American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, IL 60007-1098, (847) 434-4000, Fax: (847) 434-8000, (800) 433-9016, <http://www.aap.org/>.

American Sexually Transmitted Diseases Association, 1005 Slater Road, Suite 330, Durham, NC 27709, <http://www.astda.org/>.

Infectious Diseases Society of America, 1300 Wilson Boulevard, Suite 300, Arlington, VA 22209, (703) 299-0200, Fax: (703) 299-0204, <http://www.idsociety.org/>.

National Foundation for Infectious Diseases, 7201 Wisconsin Avenue, Suite 750, Bethesda, MD 20814, (301) 656-0003, Fax: (301) 907-0878, <http://www.nfid.org/>.

Samuel D. Uretsky, PharmD

REVIEWED BY JAMES E. WAUN, MD, RPh

Cefprozil

Definition

Cefprozil is a second-generation cephalosporin antibiotic.

Purpose

In adults, cefprozil is used to treat:

- pharyngitis and tonsillitis
- respiratory tract infections
- skin infections

In children, it is indicated for the treatment of:

- acute otitis media
- acute sinusitis
- pharyngitis and tonsillitis
- skin infections

Description

Cefprozil is an antibiotic of the cephalosporin class. It kills susceptible bacteria (bactericidal). Cefprozil is considered a second-generation cephalosporin, which means that it is somewhat more effective against some gram-negative bacteria than older (first-generation)



Cefprozil (oral suspension). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

cephalosporins, although it may be less effective against gram-positive bacteria. Cefprozil does not cross the blood-brain barrier.

U.S. brand names

Cefprozil was formerly marketed as Cefzil by Bristol Myers Squibb, but the branded product has been discontinued. It is available in generic formulations.

Recommended dosage

It is important to continue taking antibiotics for the full dosage cycle even after symptoms have cleared. Dosing varies based on age and condition being treated.

Adult

PHARYNGITIS AND TONSILLITIS. To treat pharyngitis and tonsillitis caused by the bacterium *Streptococcus pyogenes*, 500 milligrams (mg) is taken orally every day for ten days.

RESPIRATORY TRACT INFECTIONS. To treat respiratory tract infections such as bronchitis, 250–500 mg is taken by mouth every 12 hours for ten days.

SKIN INFECTIONS. To treat skin infections, 250–500 mg may be taken every 12 hours or 500 mg once per day for ten days.

KEY TERMS

Antibiotic—A chemical substance produced by a microorganism, which has the capacity to inhibit the growth of or to kill other microorganisms; antibiotics sufficiently nontoxic to the host are used in the treatment of infectious diseases.

Bactericidal—An agent that kills bacteria as opposed to one that simply inhibits bacterial growth.

Cephalosporin—The cephalosporins are a class of antibiotics originally derived from the fungus *Acremonium*. They are chemically related to penicillin.

Prothrombin—A type of protein (called a glycoprotein) that is involved in the blood-clotting process.

Pediatric

Cefprozil is not indicated for use in infants under the age of six months. Although there have been published studies dealing with the use of cephalosporins in newborn infants, there does not appear to be any indication that it should be used in younger infants.

ACUTE OTITIS MEDIA. To treat ear infections caused by otitis media, children aged 6 months to 12 years may be given 30 mg per kilogram (kg, or 2.2 lb.) per day in two divided doses every 12 hours for ten days.

ACUTE SINUSITIS. To treat acute sinus infections, children aged 6 months to 12 years may be given 30 mg/kg/day in two divided doses every 12 hours for ten days.

PHARYNGITIS AND TONSILLITIS. To treat pharyngitis and tonsillitis, children 2–12 years old may be given 15 mg/kg/day in two divided doses every 12 hours for ten days.

SKIN INFECTIONS. To treat skin infections, children 2–12 years old may be given 20 mg/kg/day for ten days.

Geriatric

There are no age-related dose adjustments required for elderly patients, although adjustments may be needed based on overall health status or use of other medications.

Other conditions and allergies

In patients with kidney problems, dosages may need to be reduced by up to 50%.

Precautions

Penicillins and cephalosporins both have a similar composition, so it has typically been standard practice to avoid using cephalosporins in patients with penicillin allergies. However, there is a growing body of research indicating that it is safe to administer second- and third-generation cephalosporins to patients allergic to penicillin; doubt remains about the safety of first-generation cephalosporins. A 2012 study published in the *International Archives of Allergy and Immunology* reported that out of 173 pediatric subjects with penicillin allergies, only one had an adverse reaction to cephalosporins.

A 2007 study conducted by the University of Rochester Medical Center and published in *Diagnostic Microbiology and Infectious Disease* concluded that “first-generation cephalosporins have a modest cross-allergy with penicillins, but cross-allergy is negligible with 2nd- and 3rd-generation cephalosporins.” Another review that appeared in the *Journal of Family Practice* reported, “The widely quoted cross-allergy risk of 10% between penicillin and cephalosporins is a myth. Cephalothin, **cephalexin**, cefadroxil, and cefazolin confer an increased risk of allergic reaction among patients with penicillin allergy. Cefprozil, cefuroxime, cefpodoxime, ceftazidime, and ceftriaxone do not increase risk of an allergic reaction.”

As with all broad-spectrum antibiotics, there is a risk of overgrowth of nonsusceptible organisms. This is greatest with high doses or prolonged use or with high-dose use in patients with renal (kidney) insufficiency. This may also lead to reduced prothrombin levels, which is associated with prolonged blood-clotting time.

Cephalosporins have been known to cause central nervous system (CNS) problems, including convulsions.

Pediatric

Safety and efficacy in pediatric patients below the age of six months have not been established for the treatment of otitis media or acute sinusitis or below the age of two years for the treatment of pharyngitis/tonsillitis or uncomplicated skin infections.

While there have been anecdotal reports on the use of cefprozil on infections other than those specifically indicated, there does not appear to be any evidence

favoring the use of the drug in children below the indicated ages.

Pregnant or breastfeeding

Cefprozil has been placed in category B by the U.S. Food and Drug Administration (FDA) for use during pregnancy. Category B means either that there have been no studies in humans but animal studies have found the drug to have no impact on a fetus or that animal studies have shown minor risks but human studies have resulted in no adverse effects to a fetus. The drug is also considered safe to use when breastfeeding.

Other conditions and allergies

Dose should be reduced in patients with renal insufficiency.

For patients with phenylketonuria, the oral suspension is sweetened with aspartame and should be avoided.

Side effects

Cefprozil is usually well tolerated. The most serious side effects are usually signs of an allergic reaction or the result of overdosing. The most commonly seen adverse effects are:

- nausea
- diarrhea
- elevated liver function test results
- diaper rash
- abdominal pain
- dizziness
- vomiting

Interactions

Drugs

Concurrent use of probenecid (Benemid), used to treat gout, may raise the levels of cefprozil in the blood.

Cefprozil may also reduce the effectiveness of live vaccines such as bacillus Calmette–Guérin (BCG), used to prevent tuberculosis.

Herbs and supplements

There are no reported interactions with herbs or dietary supplements, but patients should inform their healthcare providers of any herbs or supplements they are taking before starting treatment with cefprozil.

Food and other substances

Food will slow down the absorption of cefprozil but will not reduce its effectiveness. Cefprozil may be taken with food in order to reduce the risk of upset stomach.

Resources

BOOKS

Drug Facts and Comparisons. Philadelphia: Wolters Kluwer Health, 2013.

PERIODICALS

Harrison, C. J., et al. "Susceptibilities of *Haemophilus Influenzae*, *Streptococcus Pneumoniae*, Including Serotype 19A, and *Moraxella Catarrhalis* Paediatric Isolates from 2005 to 2007 to Commonly Used Antibiotics." *Journal of Antimicrobial Chemotherapy* 63, no. 3 (March 2009): 511–19.

Kamran, A., et al. "Clinical Outcome in the Use of Cephalosporins in Pediatric Patients with a History of Penicillin Allergy." *International Archive of Allergy and Immunology* 158 (2012): 405–10.

Pichichero, M. E. "A Review of Evidence Supporting the American Academy of Pediatrics Recommendation for Prescribing Cephalosporin Antibiotics for Penicillin-Allergic Patients." *Pediatrics* 115, no. 4 (April 2005): 1048–57.

Pichichero, M. E. "Cephalosporins Can Be Prescribed Safely for Penicillin-Allergic Patients." *Journal of Family Practice* 55, no. 2 (February 2006): 106–12.

Pichichero, M. E. "Use of Selected Cephalosporins in Penicillin-Allergic Patients: A Paradigm Shift." *Diagnostic Microbiology and Infectious Disease* 57, no. 3 suppl. (March 2007): 13S–18S.

WEBSITES

AHFS Consumer Medication Information. "Cefprozil (Oral Route)." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a698022.html> (accessed December 10, 2014).

LactMed. Toxnet, U.S. National Library of Medicine, National Institutes of Health. <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm> (accessed December 7, 2014).

Mayo Clinic staff. "Cefprozil (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/cefprozil-oral-route/description/drg-20073353> (accessed December 9, 2014).

ORGANIZATIONS

Infectious Diseases Society of America, 1300 Wilson Boulevard, Suite 300, Arlington, VA 22209, (703) 299-0200, Fax: (703) 299-0204, <http://www.idsociety.org/>.

National Foundation for Infectious Diseases, 7201 Wisconsin Avenue, Suite 750, Bethesda, MD 20814, (301) 656-0003, Fax: (301) 907-0878, <http://www.nfid.org/>.

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Cefzil see **Cefprozil**

Celebrex see **Celecoxib**

Celecoxib

Definition

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID). It belongs to a class of drugs called cyclooxygenase 2 (COX-2) inhibitors.

Purpose

Celecoxib is used mainly to treat the pain, inflammation, and soreness of osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, and ankylosing spondylitis. It is also used to treat menstrual pain and pain from dental and surgical procedures. Celecoxib works by blocking enzymes needed to produce prostaglandins. Prostaglandins are substances the body makes that cause pain and inflammation.

Off-label use

Celecoxib has been prescribed for off-label (legal but nonapproved) uses in treating schizophrenia, major depression, bipolar disorder, and polyps in the colon (large intestine).



Celecoxib, 100 mg. (© Cengage Learning®)

KEY TERMS

Ankylosing spondylitis—A type of arthritis that causes gradual loss of flexibility in the spinal column. It occurs most commonly in males between the ages of 16 and 35 and may be initiated by a food allergy component, such as an allergy to wheat.

Osteoarthritis (OA)—The most common form of arthritis, characterized by erosion of the cartilage layer that lies between the bones in weight-bearing joints. It occurs mainly in older people. OA is also known as degenerative joint disease (DJD).

Off-label use—Drugs in the United States are approved by the U.S. Food and Drug Administration (FDA) for specific uses, periods of time, or dosages based on the results of clinical trials. However, it is legal for physicians to administer these drugs for other uses, termed “off-label” or nonapproved uses. It is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Pregnancy category—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk, but no human studies exist, or adverse effects have been seen in animals but not in well-controlled human studies. Category C: No adequate human or animal studies exist, or adverse fetal effects have been seen in animal studies but there is no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk. Risks outweigh any benefits.

Prostaglandins—Prostaglandins are produced by the body and are responsible for inflammation features, such as swelling, pain, stiffness, redness and warmth, as well as being involved in smooth muscle contractions.

Rheumatoid arthritis—An autoimmune disease characterized by inflammation and degeneration of connective tissue in multiple joints at a young age. It also can affect additional organ systems.

Description

Celebrex is a white capsule taken orally (by mouth). It can be taken with or without food. Each capsule has two colored bands. One band contains the number 7767,

while the other indicates the strength of the capsule as follows:

- orange band, 50 milligrams (mg)
- blue band, 100 mg
- yellow band, 200 mg
- green band, 400 mg

U.S. brand names

Celecoxib is marketed under the brand name Celebrex. The drug is under patent in the United States, and as of early 2015, no generic version was available.

International brand names

In some overseas countries, such as the Philippines, a generic version of celecoxib is legally produced.

Origins

Celecoxib was developed by G. D. Searle & Company and Pfizer. It was first approved by the U.S. Food and Drug Administration (FDA) in 1998.

Recommended dosage

The recommended dosage depends on the disease for which celecoxib is prescribed, as follows:

- osteoarthritis: 100 mg twice daily or 200 mg once daily
- rheumatoid arthritis: 100–200 mg twice daily
- juvenile rheumatoid arthritis: for children weighing 22–55 lb. (10–25 kg), 50 mg twice daily; for children over 55 lb. (25 kg), 100 mg twice daily
- ankylosing spondylitis: 100 mg twice daily or 200 mg once daily, increasing to 400 mg daily if lower doses do not produce adequate relief
- pain relief: one dose of 400 mg followed if necessary by a dose of 200 mg, then 200 mg on subsequent days

Other conditions and allergies

Individuals with moderate liver damage should have the dosage reduced by 50%. Individuals with severe liver damage should not take celecoxib.

Precautions

After celecoxib was approved, questions arose about the safety of all COX-2 inhibitor drugs. The FDA now requires all NSAID drugs, including celecoxib, to carry a use warning:

- Use of celecoxib may cause increased blood clotting that can result in serious or fatal stroke or heart attack;

risk increases with length of use. Individuals who already have cardiovascular disease or risk factors for cardiovascular disease may be at higher risk.

- Celecoxib should not be used to treat pain after coronary artery bypass graft (CABG) surgery.
- Celecoxib can, at any time and without warning, cause serious and sometimes fatal gastrointestinal bleeding, ulcers, and perforation of the stomach or intestines; the elderly are at greatest risk.

In addition to heeding the FDA use warnings, individuals should take the following precautions before taking celecoxib:

- Individuals should tell their doctor if they have had an allergic reaction to celecoxib, **aspirin**, or other NSAIDs such as ibuprofen (Advil, Motrin) and naproxen (Aleve, Naprosyn) or sulfa medications.
- Individuals should make their doctor aware of any history of asthma, liver disease, gastrointestinal problems, heart disease, high blood pressure, stroke, bleeding disorders, anemia, or growths in the nose.
- Women should tell their doctor if they are pregnant, trying to become pregnant, or breastfeeding. The drug should be used only when essential during pregnancy.
- When taking celecoxib, individuals should drink plenty of water to stay hydrated and reduce the chance of kidney problems.

Pediatric

Celecoxib should not be used in children under two years of age and under 22 lb. (10 kg). Children with systemic onset juvenile rheumatoid arthritis are at high risk for bleeding and clotting problems.

Geriatric

Older individuals are more likely to experience serious stomach bleeding and kidney failure from celecoxib.

Pregnant or breastfeeding

Celecoxib is not recommended during the first trimester and should not be taken during the last trimester. It is considered a pregnancy category C drug during the first 30 weeks of pregnancy and a pregnancy category D drug beyond week 30, which means that it can adversely affect a fetus. The drug passes into breast milk.

Side effects

Serious allergic reactions to celecoxib are rare. Severe rash or itching; swelling, especially of the face or

tongue; trouble breathing; and severe dizziness are all signs of an allergic reaction and require immediate medical attention. Call a doctor or go to the emergency room if these symptoms appear after taking celecoxib.

Side effects that are serious and require prompt medical attention, but that are uncommon, include:

- chest pain
- weakness
- shortness of breath
- slurred speech, blurry vision, or problems with balance
- black, tarry, bloody stools or clay-colored stools
- coughing up blood or vomit that looks as if it contains coffee grounds
- dark urine or no urine output; painful urination
- ongoing nausea or pain in the upper portion of the stomach
- skin rash, easy bruising, tingling, muscle weakness
- swelling or rapid weight gain
- fever, itching, burning eyes followed by a red or purple rash, especially on the face or upper body, and peeling skin

Less serious and more common side effects that should be called to a doctor's attention if they do not go away include:

- diarrhea
- gas or bloating
- headache
- mild skin rash
- sore throat or cold symptoms

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herb, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of a drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Celecoxib is known to interact with the following pharmaceutical drugs. Other interactions are possible. An individual who develops any unusual or unexpected symptoms should contact a physician.

Interactions include:

- Anticoagulants (blood thinners), such as aspirin, **warfarin** (Coumadin), and heparin, and antiplatelet

PATIENT PROFILE

A generally healthy man aged 54 was troubled with joint pain and stiffness in the pinky fingers of both hands and in his left knee. No other joints were affected, but the almost steady pain in the affected joints made normal tasks like using his computer keyboard and lifting and carrying objects difficult. He was an avid golfer, and it was also becoming difficult to carry his clubs, swing a club, and walk any distance on the golf course, which limited the time he could spend at his favorite sport. He was not satisfied with the pain relief he was getting from frequent use of aspirin or acetaminophen and went to see his doctor for medication that might work better without taking high doses.

The doctor stated that the pain and stiffness of the patient's joints was consistent with osteoarthritis. He recommended taking celecoxib (Celebrex), a nonsteroidal anti-inflammatory drug (NSAID) that works by reducing certain hormones (prostaglandins) that cause inflammation and associated pain. A 100 mg capsule was prescribed, which should be taken with food to reduce the risk of stomach upset. Usually celecoxib is taken as needed for pain, but the patient was advised that he should take two 100 mg capsules to start and then take one 100 mg capsule twice a day, about 8 hours apart. Regular use would require monitoring his blood count every three months to make sure that levels of hemoglobin and red blood cells remained stable and to monitor for internal bleeding, a possible side effect of taking celecoxib long term. The doctor advised the patient not to take additional over-the-counter medications for pain, colds, or allergies because they may include medicine similar to celecoxib, which could increase the action of

celecoxib and result in unwanted side effects. He was also advised to avoid excessive sun exposure, since celecoxib use can result in increased sensitivity to sunlight (photosensitivity).

In the second week of regular use of celecoxib, the patient reported having an itchy, red, raised skin rash over both arms and his chest and abdomen and larger raised, puffy areas on the abdomen that looked like hives. He had played golf only one day since taking celecoxib, and his face and arms were red and hot afterward, as though he were sunburned even on a rather mild day. He was advised to stop taking celecoxib immediately and come to the doctor's office. On examination of the skin, the doctor confirmed that it was an allergic reaction to celecoxib and also sunburn on the exposed skin and that the drug must be discontinued. Although the doctor was hesitant to prescribe another NSAID, one particular NSAID known as diclofenac sodium (Voltaren) is considered to have a unique mechanism of action and is not noted for causing dermatologic reactions. Therefore, the doctor prescribed diclofenac sodium, which compared favorably to celecoxib for 24-hour pain relief but with a better side-effect profile for this patient. A 50 mg capsule was prescribed to be taken twice a day, morning and evening. The patient was advised to wait 24 hours before taking the first dose. After three days of the recommended dosage of diclofenac, the patient was enjoying 24-hour pain control. The patient's rash and hives subsided quickly after discontinuing celecoxib, and diclofenac effectively relieved his joint pain long term without side effects.

drugs (**clopidogrel**, prasugrel) increase the risk of bleeding side effects.

- Antifungals such as **fluconazole** and voriconazole increase the concentration of celecoxib in the blood.
- Antacids decrease the effectiveness of celecoxib.
- Corticosteroid drugs such as **prednisone** increase the chance of gastrointestinal bleeding.
- Diuretics (water pills) increase the risk of kidney complications.

Celecoxib decreases the effectiveness of the following drugs:

- angiotensin-converting enzyme (ACE) inhibitors such as benazepril (Lotensin), **captopril** (Capoten), **enalapril** (Vasotec), fosinopril (Monopril), **lisinopril** (Prinivil, Zestril), moexipril (Univasc), perindopril (Aceon),

quinapril (Accupril), **ramipril** (Altace), and trandolapril (Mavik)

- angiotensin II receptor antagonists such as **candesartan** (Atacand), eprosartan (Teveten), **irbesartan** (Avapro), **losartan** (Cozaar), olmesartan (Benicar), **telmisartan** (Micardis), and valsartan (Diovan)

Celecoxib also raises the concentrations of the following drugs, increasing the risk of adverse effects:

- lithium
- **methotrexate** (Trexall); fatal toxic reactions have occurred

Foods and other substances

Smoking and alcohol use increase the risk of gastrointestinal bleeding.

Resources

WEBSITES

“Celecoxib.” Drugs.com. <http://www.drugs.com/ppa/celecoxib.html> (accessed December 31, 2014).

MedlinePlus. “Celecoxib.” U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699022.html> (accessed December 31, 2014).

U.S. Food and Drug Administration (FDA). “Celebrex (Celecoxib) Information.” <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm240959.htm> (accessed January 30, 2015).

U.S. National Library of Medicine. “Celecoxib.” DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a201d754-98dc-42eb-894c-10f3e64f0ad1> (accessed January 30, 2015).

ORGANIZATIONS

Arthritis Foundation, 1330 West Peachtree Street NW, Suite 100, Atlanta, GA 30357-0669, (800) 283-7800, <http://www.arthritis.org/>.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Information Clearinghouse, 1 AMS Circle, Bethesda, MD 20892-3675, (301) 495-4484, (877) 22-NIAMS (226-4267), Fax: (301) 718-6366, TTY: (301) 565-2966, NIAMSinfo@mail.nih.gov, <http://www.niams.nih.gov/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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REVIEWED BY KEVIN GLAZA, RPH

Celexa see **Citalopram**

Cephalexin

Definition

Cephalexin is an orally active first-generation cephalosporin. It is used to treat infections such as pneumonia; urinary tract infections (UTIs); and bone, ear, and skin infections. It is effective against some penicillinase-producing methicillin-susceptible staphylococci and streptococci, but it is not effective against methicillin-resistant pathogens.

Purpose

Cephalexin is used to treat infections caused by sensitive bacteria.



Cephalexin, 500 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Prophylaxis

Sometimes antibiotics are given before an infection develops in the hope of preventing the infection; this is referred to as prophylaxis. Prescribing cephalexin in the absence of a proven or strongly suspected bacterial infection, however, is unlikely to provide benefit to the patient and may increase the risk of the development of drug-resistant bacteria.

Description

Cephalexin is available in the following formulations:

- cephalexin monohydrate oral tablets in 250 and 500 milligrams (mg)
- cephalexin monohydrate oral capsules in 250 and 500 mg
- cephalexin oral capsules in 250, 500, and 750 mg
- cephalexin oral suspension in doses of 125 mg/5 milliliters (mL) and 250 mg/5 mL

U.S. brand names

Cephalexin oral capsules are available under the brand name Keflex as well as in generic form.

Canadian brand names

Canadian brand names include Ceporex, Keflex, Apo-Cephalex, Nu-Cephalex, and PMS-Cephalexin.

KEY TERMS

Antibiotic—A drug that either kills or slows the growth of harmful bacteria.

Cephalosporin—A class of antibiotics that are derived from the fungus *Acremonium*. The cephalosporins in clinical use are semisynthetic drugs in which the chemical structure of the original compound has been modified to change the effectiveness of the compound.

Prothrombin—A type of protein (called a glycoprotein) that is involved in the blood-clotting process.

Prothrombin time—A test that determines how quickly a person's blood will clot.

Origins

Cephalexin is a semisynthetic first-generation cephalosporin antibiotic with antimicrobial activity similar to that of cephaloridine or cephalothin but somewhat less potent. It is orally active.

Recommended dosage

For the treatment of bladder, bone, ear, respiratory, skin, and urinary tract infections, 250 mg (as tablets, capsules, or oral suspensions) may be given by mouth every six hours. Regardless of the strength used (250, 500, or 750 mg), the total daily dose should fall within a range of 1–4 grams per day.

For severe infections that require doses of more than 4 grams per day, patients may receive the injectable form of cephalosporin.

Pediatric

EAR INFECTIONS. To treat ear infections (otitis media), 75–100 mg per kilogram (kg, or 2.2 lb.) of body weight may be given in divided doses throughout the day, not to exceed 4 grams per day.

STREP THROAT. To treat strep throat (streptococcal pharyngitis), 20 mg/kg may be given by mouth twice a day for ten days, not to exceed 500 mg/dose.

UNCOMPLICATED CYSTITIS. To treat uncomplicated infections of the bladder or urinary tract, patients younger than 15 years may be given 25–50 mg/kg/day by mouth, divided every six to eight hours for ten days. The total daily dosage should not exceed 4 grams per day.

For adolescents older than 15, 250 mg may be given every six hours up to a maximum of 4 grams/day. When

using strengths other than 250 mg tablets or capsules, the total daily dose should be adjusted to stay within the range of 1–4 grams/day.

OTHER INFECTIONS. For the treatment of beta-hemolytic streptococcal infections, bone infections, UTIs, and respiratory tract infections, 25–50 mg/kg may be given in divided doses throughout the day up to a maximum of 4 grams per day for ten consecutive days. Cephalexin may also be useful in treating other infections caused by susceptible organisms.

Geriatric

There are no specific doses for patients over the age of 65, although adjustments may be needed based on health status or the use of other medications.

Pregnant or breastfeeding

There are no special dose recommendations for cephalexin during pregnancy.

Other conditions and allergies

In patients with renal (kidney) impairment, the dose of cephalexin should be reduced; however, there are no formal recommendations for dose adjustments.

Precautions

Pseudomembranous colitis—an intestinal infection caused by *Clostridium difficile*—has been reported with nearly all antibacterial agents, including cephalexin, and may range from mild to life-threatening. Physicians should consider this diagnosis in patients with diarrhea that begins after administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *C. difficile* is a primary cause of antibiotic-associated colitis. Mild cases of pseudomembranous colitis usually respond to discontinuance of the drug. In moderate to severe cases, diagnosis and treatment may include sigmoidoscopy, appropriate bacteriologic studies, administration of fluids and electrolytes, protein supplementation, and administration of an antibacterial drug clinically effective against *C. difficile* colitis.

Pediatric

The safety and efficacy of cephalexin in children has been established in clinical trials. In these trials, children may have received cephalexin capsules or oral suspensions. Capsules should be used only in children and adolescents capable of ingesting and swallowing the pills.

Geriatric

Of the 701 subjects in three published clinical studies of cephalexin, 433 (62%) were 65 years of age and older. No overall differences in safety or efficacy were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, some older individuals may exhibit greater sensitivity to the drug and its side effects.

Cephalexin is known to be excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with renal function impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in selecting the proper dose, and renal function may need to be monitored.

Pregnant or breastfeeding

Cephalexin falls within the U.S. Food and Drug Administration's (FDA) category B, which means that either no human studies have been done but animal studies have not found the drug to cause any adverse effects to a fetus, or animal studies may have shown a small risk but human studies have not found the drug to cause any harm.

Cephalexin is acceptable to use during breastfeeding. Limited information indicates that maternal doses of cephalexin up to 1 gram produce low levels in milk that are not expected to cause adverse effects in breastfed infants. Occasionally, disruption of the infant's gastrointestinal flora, resulting in diarrhea or thrush, has been reported with cephalosporins, but these effects have not been adequately evaluated.

Other conditions and allergies

Patients with allergies to penicillin may exhibit hypersensitivity reactions to cephalosporins, including cephalexin. Cross-sensitivity among beta-lactam antibiotics such as cephalexin has been documented in clinical studies and may occur in 10% or less of patients with penicillin allergies. If an allergic reaction to cephalexin occurs, the patient should discontinue the drug. Serious acute hypersensitivity reactions may require administration of **epinephrine** and other emergency measures, including oxygen, intravenous (IV) fluids, IV antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and should make no exception with regard to cephalexin—the risk of reaction seems to be greater with first-generation cephalosporins such as cephalexin.

Side effects

Cephalexin is normally well tolerated. The most serious adverse effects associated with the drug are caused either by hypersensitivity (allergy) or superinfection by nonsusceptible bacteria or fungi. All antibiotics impose the risk of alterations in the balance of intestinal flora. Among the most serious is overgrowth of *C. difficile*, which causes antibiotic-associated diarrhea and colitis or pseudomembranous colitis.

Hypersensitivity reactions are also a risk with all antibiotics. They may be no more than a mild rash but can also cause severe, life-threatening conditions such as Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, exfoliative dermatitis, and anaphylaxis.

The most common adverse reactions are abdominal pain and mild diarrhea. Because cephalexin has been so widely used, a large number of adverse reactions have been reported among patients taking the drug, but there may have been other factors aside from cephalexin use contributing to the reactions.

Cephalosporins may be associated with delayed blood clotting, caused by a fall in prothrombin activity. Patients most at risk include those with kidney or liver impairment or poor nutritional state, as well as patients receiving a prolonged course of antimicrobial therapy or patients who have undergone anticoagulant therapy (use of blood thinners). Prothrombin time should be monitored in patients at risk, and vitamin K may be administered as indicated.

Pregnant or breastfeeding

There is a minor risk of diarrhea in infants being breastfed by mothers who are taking cephalexin.

Interactions

Drugs

Cephalexin reduces the effectiveness of live virus vaccines, including the bacillus Calmette–Guérin (BCG) vaccine (for tuberculosis) and the typhoid vaccine. Administration of the vaccines should be delayed until the full course of cephalexin treatment has been completed.

Cephalexin reduces the effectiveness of **oral contraceptives** and other hormone-replacement therapy drugs containing estrogen. This imposes a small risk of contraceptive failure or return of menopausal symptoms.

Cephalexin in combination with penicillins may reduce the clearance of one or the other drug, leaving the remaining drug to build up in the system. Clearance rates

should be monitored if the drug is administered with penicillin. The drugs **digoxin** (Lanoxin) and probenecid (Benemid) may also increase the levels of cephalexin in the bloodstream, or digoxin levels may increase. These levels should be monitored closely by a healthcare provider.

Several other drugs have been reported to interact with cephalexin, but the reactions have not been found to have clinical significance. To avoid complications, patients should make sure their healthcare providers are informed of all drugs they are currently taking, including over-the-counter drugs and supplements.

Herbs and supplements

Rose hip and willow bark have been reported to interact with cephalexin, but the interactions appear to have little or no clinical significance.

Food and other substances

The presence of food in the stomach may delay the absorption of cephalexin, but the effect of the drug will not be impacted. Cephalexin may be taken with food in order to reduce stomach upset.

Resources

BOOKS

Drug Facts and Comparisons. Philadelphia: Wolters Kluwer Health, 2013.

PERIODICALS

Ayazi, P., et al. "Effect of Oral Cephalexin in the Treatment of BCG Lymphadenitis." *Le Infezioni in Medicina (Infectious Diseases Journal)* 22, no. 2 (June 2014): 112–7.

Guinto, V. T., et al. "Different Antibiotic Regimens for Treating Asymptomatic Bacteriuria in Pregnancy." *Cochrane Database of Systematic Reviews* 9, art. no. CD007855 (September 8, 2010). <http://dx.doi.org/10.1002/14651858.CD007855.pub2> (accessed December 11, 2014).

Moorhead, C., A. Torres. "I PREVENT Bacterial Resistance. An Update on the Use of Antibiotics in Dermatologic Surgery." *Dermatologic Surgery* 35, no. 10 (October 2009): 1532–38.

Smith, S. C., C. F. Heal, and P. G. Buttner. "Prevention of Surgical Site Infection in Lower Limb Skin Lesion Excisions with Single Dose Oral Antibiotic Prophylaxis: A Prospective Randomised Placebo-Controlled Double-Blind Trial." *BMJ Open* 4, no. 7 (July 2014): e005270. <http://dx.doi.org/10.1136/bmjopen-2014-005270> (accessed December 11, 2014).

Swanson, A., and K. Canty. "Common Pediatric Skin Conditions with Protracted Courses: A Therapeutic Update." *Dermatologic Clinics* 31, no. 2 (April 2013): 239–49.

WEBSITES

LactMed. Toxnet, U.S. National Library of Medicine, National Institutes of Health. <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm> (accessed December 7, 2014).

MedlinePlus. "Cephalexin." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682733.html> (accessed December 7, 2014).

U.S. National Library of Medicine. "Cephalexin–Cephalexin Capsule." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=8226> (accessed December 7, 2014).

ORGANIZATIONS

American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, IL 60007-1098, (847) 434-4000, Fax: (847) 434-8000, (800) 433-9016, <http://www.aap.org/>.

Infectious Diseases Society of America, 1300 Wilson Boulevard, Suite 300, Arlington, VA 22209, (703) 299-0200, Fax: (703) 299-0204, <http://www.idsociety.org/>.

National Foundation for Infectious Diseases, 7201 Wisconsin Avenue, Suite 750, Bethesda, MD 20814, (301) 656-0003, Fax: (301) 907-0878, <http://www.nfid.org/>.

Samuel D. Uretsky, PharmD

REVIEWED BY JAMES E. WAUN, MD, RPH

Cetirizine

Definition

Cetirizine is an H₁ receptor blocker antihistamine. Histamine is a chemical produced within the body that causes inflammation and allergy symptoms.

Purpose

Cetirizine is used most often to treat allergies. Other uses include:

- vasomotor (nonallergy) rhinitis
- common cold
- urticaria (hives)
- angioedema (facial swelling)
- anaphylactic reactions
- pruritus (itching)
- allergic conjunctivitis



Cetirizine syrup, 1 mg/mL. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Description

Cetirizine is marketed in a large number of dosage forms, mostly labeled for over-the-counter (nonprescription) sale. The drug is also available in a variety of packaging, both bottles and blister packs. Formulations include:

- oral tablets, 5 and 10 milligrams (mg)
- chewable tablets, 5 and 10 mg
- oral solution or syrup, 1 mg per milliliter (mL)—labeled for prescription use, although other companies provide a similar product with over-the-counter labeling
- capsule, 10 mg

U.S. brand names

In the United States, cetirizine is sold under the brand names Zyrtec, Aller-Tec, and Alleroff as well as in its generic form.

Canadian brand names

In Canada, cetirizine is sold under the brand name Reactine.

Recommended dosage

The average dose is 5–10 mg per day. Individuals should not take more than 10 mg/day.

Pediatric

To treat allergies and urticaria in children, the following dosing schedules are recommended:

- 6 to 12 months: 2.5 mg daily
- 12 months to 2 years: 2.5 mg daily; may be increased to 2.5 mg twice daily (5 mg per day)
- 2 to 5 years: 2.5 mg daily; may be increased to 5 mg/day if needed but should not exceed that amount
- 6 years and older: 5–10 mg daily, depending on the severity of symptoms; should not exceed 10 mg/day

Geriatric

The maximum daily dose in elderly patients should not exceed 5 mg.

Precautions

Although cetirizine produces a less severe sedative effect than older antihistamines, some percentage of people do experience sedation after taking cetirizine. Individuals should avoid the use of alcohol and other drugs that also cause drowsiness.

Cetirizine may cause central nervous system depression, which means that the brain can experience a delayed rate of functioning. Individuals taking cetirizine should avoid activities requiring mental alertness, including driving, until they know how the medication affects them.

Geriatric

The elderly may be more sensitive to the adverse effects of cetirizine.

Pregnant or breastfeeding

Cetirizine has been assigned to pregnancy category B by the U.S. Food and Drug Administration (FDA). This means that high-dose animal studies have shown no abnormal effects on a fetus, although there have been no comparable studies in humans. Cetirizine is recommended for use during pregnancy when the benefits outweigh the risks. Less is known about the use of cetirizine in combination with a decongestant; this combination is classified as category C, which means that animal studies have found some adverse effect on a fetus. Because there are no comparable studies in humans, the potential benefits of the drug combination may warrant its use, despite the potential risks.

Cetirizine is excreted into human milk. The manufacturer does not recommend the use of cetirizine in nursing mothers. The U.S. National Library of Medicine states that small occasional doses of cetirizine

KEY TERMS

Angioedema—A reaction occurring deep within the skin causing swelling of the face due to expansion of the capillaries (smallest blood vessels).

Anaphylactic—Describing a serious state of shock brought about by hypersensitivity (anaphylaxis) to an allergen such as a drug, foreign protein, or toxin.

Anticholinergics—A class of drugs that block the action of the neurotransmitter acetylcholine in the brain. Acetylcholine dilates blood vessels, lowers blood pressure, and slows heartbeat. Anticholinergics are used to treat diseases like asthma, incontinence, gastrointestinal cramps, and muscular spasms by blocking involuntary muscle movements.

Antihistamine—A drug that counteracts the effects of histamine. There are two kinds of antihistamines. The H₁ receptor blockers counteract the effects of colds and mild allergies, such as sneezing, runny nose, and itching. The H₂ receptor blockers stop the secretion of stomach acid and are used to treat heartburn and ulcers.

Conjunctivitis—Inflammation or redness of the lining of the white part of the eye and the underside of the eyelid (conjunctiva) that can be caused by infection, allergic reaction, or physical agents like infrared or ultraviolet light.

Pruritus—Itching.

Urticaria—Hives. Vascular reaction of the upper dermis marked by transient appearance of slightly elevated patches (wheals) that are redder or paler than the surrounding skin and often attended by severe itching.

Vasomotor rhinitis—Nasal irritation that is not caused by allergies; symptoms include a stuffy or runny nose.

are probably acceptable during breastfeeding, but larger doses or more prolonged use may cause drowsiness and other effects in the infant or decrease the milk supply, particularly in combination with a sympathomimetic such as pseudoephedrine or before lactation is well established. The British Society for Allergy and Clinical Immunology recommends cetirizine at its lowest dose as a preferred choice if an antihistamine is required during breastfeeding.

Other conditions and allergies

Cetirizine should not be used in patients with a documented hypersensitivity to cetirizine or its precursor drug **hydroxyzine**.

Because cetirizine is metabolized in the liver, the drug should be used with care in patients with impaired liver function.

The anticholinergic effects of antihistamines may cause urinary retention in patients with benign prostatic hypertrophy, but this is less likely in second-generation antihistamines such as cetirizine than in older drugs.

Side effects

Cetirizine is normally well tolerated, but a number of adverse effects have been reported. The most common are tiredness and headache. Less common side effects include:

- fatigue
- dry mouth
- dizziness
- diarrhea
- malaise
- cough
- vomiting
- nose bleeds

Geriatric

Feelings of drowsiness may be exacerbated in older patients.

Interactions*Drugs*

The monoamine oxidase inhibitors (MAOIs) isocarboxazid and tranylcypromine should not be administered with antihistamines because of the risk of increasing sedative and anticholinergic effects.

Perampanel (Fycompa, an antiepileptic drug) may increase the central nervous system depressant effects of cetirizine. Increased levels of confusion, depression, anger, and aggression may occur.

Use at the same time as topical antihistamines may cause an additive effect to occur.

Food and other substances

Alcohol use should be avoided while taking cetirizine.

Resources

BOOKS

Drug Facts and Comparisons 2013. Philadelphia: Lippincott Williams & Wilkins, 2012.

PERIODICALS

- Afonso, N., et al. "Cetirizine-Induced Anaphylaxis: A Rare Adverse Drug Reaction." *British Journal of Clinical Pharmacology* 67, no. 5 (2009): 577–78.
- Etwel, F., et al. "The Fetal Safety of Cetirizine: An Observational Cohort Study and Meta-Analysis." *Journal of Obstetrics and Gynaecology* 34, no. 5 (2014): 392–99.
- Ozdemir, P. G., et al. "Assessment of the Effects of Antihistamine Drugs on Mood, Sleep Quality, Sleepiness, and Dream Anxiety." *International Journal of Psychiatry in Clinical Practice* 18, no. 3 (2014): 161–68.
- Rutkowski, K., and A. Wagner. "Cetirizine Anaphylaxis." *Annals of Allergy, Asthma & Immunology* 113, no. 3 (2014): 247–49.
- Skoner, D. P., et al. "Effect of Cetirizine on Symptom Severity and Quality of Life in Perennial Allergic Rhinitis." *Allergy Asthma Proceedings* 35, no. 4 (2014): 338–45.

WEBSITES

- AHFS Consumer Medication Information. "Cetirizine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a698026.html> (accessed March 1, 2015).
- U.S. National Library of Medicine. "LactMed: Cetirizine." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?db+ lactmed: @term+ @DOCNO+62> (accessed January 12, 2015).

ORGANIZATIONS

- American Academy of Allergy, Asthma & Immunology (AAAAI), 555 East Wells Street, Suite 1100, Milwaukee, WI 53202-3823, (414) 272-6071, <http://www.aaaai.org/>.
- Asthma and Allergy Foundation of America, 8201 Corporate Drive, Suite 1000, Landover, MD 20785, (800) 7-ASTHMA (727-8462), info@aafa.org, <http://www.aafa.org/>.

Samuel D. Uretsky, PharmD

REVIEWED BY KEVIN GLAZA, RPh

Cetuximab

Definition

Cetuximab is an anticancer chemotherapeutic drug used to treat colorectal cancer and malignant tumors of the head and neck.



Erbitux (cetuximab). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Purpose

Cetuximab is used to treat a type of colorectal cancer called colorectal carcinoma with epidermal growth factor receptor (EGFR) expression. It is used for treatment of EGFR-expressing colorectal cancer that has failed to respond to other chemotherapeutic agents. Cetuximab may be used in combination with other chemotherapeutic agents, such as the drug irinotecan to treat metastatic colorectal cancer that does not respond to other agents or to irinotecan alone.

Cetuximab is also used to treat malignant (cancerous) tumors of the head and neck. Cetuximab is used in combination with radiation therapy for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck, especially in patients who cannot tolerate platinum-based chemotherapies with radiation therapy.

Description

Cetuximab specifically targets the EGFR expressed by cancer cells, to prevent cancer cell growth and replication. The EGFR is a type of chemical receptor that sits on the outer membrane of both normal cells and cancer cells. Chemical receptors in the body activate a sequence of cellular events known as a chemical cascade or signaling pathway. It is these signaling pathways that are responsible for many normal body functions. Drugs or natural chemicals that bind to and activate the receptor signaling pathway are known as receptor agonists. Drugs

KEY TERMS

Chemotherapy—Administration, by injection or orally, of special cell-killing drugs into the body, where they will circulate and kill cancer cells.

Colorectal cancer—Cancer involving both the colon and the rectum of the gastrointestinal tract.

Epidermal growth factor receptor (EGFR)—A protein on the cell surface that can initiate growth and proliferation.

Radiation therapy—The use of high-energy radiation from x-rays, cobalt, radium, and other sources to kill cancer cells and shrink tumors.

Receptor—A molecular structure in a cell or on the surface of a cell that allows binding of a specific substance that causes a specific physiologic response.

or natural chemicals that bind to the receptor and block them from creating a signaling pathway are known as receptor antagonists, because they antagonize the effects of that receptor. EGFR are receptors that create signaling cascades that are a natural part of cell development and necessary for normal cell growth. The agonist that normally binds to the EGFR is epidermal growth factor (EGF). When EGF binds to the EGFR, it initiates chemical signals that tell the cell how to grow and replicate. Some cancer cells have a mutated form of the EGFR, so the cells continue to multiply. Drugs like cetuximab can differentiate between the normal and mutated EGFR and prevent the excessive growth from happening.

In clinical trials, cetuximab treatment was shown to increase median survival time compared to placebo. Median survival time is a term used to describe the time from either diagnosis or treatment at which half of the patients with a given disease are expected to still be alive. In a clinical trial designed to test out a cancer drug in humans, median survival time is a way to measure how effective a treatment is.

U.S. brand names

Cetuximab is marketed by Bristol-Myers Squibb under the trade name Erbitux.

Recommended dosage

Cetuximab is administered intravenously. The maximum infusion rate should not exceed 10 milligrams (mg) per minute. The initial dose is given over two hours, with

the remainder of doses given once weekly over one hour each.

For previously treated EGFR-expressing metastatic colorectal cancer, cetuximab may be used either as a single agent or in combination with the chemotherapeutic drug irinotecan. The initial dose of cetuximab is 400 mg per square meter (m^2) of the body surface area, given as an infusion over two hours. The remainder of the treatments are a dose of 250 mg/m^2 given as an infusion over one hour once a week. Treatment is continued until disease progression occurs or until intolerable adverse effects occur, whichever comes first.

For the treatment of locally or regionally advanced squamous cell cancer of the head and neck, cetuximab may be used in combination with radiation therapy. The initial dose of cetuximab is 400 mg/m^2 , given as an infusion over two hours. The initial dose is given one week prior to the initiation of radiation therapy. Radiation therapy is given over six to seven weeks. During that time, cetuximab is given at a dose of 250 mg/m^2 as an infusion over one hour once a week. Administration of cetuximab must be completed one hour prior to radiation therapy during this time.

Precautions

Cetuximab intravenous therapy is associated with severe infusion reactions, ranging from skin inflammation and itching to life-threatening drop in blood pressure, difficulty breathing, heart attack, collapse of the blood vessels, and shock. To help prevent infusion reactions, 50 mg intravenous **diphenhydramine** (Benadryl) is given 30 to 60 minutes prior to the cetuximab infusion for the initial dose. Further doses of diphenhydramine may be given in later doses if indicated. Cetuximab treatment has caused fatal respiratory disease, cardiac arrest, and sudden death. Fatal toxic skin infections and kidney failure have also been reported.

Cetuximab treatment used at the same time as radiation therapy as opposed to in staggered doses is associated with formation of a moderate to severe rash. The incidence of late radiation toxicity is higher in patients receiving both cetuximab and radiation therapy than in those receiving radiation therapy alone.

Pediatric

Cetuximab has not been approved for use in patients younger than 18 years.

Pregnant or breastfeeding

Cetuximab is a pregnancy category C drug. Pregnancy category C drugs are drugs in which animal studies show adverse effects on the fetus but there is not

sufficient data in humans. However, if the potential benefits to the patient are determined to outweigh the potential risks to the fetus, the drug may be used during pregnancy. Cetuximab is contraindicated with breastfeeding both during treatment and within 60 days of the last dose.

Other conditions and allergies

Cetuximab may not be appropriate for use in patients who have a form of respiratory inflammation known as interstitial pneumonitis or in patients with a respiratory disorder known as pulmonary fibrosis.

Side effects

Cetuximab is used when the potential benefits to the patient are considered greater than the potential risks of adverse effects. Some potential side effects seen with cetuximab treatment are:

- abdominal pain and cramping
- abnormal liver function tests
- acne
- anemia
- back pain
- conjunctivitis
- constipation
- cough
- diarrhea
- difficulty breathing
- depression
- difficulty swallowing
- dizziness
- dry mouth
- dry skin, itchiness, or rash
- fever
- hair loss
- headache
- increased infections
- insomnia
- kidney failure
- loss of appetite or weight loss
- nausea or vomiting
- sore throat
- weakness

Interactions

Patients should make their doctor aware of any and all medications or supplements they are taking before using cetuximab. Cetuximab interacts with many other

drugs. Some drug interactions may make cetuximab unsuitable for use, while others may be monitored and attempted.

Drugs

Certain combinations of cancer treatments including cetuximab have been associated with heart toxicity and death. The combination of cetuximab, the drug cisplatin, and radiation therapy have caused both these sequelae.

Resources

BOOKS

- Hamilton, Richard J., editor. *Tarascon Pharmacopoeia Library Edition*. MA: Jones and Bartlett Publishers, 2009.
- Wilkes, Gail M., and Margaret Barton-Burke. *2013 Oncology Nursing Drug Handbook*. Burlington, MA: Jones & Bartlett Learning, 2013.

PERIODICALS

- Hu, M. H., et al. "Cisplatin-Based Chemotherapy versus Cetuximab in Concurrent Chemoradiotherapy for Locally Advanced Head and Neck Cancer Treatment." *BioMed Research International*, art. ID 904341 (2014). <http://dx.doi.org/10.1155/2014/904341> (accessed February 20, 2015).

WEBSITES

- American Cancer Society. "Cetuximab." <http://www.cancer.org/treatment/treatmentsandsideeffects/guidetocancerdrugs/cetuximab> (accessed February 20, 2015).
- National Cancer Institute. "FDA Approval for Cetuximab." <http://www.cancer.gov/cancertopics/druginfo/fda-cetuximab> (accessed February 20, 2015).
- The Scott Hamilton CARES Initiative. "Cetuximab." Chemocare.com. <http://chemocare.com/chemotherapy/drug-info/cetuximab.aspx> (accessed February 20, 2015).
- U.S. Food and Drug Administration. "Cetuximab (Erbix)."
<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm278957.htm> (accessed February 20, 2015).

ORGANIZATIONS

- American Cancer Society, 250 Williams Street NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org/>.
- National Cancer Institute, 9609 Medical Center Drive, BG 9609 MSC 9760, Bethesda, MD 20892-9760, (800) 4-CANCER (422-6237), <http://www.cancer.gov/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Maria Basile, PhD

REVIEWED BY KEVIN GLAZA, RPH

Chantix see **Varenicline**

Chlordiazepoxide

Definition

Chlordiazepoxide is used to treat anxiety and also to control agitation brought on by alcohol withdrawal. It is a member of the benzodiazepine family of drugs, which slow the central nervous system to ease tension or nervousness.

Purpose

Chlordiazepoxide is used for short-term relief of symptoms of anxiety and for the management of anxiety disorders. It is also used for treating symptoms of withdrawal from acute alcoholism and alcoholic intoxication. When combined with **amitriptyline**, it is used to treat depression that accompanies anxiety or tension.

Description

Chlordiazepoxide is useful when treating anxiety for short periods of time. It has sedative properties that are effective for these brief periods of use. In addition, it is occasionally used to stimulate appetites and is a weak analgesic (pain reliever). Its precise mechanism of action is unknown, and several hours are needed until peak levels of the drug are reached and its effects felt. Chlordiazepoxide is available in 5, 10, and 25 milligram (mg) capsules.



Chlordiazepoxide, 5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

U.S. brand names

In the United States, chlordiazepoxide is sold under the trade names of Librium and Librax, and as Limbitrol when it is combined with another drug, amitriptyline.

Recommended dosage

The recommended dosage varies with diagnosis. The lowest possible dosage that provides relief from symptoms should be used, as the drug has a high potential for causing physiological and psychological dependence. When used in adults for the treatment of moderate anxiety, the usual oral dosage is 5–10 mg three or four times per day. When used for the treatment of more severe anxiety and anxiety disorders, the usual oral dosage is 20–25 mg three or four times per day. When used to treat symptoms of acute alcoholism, the usual initial oral dosage is 50–100 mg, repeated as needed until agitation is adequately controlled. The recommended maximum dosage is 300 mg per day.

Chlordiazepoxide is sometimes used to relieve symptoms of preoperative apprehension or anxiety. For this purpose, 50–100 mg is given via intramuscular (IM) injection.

Pediatric

The usual dosage for children is 5 mg two to four times per day.

Geriatric

The dosage for elderly patients is usually 5 mg two to four times per day.

Precautions

Persons with suicidal tendencies should be closely monitored, as chlordiazepoxide may lower the threshold for action in attempting suicide. Children and adolescents up to 24 years of age are especially at risk when taking the chlordiazepoxide/amitriptyline combination, as are individuals with a history or family history of bipolar disorder. The drug has a high potential for causing physiological or psychological dependence.

Benzodiazepines, including chlordiazepoxide, carry the risk of inducing anterograde amnesia (the loss of the ability to make new memories).

Geriatric

Chlordiazepoxide is slow to metabolize and is not generally advised for use in the elderly, as the slow elimination rate can lead to accumulation in the body, producing prolonged effects. This is especially dangerous to elderly patients, who are at risk for falls.

KEY TERMS

Anterograde amnesia—The inability to form new memories.

Anxiety—An emotion that can be experienced as a troubled feeling, sense of dread, fear of the future, or distress over a possible threat to a person's physical or mental well-being.

Benzodiazepines—A group of central nervous system depressants used to relieve anxiety or to induce sleep.

Dependence—A state in which a person requires a steady concentration of a particular substance in order to avoid withdrawal symptoms.

Depression—A mental state characterized by feelings of sadness, despair, discouragement, and low energy, sometimes accompanied by oversleeping and overeating.

Pregnant or breastfeeding

This drug is known to increase the risk of birth defects in the fetus when taken by a woman during the first three months of pregnancy, and it also can cause dependency in the developing baby that can result in withdrawal symptoms following birth. Chlordiazepoxide passes into the breast milk and can cause breathing trouble and slow heartbeat in babies.

Other conditions and allergies

Chlordiazepoxide use may exacerbate porphyria, which is a group of inherited disorders characterized by abnormally increased production of substances called porphyrins.

Side effects

Other than physiological and psychological dependence, few adverse effects have been reported. The most common side effects include drowsiness, confusion, and movement difficulties. These are more common among older patients. Occasionally, transient loss of consciousness has been reported.

Other adverse effects include:

- edema (abnormal accumulation of fluid in bodily tissues)
- minor menstrual irregularities
- nausea
- constipation
- changes in libido (sex drive)

Also, chlordiazepoxide may impair mental or physical skills needed to perform complex motor tasks. For this reason, persons using this drug are advised not to drive automobiles or operate machinery.

Interactions

To avoid the risk of interactions, patients should report all of their current medications, prescribed or over the counter, to their healthcare provider before taking chlordiazepoxide.

Drugs

A small number of reports of interactions with oral anticoagulants have been received.

Food and other substances

Chlordiazepoxide may increase the effect of alcohol or other substances that depress central nervous system functions. For this reason, they should not be used at the same time.

Resources

BOOKS

- Albers, Lawrence J., Rhoda K. Hahn, and Christopher Reist. *Handbook of Psychiatric Drugs*. Laguna Hills, CA: Current Clinical Strategies, 2011.
- American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda, MD: ASHP, 2015.
- Graham, George. *The Disordered Mind: An Introduction to Philosophy of Mind and Mental Illness*. 2nd ed. New York: Routledge, 2013.
- Holland, Leland Norman, and Michael Patrick Adams. *Core Concepts in Pharmacology*. 4th ed. New York: Prentice Hall, 2014.
- North, Carol, and Sean Yutzy. *Goodwin and Guze's Psychiatric Diagnosis*. 6th ed. New York: Oxford University Press, 2010.
- Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger, 2013.

PERIODICALS

- Mansour, M. F., et al. "Simultaneous Determination of Chlordiazepoxide and Selected Antidepressants Using CZE." *Journal of Separation Science* 36, no. 20 (2013): 3432–39.
- Ortega, L. A., et al. "Memory Interfering Effects of Chlordiazepoxide on Consummatory Successive Negative Contrast." *Pharmacology, Biochemistry, and Behavior* 116 (January 2014): 96–106.
- Reddy, V. K., et al. "Cost-Effectiveness Analysis of Baclofen and Chlordiazepoxide in Uncomplicated Alcohol-Withdrawal Syndrome." *Indian Journal of Pharmacology* 46, no. 4 (2014): 372–77.

WEBSITES

National Health Service (NHS). "Chlordiazepoxide (Chlordiazepoxide 10mg Capsules)." <http://www.nhs.uk/medicine-guides/pages/medicineoverview.aspx?condition=alcohol+withdrawal&medicine=chlordiazepoxide> (accessed February 23, 2015).

Physicians' Desk Reference. "Librium." PDR Health. <http://www.pdrhealth.com/drugs/librium> (accessed February 23, 2015).

ORGANIZATIONS

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.

Anxiety Disorders Association of America, 8701 Georgia Avenue, Suite 412, Silver Spring, MD 20910, (240) 485-1001, Fax: (240) 485-1035, <http://www.adaa.org/>.

Mental Health America, 2000 N. Beauregard Street, 6th Floor, Alexandria, VA 22311, (703) 684-7722, (800) 969-6642, Fax: (703) 684-5968, <http://www1.nmha.org/>.

National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.

National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

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Chlorhexidine

Definition

Chlorhexidine by prescription is a widely used anti-infective agent for topical use. It also has a large number of nonprescription applications.

Purpose

Chlorhexidine is used in both prescription and nonprescription formulations. The prescription preparations are 0.12% solutions used to treat gingivitis, an infection of the gums.

Nonprescription uses are extensive, although the product is widely used for skin disinfection as a scrub or incorporated into sponges and cloths. Chlorhexidine is also incorporated into both venous and urinary catheters to reduce the risk of infection.



Chlorhexidine oral rinse. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Description

Prescription chlorhexidine comes in a solution that contains 0.12% chlorhexidine gluconate. It is used as a mouth rinse, although the clinical benefits of reduction in oral bacteria is not clear. In studies of the effectiveness of chlorhexidine rinse, oral bacteria were reduced by 65%–97% after six months of use. However, there was no evidence of significant changes in bacterial resistance, and the bacteria returned three months later. There is also a chlorhexidine-impregnated chip that is nonprescription but must be implanted into a dental abscess by a dental professional at three-month intervals.

U.S. brand names

In the United States, chlorhexidine is sold under the brand names Paroex, Peridex, and Periogard.

Canadian brand names

In Canada, chlorhexidine is sold as Stanhexidine.

Origins

Chlorhexidine was discovered in the early 1950s and was introduced as a commercial disinfectant and topical antiseptic in 1954. Its first use as an oral agent was in 1976.

KEY TERMS

Anaphylaxis—An abrupt and intense allergic reaction. In extreme cases, it can be fatal.

Antiseptic—A substance that kills or inhibits the growth of microorganisms.

Calculus—Calcium salt deposits on the teeth; may cause gum irritation.

Gingivitis—Inflammation of the gums.

Subgingival—Beneath the gum line.

Recommended dosage

For gingivitis, 0.5 fluid ounces (oz.) of undiluted chlorhexidine gluconate oral rinse can be used twice daily. The rinse should be swished around in the mouth for 30 seconds and then spit out.

Precautions

Chlorhexidine can cause staining of the tooth surfaces and the tongue. Because of this, patients who have had surface restorations of their front teeth may not wish to use chlorhexidine oral rinse.

Some patients may experience a temporary alteration in taste perception while undergoing treatment with chlorhexidine oral rinse. Instances of permanent taste alteration following chlorhexidine use have been reported, but they have been rare.

In some clinical trials, an increase in calcium deposits beneath the gums (subgingival calculus) was noted in users of chlorhexidine rinse. It is not known if chlorhexidine use results in an increase in subgingival calculus.

Pediatric

Clinical safety and efficacy of chlorhexidine oral rinse have not been established in children younger than 18 years.

Geriatric

There are no special precautions required for use of chlorhexidine in the elderly.

Pregnant or breastfeeding

Chlorhexidine oral rinse is safe to use during pregnancy and while breastfeeding.

Other conditions and allergies

Anaphylaxis, as well as serious allergic reactions, have been reported during use of dental products containing chlorhexidine.

Side effects

The most common side effects associated with chlorhexidine oral rinses are an increase in staining of teeth and other oral surfaces, an increase in calcium deposit formation, and an alteration in taste perception. Taste perceptions typically return to normal within four days after the last chlorhexidine rinse.

Other, less frequent side effects include irritation to tissues of the mouth, including redness and swelling.

Interactions

No interactions with chlorhexidine oral rinse have been reported.

Resources

BOOKS

Drug Facts and Comparisons 2014. Philadelphia: Lippincott Williams & Wilkins, 2013.

PERIODICALS

al-Tannir, M. A., and H. S. Goodman. "A Review of Chlorhexidine and Its Use in Special Populations." *Special Care in Dentistry* 14, no. 3 (1994): 116–22.

Bagis, B., et al. "Evaluation of Chlorhexidine Gluconate Mouthrinse-Induced Staining Using a Digital Colorimeter: An In Vivo Study." *Quintessence International* 42, no. 3 (2011): 213–23.

Charugundla, B., S. Anjum, and M. Mocherla. "Comparative Effect of Fluoride, Essential Oil and Chlorhexidine Mouth Rinses on Dental Plaque and Gingivitis in Patients with and without Dental Caries: A Randomized Controlled Trial." *International Journal of Dental Hygiene* (July 5, 2014): e-pub ahead of print. <http://dx.doi.org/10.1111/idh.12094> (accessed March 2, 2015).

Keijser, J. A., et al. "Comparison of 2 Commercially Available Chlorhexidine Mouthrinses." *Journal of Periodontology* 74, no. 2 (2003): 214–18.

Munro, C.L. "Oral Health: Something to Smile About!" *American Journal of Critical Care* 23, no. 4 (2014): 282–88.

Supranoto, S., et al. "The Effect of Chlorhexidine Dentifrice or Gel versus Chlorhexidine Mouthwash on Plaque, Gingivitis, Bleeding and Tooth Discoloration: A Systematic Review." *International Journal of Dental Hygiene* (July 24, 2014): e-pub ahead of print. <http://dx.doi.org/10.1111/idh.12078> (accessed March 2, 2015).

Wang, M. F., L. E. Marks, and M. E. Frank. "Taste Coding after Selective Inhibition by Chlorhexidine." *Chemical Senses* 34, no. 8 (2009): 653–66.

WEBSITES

- Healthwise. "Chlorhexidine Gluconate." Cigna. <http://www.cigna.com/healthwellness/hw/medications/chlorhexidine-gluconate-d01231a1> (accessed March 2, 2015).
- U.S. National Library of Medicine. "Chlorhexidine Gluconate—Chlorhexidine Gluconate Oral Rinse." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a2d2d555-89a5-42d7-81d5-50fd7e741f83> (accessed March 2, 2015).

ORGANIZATIONS

- American Dental Association, 211 East Chicago Avenue, Chicago, IL 60611-2678, (312) 440-2500, <http://www.ada.org/>.
- American Dental Hygienists' Association, 444 North Michigan Avenue, Suite 3400, Chicago, IL 60611-3980, Fax: (312) 440-8900, <http://www.adha.org/>.
- American Academy of Oral and Maxillofacial Pathology, 214 North Hale Street, Wheaton, IL 60187, (630) 510-4552, Fax: (630) 510-4501, (888) 552-2667, <http://www.aaomp.org/>.

Samuel D. Uretsky, PharmD

REVIEWED BY KEVIN GLAZA, RPh

Cholesevelam see **Colesevelam**

Cialis see **Tadalafil**

Cipro see **Ciprofloxacin**

Ciprodex otic see **Ciprofloxacin/
dexamethasone**

Ciprofloxacin

Definition

Ciprofloxacin is an antibacterial agent, the first of the second-generation quinolones (known as fluoroquinolones). Quinolones are broad-spectrum antibiotic drugs. Ciprofloxacin works by inhibiting an enzyme that is needed by bacterial cells to reproduce, thus stopping their spread.

Purpose

Ciprofloxacin is a broad-spectrum antibiotic used to treat bacterial infections. However, nearly all species of bacteria quickly built up a resistance to fluoroquinolones soon after their introduction. The drug is now reserved for treatment of infections of known sensitivity.

Off-label use

Ciprofloxacin has also been used for other purposes without U.S. Food and Drug (FDA) approval. This is referred to as an off-label use. It is legal for



Ciprofloxacin, 750 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

healthcare providers to administer drugs for off-label uses, but the drugs cannot be marketed as treatments for those uses.

Description

Ciprofloxacin is an extremely versatile drug that is available in a number of dosage forms. These include:

- otic solution, 0.2%
- ophthalmic solution, 0.3%
- ophthalmic ointment, 0.3%
- oral tablets, 250, and 500, and 750 milligrams (mg)
- oral suspension, 250, 500 mg per 5 milliliters (mL)
- intravenous solution, 200 mg/100 mL
- extended-release tablet, 500 and 1,000 mg (used only for urinary tract infections, or UTIs)

U.S. brand names

Ciprofloxacin is sold under different brand names, depending on the drug format:

- Oral tablets, oral suspensions, and intravenous solutions are sold as Cipro.
- The otic solution is sold as Cetraxal.
- Ophthalmic solutions and ointments are sold as Ciloxan.

Canadian brand names

In Canada, ciprofloxacin is sold as Bernoflox and Cifloxin.

International brand names

Ciprofloxacin is marketed worldwide with over three hundred different brand names. Among these are Bayclip, Ciproxin, and Proquin.

Origins

The original quinolone, nalidixic acid, was used almost exclusively for treatment of UTIs. Ciprofloxacin was first patented in Europe in 1982. It was approved for use in the United States in 1987, and its U.S. patent was approved in 1996.

Recommended dosage

The dosage varies depending on the condition being treated. The average oral dose of ciprofloxacin is 500 mg every 12 hours. This applies to acute sinus infections (sinusitis), mild bone and joint infections, bacterial prostatitis, infectious diarrhea, anthrax, intra-abdominal infections, lower respiratory tract infections, mild skin infections, and severe UTIs. Dosages for other conditions and intravenous dosages vary. Individuals should always follow the instructions of their healthcare provider and should take the full course of antibiotics prescribed, even if they stop showing symptoms.

Pediatric

KIDNEY OR URINARY TRACT INFECTIONS OR PYELONEPHRITIS. In treating complicated UTIs or kidney infections (pyelonephritis), ciprofloxacin may be prescribed to children older than one year. The safety and efficacy of ciprofloxacin in children younger than one year have not yet been established. When given orally, 10–20 mg per kilogram (kg, or 2.2 lb.) of body weight is administered every 12 hours, with the maximum dose not to exceed 750 mg every 12 hours. If administered intravenously, the dose is 6–10 mg/kg every 8 hours, with the maximum dose not to exceed 400 mg. The drug may be taken from 10 to 21 days.

CHOLERA. If given as a single dose, 30 mg/kg is administered. This dose may also be given every 12 hours, up to three days.

Geriatric

There are no unique dosing schedules for elderly patients.

Other conditions and allergies

Adults with kidney function impairment may require dose adjustments.

KEY TERMS

Anaphylaxis—A sudden and severe allergic reaction.

Antibiotic resistance—The ability of infectious agents to change their biochemistry in such a way as to make an antibiotic no longer effective.

Pyelonephritis—A urinary tract infection that progresses up the urinary system to the kidneys and ureters.

Quinolone—A group of synthetic antibacterial agents. Fluoroquinolones have a fluorine atom attached to the central ring system.

Superinfection—Infection by a second virus after a previous infection by a different virus has become well established.

Tendinitis—An inflammation or irritation of a tendon, a thick cord that attaches bone to muscle.

Precautions

Ciprofloxacin and fluoroquinolones carry an FDA-issued boxed warning. The drugs have been associated with an increased risk of tendinitis and tendon rupture. This risk is further increased in individuals over the age of 60, who are taking corticosteroid drugs, or who have undergone a kidney, heart, or lung transplant. Fluoroquinolones may also exacerbate muscle weakness in persons with myasthenia gravis.

Use of ciprofloxacin has been associated with peripheral neuropathy, or nerve damage, which may occur quickly after starting treatment and could become permanent.

Cases of severe liver damage, including life-threatening liver failure, have been reported. Injury to the liver is often rapid in onset (within 1–39 days) and is often associated with hypersensitivity to the medication.

Convulsions, increased intracranial pressure, and substance-induced psychosis have been reported in some patients taking quinolones, including ciprofloxacin. Ciprofloxacin may also affect the central nervous system (CNS), causing dizziness, confusion, tremor, hallucinations, depression, and, rarely, suicidal thoughts or acts. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued. All quinolones, including ciprofloxacin, should be used with caution in patients with known or suspected CNS disorders that may predispose them to seizures.

Use of ciprofloxacin may cause increased sensitivity to light, resulting in skin irritation on areas exposed

to the sun. Sunscreen and other preventive measures should be used.

When used for an extended time, bacterial resistance to the drug can occur, resulting in superinfections.

Pediatric

Due to the risk of adverse effects, ciprofloxacin is not preferred for use in children except as a treatment for anthrax or when other treatments have failed.

Geriatric

There are no special precautions applicable to elderly patients; however, the risk of tendon problems has been greater in patients over the age of 60.

Pregnant or breastfeeding

Ciprofloxacin is in the FDA pregnancy category C. This means either that there have been no well-controlled studies of the drug in pregnant women but studies in animals have shown adverse effects to a fetus, or there have been no studies done in humans or animals. The drug may be used with caution if the benefits outweigh the risks. An expert review by Teratogen Information System (TERIS) of published data on ciprofloxacin use during pregnancy concluded that therapeutic doses during pregnancy were unlikely to pose a substantial risk to a fetus, but there is not enough data to assert that there is no risk.

Ciprofloxacin is excreted in breast milk; however, the American Academy of Pediatrics states that ciprofloxacin may be used while breastfeeding. According to the U.S. National Library of Medicine's LactMed database, fluoroquinolones have traditionally been avoided due to concern of adverse effects on an infants' developing joints. However, recent studies indicate little risk. It has been theorized that the calcium in milk might prevent absorption of the fluoroquinolones, but there is not enough data to confirm this theory.

Other conditions and allergies

Though rare, serious and occasionally fatal reactions have been reported in patients taking quinolones such as ciprofloxacin. These effects range in severity and occur following the administration of multiple doses. Possible symptoms include fever, rash or other skin reaction, joint or muscle pain, anemia, kidney or liver failure, loss of consciousness, tingling, facial edema (swelling), and trouble breathing.

Side effects

Ciprofloxacin carries the risk of severe adverse effects, but overall the drug is well tolerated. The most

common adverse effect in adults is nausea, followed by diarrhea and abnormal liver function. Rash and vomiting are less frequent.

A vast number of other effects have been reported, but all in fewer than 1% of patients. These include sleep problems and different types of pain.

Interactions

Drugs

Ciprofloxacin has a large number of drug interactions. While there are no specifically contraindicated drugs, the following drugs may cause serious problems, and use of alternative drugs is recommended:

- alosetron (Lotronex)
- aluminum hydroxide
- bacillus Calmette–Guérin (BCG) vaccine, live
- carbonyl iron
- cisapride (Propulsid)
- clomipramine (Anafranil)
- **clozapine** (Clozaril)
- didanosine (Videx)
- dronedarone (Multaq)
- ibrutinib (Imbruvica)
- **imipramine** (Tofranil)
- iron sucrose
- ivacaftor (Kalydeco)
- mefloquine (Lariam)
- **ondansetron** (Zofran)
- pomalidomide (Celgene)
- rasagiline (Azilect)
- saquinavir (Invirase)
- theophylline
- **tizanidine** (Zanaflex)
- toremifene (Fareston)
- tretinoin (Retin A)
- typhoid vaccine, live
- umecclidinium bromide/vilanterol inhaled
- vandetanib (Caprelsa)
- vemurafenib (Zelboraf)
- vilanterol/fluticasone furoate inhaled
- **warfarin** (Coumadin)

Food and other substances

Ciprofloxacin may interact with caffeine and dairy products. Individuals should consult with their healthcare provider before consuming products containing caffeine, dairy, or beverages fortified with calcium.

Resources

BOOKS

Drug Facts and Comparisons. Philadelphia: Wolters Kluwer Health, 2013.

PERIODICALS

Alshammari, T. M., et al. "Risk of Hepatotoxicity Associated with Fluoroquinolones: A National Case-Control Safety Study." *American Journal of Health System Pharmacy* 71, no. 1 (2014): 37–43.

Brunner, A., et al. "Incidence and Antimicrobial Susceptibility of *Neisseria Gonorrhoeae* Isolates from Patients Attending the National *Neisseria Gonorrhoeae* Reference Laboratory of Hungary." *BMC Infectious Diseases* 14 (2014): 433.

Lane, M. A., A. Zeringue, and J. R. McDonald. "Serious Bleeding Events due to Warfarin and Antibiotic Co-Prescription in a Cohort of Veterans." *American Journal of Medicine* 127, no. 7 (2014): 657–63.

Lee, J. H., et al. "The Changes of PCR Ribotype and Antimicrobial Resistance of *Clostridium Difficile* in a Tertiary Care Hospital over 10 Years." *Journal of Medical Microbiology* 63, no. 6 (2014): 819–23.

Nydert, P., S. Lindemalm, and A. Nemeth. "Off-Label Drug Use Evaluation in Paediatrics—Applied to Ciprofloxacin When Used as Treatment of Cholangitis." *Pharmaco-epidemiology and Drug Safety* 20, no. 4 (2011): 393–98.

Saperston, K. N., et al. "A Comparison of Inpatient versus Outpatient Resistance Patterns of Pediatric Urinary Tract Infection." *Journal of Urology* 191, no. 5 suppl. (2014): 1608–13.

OTHER

U.S. Food and Drug Administration. "Cipro (Ciprofloxacin Hydrochloride) Tablets." http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019537s073,020780s0301bl.pdf (accessed January 25, 2015).

WEBSITES

Centers for Disease Control and Prevention. "Quinolones and the Clinical Laboratory." <http://www.cdc.gov/HAI/settings/lab/Quinolones-Clinical-Laboratory.html> (accessed January 25, 2015).

Mayo Clinic staff. "Ciprofloxacin (Oral Route)" MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/ciprofloxacin-oral-route/description/drg-20072288> (accessed January 25, 2015).

MedlinePlus. "Ciprofloxacin." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a688016.html> (accessed January 25, 2015).

Medscape Reference. "Ciprofloxacin." <http://reference.medscape.com/drug/cipro-xr-ciprofloxacin-342530#0> (accessed January 25, 2015).

U.S. National Library of Medicine TOXNET Database. <http://toxnet.nlm.nih.gov/> (accessed January 30, 2015).

ORGANIZATIONS

Infectious Diseases Society of America (IDSA), 1300 Wilson Boulevard, Suite 300, Arlington, VA 22209, (703) 299-0200, Fax: (703) 299-0204, <http://www.idsociety.org/>.

National Institute of Allergy and Infectious Diseases, NIAID Office of Communications and Government Relations 5601 Fishers Lane, MSC 9806, Bethesda, MD 20892, (301) 496-5717, (866) 284-4107, TTY: (800) 877-8339, <http://www.niaid.nih.gov/>.

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Ciprofloxacin/dexamethasone

Definition

Ciprofloxacin/dexamethasone otic suspension is an ear drop containing the quinolone antibiotic drug **ciprofloxacin** (0.3%) and the corticosteroid anti-inflammatory drug dexamethasone (0.1%).

Purpose

Ciprofloxacin/dexamethasone is used to treat ear infections. It is indicated for the treatment of infections in the outer ear (otitis externa) in patients six months and older caused by the bacteria *Staphylococcus aureus* or *Pseudomonas aeruginosa*. It is also used for treating infections of the eardrum (otitis media) in patients six months and older with tympanostomy tubes and infections caused by *S. aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, or *P. aeruginosa*.

Description

Ciprofloxacin/dexamethasone otic suspension is a liquid formula that is dropped into the ear. Treatment of ear infections is normally performed with local (topical) therapy since this ensures a high concentration of drug at the site of infection and minimizes the risk of adverse reactions to other areas of the body. Studies indicate that there is relatively little antibiotic resistance among the pathogens that cause ear infections, which means that they still respond well to antibiotic drugs. There are a number of alternative treatments available for ear infections, including a combination of polymyxin B, neomycin sulfate, and hydrocortisone. Studies indicate that these treatments are roughly equal in effectiveness, although ciprofloxacin/dexamethasone seems to produce quicker results. Adverse effects are similar for all of the drugs.



Ciprodex (ciprofloxacin/dexamethasone). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

U.S. brand names

In the United States, ciprofloxacin/dexamethasone is marketed as Ciprodex. There is no generic equivalent.

Canadian brand names

Ciprofloxacin/dexamethasone is also sold as Ciprodexin in Canada.

Origins

Ciprodex was approved by the U.S. Food and Drug Administration (FDA) in 2003.

Recommended dosage

For treating acute otitis externa or acute otitis media, four drops are instilled into the affected ear(s) twice daily for seven days.

Before applying the drops to the ear, the bottle should be warmed by holding in the hands for one to two minutes. If a cold suspension is applied, it may cause dizziness. The suspension should be shaken well immediately before using. The patient should lie down on his or her side with the affected ear facing upward and should remain in this position for one minute following application. The drops should be instilled directly into the tympanostomy tube (if present) or the tragus (the prominence in front of the external opening of the ear) may be pumped five times to facilitate penetration into the middle ear.

Precautions

Ciprofloxacin/dexamethasone otic suspension should not be used in patients with a sensitivity to ciprofloxacin, to other quinolone antibiotics, or to any of the other components in this medication. This product should not be used to treat viral infections, including herpes simplex infections.

Topical products such as an otic suspension are unlikely to pass into the blood at high enough levels to cause a reaction elsewhere in the body, but in rare instances, this has occurred.

Ciprofloxacin/dexamethasone otic suspension should be instilled into the ear only. It is not suitable for injection and should not be applied to the eyes (ophthalmic use).

If a rash or allergic reaction occurs, patients should discontinue use of the drops immediately and contact their healthcare provider.

Pediatric

Ciprodex is approved for use in patients six months and older. It has not been tested on children younger than six months.

Pregnant or breastfeeding

No information is available on the safety of ciprofloxacin/dexamethasone use during pregnancy or while breastfeeding. The otic drops have not been listed in the U.S. National Library of Medicine's LactMed database, which provides information on whether certain drugs may be used while nursing. The FDA has classified ciprofloxacin/dexamethasone as a category C drug, which means that the risks are not known. No studies (human or animal) have been conducted to see if the drug causes adverse effects to a fetus. Some adverse events have been observed in other animal studies with ciprofloxacin. When administered orally or intravenously (IV), ciprofloxacin crosses the placenta, but the amount of ciprofloxacin present in the body following application of the otic drops is expected to be significantly less than with oral or IV doses.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically (throughout the body) at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after application to the skin in laboratory animals.

The Ciprodex package insert states that ciprofloxacin and corticosteroids do appear in milk when taken orally. Dexamethasone in breast milk could suppress infant growth, interfere with natural corticosteroid

KEY TERMS

Acute—Rapid and severe in onset but lasting only a short time.

Otitis externa—Inflammation of the outer ear, between the eardrum and the external opening.

Otitis media—Inflammation of the eardrum.

Teratogenic—Causing developmental malformations in a fetus.

Tympanostomy—A method of treating recurrent ear infections. In this procedure, a tiny tube is inserted through the eardrum to balance the outside pressure with the pressure in the middle ear. According to the *Merck Manual*, “Doctors recommend ventilating tubes for some children who have had recurring ear infections (acute otitis media) ... or recurring or persistent collections of fluid in their middle ears (chronic secretory otitis media).”

production, or produce other effects. It is unknown whether ciprofloxacin or dexamethasone administered into the ear passes into human milk. Because of the potential for adverse effects, the mother may wish to stop taking the drug or stop nursing, depending on the importance of the medication for the mother.

Side effects

The most common adverse effect is ear pain. Some patients have reported irritability and changes in taste sensation. Tympanostomy tube blockage, ear itching, oral fungal overgrowth (thrush), crying, and dizziness have also been reported. Rare effects include superinfection of the ear, debris collection in the ear canal, and decreased hearing (one instance).

Interactions

Ciprofloxacin/dexamethasone otic suspension has no known clinically significant interactions.

Resources

BOOKS

Drug Facts and Comparisons. Philadelphia: Wolters Kluwer Health, 2013.

PERIODICALS

Kavanagh, K. R., K. Parham, and S. R. Schoem. “Auditory Function after a Prolonged Course of Ciprofloxacin-Dexamethasone Otic Suspension in a Murine Model.” *Archives of Otolaryngology Head and Neck Surgery* 135, no. 3 (2009): 238–41.

Kutz, J. W. Jr., P. S. Roland, and K. H. Lee. “Ciprofloxacin 0.3% + Dexamethasone 0.1% for the Treatment for Otitis Media.” *Expert Opinion on Pharmacotherapy* 14, no. 17 (2013): 2399–405.

Rahman, A., et al. “Pooled Analysis of Two Clinical Trials Comparing the Clinical Outcomes of Topical Ciprofloxacin/Dexamethasone Otic Suspension and Polymyxin B/Neomycin/Hydrocortisone Otic Suspension for the Treatment of Acute Otitis Externa in Adults and Children.” *Clinical Therapeutics* 29, no. 9 (2007): 1950–56.

Roland, P. S., and M. Wall. “Ciprofloxacin 0.3%/Dexamethasone 0.1% Topical Drops for the Management of Otic Infections.” *Expert Opinion on Pharmacotherapy* 9, no. 17 (2008): 3129–35.

Wall, G. M., et al. “Ciprofloxacin 0.3%/Dexamethasone 0.1% Sterile Otic Suspension for the Topical Treatment of Ear Infections: A Review of the Literature.” *Pediatric Infectious Disease Journal* 28, no. 2 (2009): 141–44.

WEBSITES

Mayo Clinic staff. “Ciprofloxacin and Dexamethasone (Otic Route).” MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/ciprofloxacin-and-dexamethasone-otic-route/description/DRG-20061674> (accessed January 25, 2015).

MedlinePlus. “Ciprofloxacin and Dexamethasone Otic.” U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a607010.html> (accessed January 25, 2015).

U.S. Food and Drug Administration. “Drug Approval Package: Ciprodex (Ciprofloxacin & Dexamethasone) Sterile Otic Solution.” http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/021537_Ciprodex.cfm (accessed January 25, 2015).

U.S. National Library of Medicine Drugs and Lactation Database (LactMed). <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm> (accessed January 30, 2015).

ORGANIZATIONS

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Citalopram

Definition

Citalopram is an antidepressant drug. It belongs to the class of drugs known as selective serotonin reuptake inhibitors (SSRIs).

Purpose

Citalopram is approved by the U.S. Food and Drug Administration (FDA) for the treatment of depression.

Off-label use

Possible off-label uses include the treatment of panic disorder, obsessive-compulsive disorder (OCD), alcoholism, social phobia, post-traumatic stress disorder (PTSD), eating disorders, and premenstrual dysphoric disorder (PMDD); however, these uses are not approved by the FDA.

Description

Serotonin is a brain chemical that carries nerve impulses from one nerve cell to another. Researchers think that depression and certain other mental disorders may be caused, in part, because there is not enough serotonin being released and transmitted in the brain. Like the other SSRI antidepressants—fluoxetine (Prozac), **sertraline** (Zoloft), and **paroxetine** (Paxil)—citalopram increases the level of serotonin (also known as 5-HT). Increased serotonin levels in the brain may be beneficial in patients with OCD, alcoholism, certain types of headaches, PTSD, premenstrual tension and mood swings, and panic disorder.

Citalopram is available in 20, 40, and 60 milligram (mg) tablets.

U.S. brand names

Citalopram is sold in the United States under brand name Celexa.

Recommended dosage

The daily dosage of citalopram for depression is 20–60 mg. The initial dosage is usually 20 mg per day. This dosage may then be increased to 40 mg per day after no less than one week. Most patients experience relief from depression at this dosage and do not require more than 40 mg per day. The dosage is taken once daily, either in the morning or in the evening.

Patients who are being treated for panic disorder receive doses ranging from 20 to 60 mg daily. A dosage of 20–30 mg daily appears to be optimal for the treatment of many patients with panic disorders.

Precautions

Patients with history of mania, suicide attempts, or seizure disorders should start taking citalopram with caution and only under close physician supervision.



Celexa (citalopram), 20 mg. (© Cengage Learning®)

Children and young people up to age 24 are at a higher risk of developing suicidal thoughts and actions.

Use of SSRIs may increase the risk of gastrointestinal bleeding.

Pediatric

In general, children under 18 are not advised to take citalopram.

Geriatric

Patients over age 65 typically start at reduced dosages of the drug.

Other conditions and allergies

Patients who are allergic to citalopram, any other SSRI drug, or any component of the preparation should not take citalopram.

Patients with liver problems need to take smaller amounts of the drug. Dosages start at 20 mg but can be increased to 40 mg daily if needed.

Side effects

More than 15% of patients develop insomnia while taking citalopram. Nausea and dry mouth occur in about

KEY TERMS

Anxiety—An emotion that can be experienced as a troubled feeling, sense of dread, fear of the future, or distress over a possible threat to a person's physical or mental well-being.

Depression—A mental state characterized by feelings of sadness, despair, discouragement, and low energy, sometimes with oversleeping and overeating.

Insomnia—The inability to fall asleep or remain asleep.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Selective serotonin reuptake inhibitors (SSRIs)—A class of antidepressants that works by blocking the reabsorption of serotonin in brain cells, raising the level of the chemical in the brain.

Serotonin—5-Hydroxytryptamine; a substance that occurs throughout the body with numerous effects, including neurotransmission. Low serotonin levels are associated with mood disorders, particularly depression and obsessive-compulsive disorder.

20% patients being treated with citalopram. Patients also experience tremor, anxiety, agitation, yawning, headaches, dizziness, restlessness, and sedation with citalopram therapy. These side effects usually diminish or disappear with continued use of the drug, although it may take up to four weeks for this to occur.

A drop in blood pressure and increased heart rate have been associated with citalopram use. In general, patients do not experience weight gain or loss after starting citalopram.

Sexual dysfunction, which includes decreased sex drive in women and difficulty ejaculating in men, is associated with the use of citalopram. In some patients, it may take up to 12 weeks for these side effects to disappear, and for others, these sexual side effects never resolve. If sexual side effects continue, the dose of citalopram may be reduced. Patients can also take drug holidays, where the weekend dose is either decreased or skipped, or they can discuss with their physician the risks and benefits of switching to another antidepressant.

Interactions

Citalopram interacts with many other medications. Individuals who are starting this drug should review the other medications they are taking with their physician and pharmacist for possible interactions. Patients should always inform all their healthcare providers, including dentists, that they are taking citalopram.

Drugs

Certain antifungal medications such as itraconazole, **fluconazole**, and **ketoconazole**, as well as the antibiotic **erythromycin**, can increase the levels of citalopram in the body. This can cause increased side effects. Levomethadyl, a medication used to treat opioid dependence, may cause toxicity to the heart if used together with citalopram.

Serious side effects called serotonin syndrome have resulted from the combination of antidepressants such as citalopram and members of another class of antidepressants known as monoamine oxidase inhibitors (MAOIs). Serotonin syndrome usually consists of at least three of the following symptoms: diarrhea, fever, sweatiness, mood or behavior changes, overactive reflexes, fast heart rate, restlessness, and shivering or shaking. Because of this syndrome, citalopram should never be taken in combination with MAOIs. MAOIs include isocarboxazid, nialamide, pargyline, selegiline, phenelzine, procarbazine, iproniazid, and clorgyline. Patients taking any MAOIs should stop the MAOI and then wait at least 14 days before starting citalopram or any other antidepressant. The same holds true when discontinuing citalopram and starting an MAOI.

Bupirone, an antianxiety medication, should not be used together with citalopram.

Due to the risk of gastrointestinal bleeding, patients should inform their doctors if they are taking anticoagulants (blood thinners).

Herbs and supplements

Ginkgo biloba and St. John's wort, herbal supplements that are common in the United States, should not be taken together with citalopram.

Resources

BOOKS

Albers, Lawrence J., Rhoda K. Hahn, and Christopher Reist. *Handbook of Psychiatric Drugs*. Laguna Hills, CA: Current Clinical Strategies, 2011.

American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda, MD: ASHP, 2015.

- Graham, George. *The Disordered Mind: An Introduction to Philosophy of Mind and Mental Illness*. 2nd ed. New York: Routledge, 2013.
- Holland, Leland Norman, and Michael Patrick Adams. *Core Concepts in Pharmacology*. 4th ed. New York: Prentice Hall, 2014.
- Miller, Mark D., and Charles F. Reynolds III. *Depression and Anxiety in Later Life: What Everyone Needs to Know*. Baltimore, MD: Johns Hopkins University Press, 2012.
- North, Carol, and Sean Yutzy. *Goodwin and Guze's Psychiatric Diagnosis*. 6th ed. New York: Oxford University Press, 2010.
- O'Connor, Richard. *Undoing Depression: What Therapy Doesn't Teach You and Medication Can't Give You*. 2nd ed. New York: Little, Brown, 2010.
- Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger, 2013.

PERIODICALS

- Li, H., et al. "Citalopram and Escitalopram in the Treatment of Major Depressive Disorder: A Pooled Analysis of 3 Clinical Trials." *Annals of Clinical Psychiatry* 26, no. 4 (2014): 281–87.
- Payandemehr, B., M. Ghasemi, and A. R. Dehpour. "Citalopram as a Good Candidate for Treatment of Depression in Patients with Epilepsy." *Epilepsy & Behavior* 44C (February 3, 2015): 96–97.

WEBSITES

- AHFS Consumer Medication Information. "Citalopram." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699001.html> (accessed February 23, 2015).
- National Alliance on Mental Illness (NAMI). "Citalopram (Celexa)." [http://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Citalopram-\(Celexa\)](http://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Citalopram-(Celexa)) (accessed February 23, 2015).
- U.S. Food and Drug Administration (FDA). "FDA Drug Safety Communication: Revised Recommendations for Celexa (Citalopram Hydrobromide) Related to a Potential Risk of Abnormal Heart Rhythms with High Doses." <http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm> (accessed February 23, 2015).

ORGANIZATIONS

- American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.
- American Psychological Association, 750 First Street NE, Washington, DC 20002-4242, (202) 336-5500, (800) 374-2721, TTY: (202) 336-6123, <http://www.apa.org/>.
- Depression and Bipolar Support Alliance, 55 E. Jackson Boulevard, Suite 490, Chicago, IL 60604, (800) 826-3632, Fax: (312) 642-7243, <http://www.dbsalliance.org/>.
- Mental Health America, 2000 N. Beauregard Street, 6th Floor, Alexandria, VA 22311, (703) 684-7722, (800) 969-6642, Fax: (703) 684-5968, <http://www1.nmha.org/>.
- National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600,

(800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.

National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Clarithromycin

Definition

Clarithromycin is an antibiotic of the macrolide family, similar to the drug **erythromycin**. It is particularly useful for treatment of infections of the respiratory tract, such as pharyngitis (sore throat), tonsillitis, sinusitis, acute exacerbation of chronic obstructive pulmonary disease (COPD), and pneumonia. It can also be used to treat recurrent ulcers caused by bacterial infections and Lyme disease. It has excellent penetration into most body tissues.

Although clarithromycin and the closely related antibiotic azithromycin have been widely used to treat patients with the symptoms of respiratory tract infections, studies have suggested that these should be considered second-line drugs, both to reduce costs and avoid the development of bacterial resistance.

Purpose

Clarithromycin is approved for the following indications:

- pharyngitis
- tonsillitis
- community-acquired pneumonia
- skin infections
- endocarditis prophylaxis (prevention)
- Crohn's disease

It is recommended that clarithromycin be prescribed only for infections caused by bacteria (rather than viruses) to help reduce antibiotic resistance. Bacterial resistance to macrolide antibiotics is an ongoing concern. Although a large number of bacterial species remain



Clarithromycin, 500 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

sensitive to clarithromycin, there is increasing resistance by *Helicobacter pylori*, the causative agent in recurrent gastric ulcers and a cause of gastric cancer.

Some studies have indicated that an inhalation form of clarithromycin may be useful in treating respiratory tract infections, but this will require further research.

Description

Clarithromycin is available in the following dosage forms:

- tablets, short acting, 250 milligrams (mg), 500 mg
- tablets, extended release, 500 mg
- oral suspension, 125 mg per 5 milliliters (mL), 250 mg/5 mL

U.S. brand names

In the United States, clarithromycin is sold under the brand name Biaxin.

Canadian brand names

Clarithromycin is also sold as Biaxin in Canada.

International brand names

Clarithromycin may be sold under additional names in other countries.

Recommended dosage

Normal clarithromycin tablets may be taken without regard to meals; however, the extended-release (XL) tablets should be taken with food.

Adults

CHRONIC BRONCHITIS. To treat acute chronic bronchitis, 250–500 mg is taken by mouth every 12 hours for one to two weeks (7–14 days).

For extended release tablets, 1,000 mg is taken by mouth once daily for 7 days.

SINUSITIS. To treat acute maxillary sinusitis, 500 mg is taken by mouth every 12 hours for 14 days.

For extended release tablets, 1,000 mg is taken by mouth once daily for 14 days.

MYCOBACTERIAL INFECTIONS. Mycobacteria are responsible for a number of infections, including tuberculosis and other lung infections. To treat or prevent mycobacterial infections, clarithromycin may be prescribed as part of a combination treatment with other antimycobacterial drugs. The patient may take 500 mg by mouth every 12 hours for 7–14 days.

PEPTIC ULCER DISEASE. Clarithromycin may be prescribed as part of a two- or three-drug combination regimen with bismuth subsalicylate, **amoxicillin**, and an acid inhibitor (histamine H_2 inhibitor or proton pump inhibitor). It is dosed as 500 mg by mouth every 8–12 hours for 10–14 days.

PHARYNGITIS OR TONSILLITIS. To treat infections of the throat or tonsils, 250 mg is taken by mouth every 12 hours for 10 days.

COMMUNITY-ACQUIRED PNEUMONIA. To treat pneumonia that was contracted outside of a healthcare facility, 250 mg is taken by mouth every 12 hours for 7–14 days.

For extended release tablets, 1,000 mg is taken by mouth once daily for 7 days.

SKIN INFECTIONS. The dosage for treating skin and skin-structure infections is 250 mg taken by mouth every 12 hours for 7–14 days.

ENDOCARDITIS PROPHYLAXIS. For prevention of endocarditis, 500 mg is taken by mouth 30–60 minutes before undergoing a surgical procedure.

Pediatric

Pediatric dosages apply to children older than six months (unless otherwise noted).

COMMUNITY-ACQUIRED PNEUMONIA, SINUSITIS, BRONCHITIS, AND SKIN INFECTIONS. The recommended

KEY TERMS

Acute—Either of abrupt onset or of short duration.

Antibiotic—A drug that either kills or stops the growth of bacteria.

Antibiotic resistance—The ability of infectious agents to change their biochemistry in such a way as to make an antibiotic no longer effective.

Cholestatic—Referring to total or partial blockage of the flow of bile from the liver.

Chronic—The opposite of acute; developing or progressing slowly.

Community acquired—Contracted outside of a hospital or health facility. Because of the widespread use of antibiotics, bacteria found in hospitals may be more resistant to antibiotic therapy than bacteria found outside hospitals.

Endocarditis—Inflammation of the endocardium, the layer of tissue that lines the inside of the heart.

Mycobacteria—A group of bacteria that includes *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis, and other forms that cause related illnesses.

Respiratory tract—The parts of the body devoted to breathing. The respiratory tract runs from the nose to the lungs and includes the larynx, trachea, bronchi, and bronchioles, as well as the different parts of the lungs.

dose is 15 mg per kilogram (kg, or 2.2 lb.) of body weight each day, divided into two doses every 12 hours for 10 days.

MYCOBACTERIAL INFECTIONS. The recommended dose is 7.5 mg/kg by mouth every 12 hours; doses should not exceed 500 mg.

ENDOCARDITIS PROPHYLAXIS. The recommended dose is 15 mg/kg taken 30–60 minutes before a surgical procedure; doses should not exceed 500 mg.

STREPTOCOCCAL PHARYNGITIS. To treat strep throat, 7 mg/kg is taken by mouth every 12 hours; doses should not exceed 500 mg.

PERTUSSIS. Clarithromycin may be used to treat whooping cough in children younger than six months. Safety and efficacy are not established in children younger than one month. The following dosages are recommended:

- 1–6 months: 7.5 mg/kg every 12 hours for 7 days
- 6 months and older: 7.5 mg/kg by mouth every 12 hours for 7 days

A 2014 study from the University of Basel, Switzerland, published in the *Pediatric Infectious Disease Journal*, reported that 7 days may not be sufficient to fully eradicate pertussis. Parents and caregivers should follow their healthcare provider's instructions.

Other conditions and allergies

For patients with kidney disease and a creatinine clearance lower than 30 mL per minute, the dose should be reduced by 50%. Creatinine is a waste material that is filtered out of the body by the kidneys. Low levels of creatinine in the urine indicate that the kidneys are not functioning properly. This means that drugs stay in the body longer, which can lead to toxic buildup if dosages are not reduced.

Precautions

Clarithromycin may cause liver damage. While this is usually reversible, it can be severe and has been known to be fatal. Clarithromycin should be discontinued at the first signs of liver damage, which include loss of appetite, jaundice, dark urine, pruritus (itching), or tender abdomen.

Clarithromycin also carries several contraindications, or circumstances in which it should not be used:

- Clarithromycin is contraindicated in patients with a known hypersensitivity to clarithromycin or any of its excipients, erythromycin, or any of the macrolide antibiotics.
- Clarithromycin is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of clarithromycin.
- Concomitant administration of clarithromycin and any of the following drugs is contraindicated: cisapride, pimozide, astemizole, terfenadine, and ergotamine or dihydroergotamine. There have been post-marketing reports of drug interactions when clarithromycin or erythromycin are coadministered with cisapride, pimozide, astemizole, or terfenadine, resulting in cardiac arrhythmias (irregular heartbeat) most likely due to inhibition of metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported.
- Concomitant administration of clarithromycin and **colchicine** is contraindicated in patients with liver or kidney impairment.

- Clarithromycin should not be given to patients with history of QT prolongation or ventricular cardiac arrhythmia, including torsades de pointes.
- Clarithromycin should not be used with **lovastatin** or **simvastatin** due to the increased risk of myopathy (a type of muscle disorder), including rhabdomyolysis. This is caused by elevated blood levels, since both these statins and clarithromycin are metabolized by the same enzyme. Patients should consider using a different method for cholesterol reduction or use fluvastatin, which is metabolized differently than the other drugs.

Pregnant or breastfeeding

Clarithromycin should not be used in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking this drug, the patient should be educated on the potential hazard to the fetus. Clarithromycin has demonstrated adverse effects on pregnancy outcome and embryo-fetal development in animal studies.

Other conditions and allergies

Like all other antibiotics, there is a risk of the overgrowth of resistant bacteria and other pathogenic microorganisms. This may range from mild diarrhea to severe colitis, which may be fatal. *Clostridium difficile*-associated diarrhea (CDAD) should be considered in all patients who develop diarrhea after antibiotic therapy. If CDAD is suspected or confirmed, the antibiotic should be discontinued and treatment should be directed against the CDAD.

Side effects

The most common adverse reactions to clarithromycin therapy for both adults and children are abdominal pain, diarrhea, nausea, vomiting, and altered taste sensations. These adverse reactions are similar to those seen with related antibiotics such as erythromycin.

Clarithromycin is generally well tolerated. A number of other side effects have been reported, including headache, insomnia, and rash, but they are rare.

Interactions

Drugs

Clarithromycin has a very large number of serious interactions. The treating physician and pharmacist should be informed of all drugs a patient is currently taking, including over-the-counter drugs and herbal or dietary supplements.

The following drugs interact the most severely with clarithromycin and should not be used:

- astemizole
- cisapride
- colchicine
- conivaptan
- dihydroergotamine
- dihydroergotamine intranasal
- eliglustat
- ergotamine
- ibutilide
- indapamide
- lomitapide
- lovastatin
- lurasidone
- naloxegol
- pentamidine
- pimozone
- quinidine
- regorafenib
- rifabutin
- simvastatin
- terfenadine

Many other drugs interact with clarithromycin, and patients should consult with their healthcare providers.

Herbs and supplements

Clarithromycin is metabolized in the liver. Some herbs are known to increase the levels of the enzyme (CYP3A4) that assists in metabolism, which means that clarithromycin would be removed from the body too quickly, leading to treatment failure. Individuals should not take any herbs or supplements at the same time as clarithromycin without consulting their healthcare provider to see how they are metabolized.

Food and other substances

Short-acting forms of clarithromycin may be taken without regard to meals; however, the sustained-action tablets should be taken with food.

Resources

PERIODICALS

- Dierig, A., C. Beckmann, and U. Heininger. "Antibiotic Treatment of Pertussis—Are 7 Days Really Sufficient?" *Pediatric Infectious Disease Journal* (2014). <http://dx.doi.org/10.1097/INF.0000000000000567> (accessed February 10, 2015).
- Siekmeier, R., T. Hofmann, and G. Scheuch. "Inhalation of Macrolides: A Novel Approach to Treatment of Pulmonary Infections." *Advances in Experimental*

Medicine and Biology 839 (2015): 13–24. http://dx.doi.org/10.1007/5584_2014_50 (accessed February 10, 2015).

OTHER

U.S. Food and Drug Administration. “Biaxin.” http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050662s048,050698s029,050775s018lbl.pdf (accessed January 25, 2015).

WEBSITES

MedlinePlus. “Clarithromycin.” U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a692005.html> (accessed January 25, 2015).

Medscape Reference. “Clarithromycin.” <http://reference.medscape.com/drug/biaxin-xl-clarithromycin-342524> (accessed January 25, 2015).

Physicians’ Desk Reference. “Biaxin XL.” PDR Health. <http://www.pdrhealth.com/drugs/biaxin-xl> (accessed February 10, 2015).

U.S. National Library of Medicine, National Institutes of Health. “Biaxin” DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aa44552c-3cfe-4111-8aa5-4251aeed9be9> (accessed January 25, 2015).

ORGANIZATIONS

Infectious Diseases Society of America, 1300 Wilson Boulevard, Suite 300, Arlington, VA 22209, (703) 299-0200, Fax: (703) 299-0204, <http://www.idsociety.org/>.

National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, MSC 9806, Bethesda, MD 20892, (301) 402-1663, Fax: (301) 402-0120, ocpostoffice@niaid.nih.gov, <http://www.niaid.nih.gov/>.

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REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Clavulanic acid/amoxicillin see **Amoxicillin/clavulanic acid**

Cleocin see **Clindamycin**

Clindamycin

Definition

Clindamycin is an antibiotic that is a member of the lincosamide class. There are two others in the lincosamide class—lincomycin, which is rarely used in the United States because clindamycin usually works as well with fewer side effects, and pirlimycin, which is approved only for veterinary use for the treatment of mastitis (infections of the udder) in dairy cattle.

Purpose

Clindamycin is used to treat infections caused by anaerobic bacteria (bacteria that grow in the absence of air). These bacteria are commonly found in the intestines and other parts of the digestive tract as well as other body cavities, such as the mouth and vagina. It has also been used topically (on the skin) as a treatment for acne.

Off-label use

Clindamycin has been studied for a number of other infections, but it does not have U.S. Food and Drug Administration (FDA) approval for these uses. Still, a large number of infections may be treated with clindamycin. Relatively few antibiotics are effective against anaerobic bacteria, so clindamycin therapy may be appropriate when:

- The infection is caused by a species of bacteria that is susceptible to clindamycin and could not be treated with a different drug, such as penicillin G.
- The infection is in a tissue where clindamycin reaches high enough concentrations to be effective. Although clindamycin reaches therapeutic levels in most body tissues, it is not effective in the central nervous system (brain and spinal cord).

Individuals should take clindamycin only for unapproved uses if recommended and prescribed by their healthcare provider.



Clindamycin hydrochloride, 150 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Description

Clindamycin may be administered by mouth (as capsules or an oral suspension) or by injection, either into the muscle tissue (intramuscularly) or directly into the bloodstream (intravenously). Oral administration is the safest and easiest way to give the drug, and the absorption of a single dose is about 90%. Intravenous administration, although more difficult, ensures that 100% of the dose reaches the bloodstream and that it does so more quickly than with an oral dose. With clindamycin, as well as other drugs, the physician may choose to start treatment with intravenous therapy and then switch to oral dosing.

U.S. brand names

Oral and intravenous forms of clindamycin are sold under the following brand names in the United States:

- Cleocin
- Cleocin in D5W
- Cleocin Phosphate
- Cleocin Pediatric

Topical forms of clindamycin are sold under the following brand names in the United States:

- Cleocin
- Cleocin-T
- Clindacin ETZ
- Clindacin Pac
- Clindacin-P
- Clindagel
- ClindaMax
- Clindesse
- Evoclin

Most clindamycin formulations are also available as generics.

Canadian brand names

Oral and intravenous forms of clindamycin are sold under the following brand names in Canada:

- Apo-Clindamycin
- Ava-Clindamycin
- Clindamycin Injection, USP
- Clindamycine
- Dalacin C
- Mylan-Clindamycin
- PMS-Clindamycin
- Riva-Clindamycin
- Teva-Clindamycin

Topical forms of clindamycin are sold under the following brand names in Canada:

- Clinda-T
- Clindasol
- Clindets
- Dalacin T
- Dalacin Vaginal
- Taro-Clindamycin

International brand names

Clindamycin is sold under a variety of other brand names internationally and as part of combination products with other drugs.

Recommended dosage

Adults

INFECTIONS. The standard dose for most infections caused by anaerobic bacteria ranges from 150 to 450 milligrams (mg) taken every 6–8 hours. The exact dose depends on the severity of the infection. The total daily dose should not exceed 1,800 mg, or 1.8 grams (g).

The average injected dose is 1.2–2.7 g per day, divided into doses every 6–12 hours. The maximum dose should not exceed 4.8 g per day.

Additional dosages vary based on the condition being treated.

AMNIONITIS. Amnionitis is a rare complication of pregnancy in which the uterus, amniotic sac, and sometimes even the fetus become infected. To treat amnionitis, 450–900 mg of clindamycin may be administered intravenously every 8 hours.

BACTERIAL VAGINOSIS. Bacterial vaginosis is a common vaginal infection. The recommended dose is 300 mg, taken every 12 hours for seven days.

SURGICAL PROPHYLAXIS. Clindamycin may be given to help prevent infections in patients undergoing surgeries associated with a high risk of infection (such as abdominal surgery). It may be administered either by mouth or intravenously at a dose of 900 mg given one hour before the procedure. Another dose may be given six hours later, if needed.

BITE WOUNDS. To prevent or treat infections caused by bite wounds, 300 mg of clindamycin is taken every 6 hours.

GANGRENE. If gangrene is present in a muscle infection, clindamycin may be given intravenously at a dose of 900 mg every 8 hours. It is commonly administered with penicillin G.

KEY TERMS

Anaerobic bacteria—Bacteria that can grow in areas with low oxygen, such as the abdomen, intestines, mouth, and vagina, and cause specific types of infections, such as gangrene and tetanus.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

***Clostridium difficile*-associated diarrhea (CDAD)**—Diarrhea caused by *Clostridium difficile*, a type of bacteria that can develop with antibiotic use.

Vaginosis—A bacterial infection of the vagina that causes a bad-smelling white discharge.

GROUP B STREPTOCOCCUS (GBS). To treat GBS that occurs during pregnancy, 900 mg of clindamycin may be administered intravenously every 8 hours until delivery.

ORAL AND FACIAL INFECTIONS. Infections of the mouth or face may be treated with clindamycin either orally or intravenously. The oral dose is 150–450 mg every 6 hours for at least seven days, not to exceed 1.8 g/day. If given intravenously, the dose is 600–900 mg every 8 hours.

MULTIDRUG REGIMENS. Clindamycin may be used as part of a multidrug regimen in treating pelvic inflammatory disease (PID) and toxic shock syndrome (TSS). The drug is started intravenously in the hospital, but the patient is transitioned to oral doses throughout the course of therapy. The other drugs used in the regimens and the dosages depend on the condition being treated.

Pediatric

The recommended doses for treating infections in children are:

- serious infections: 8–12 mg per kilogram (kg) of body weight per day (4–6 mg/lb.), divided into three or four equal doses.
- severe infections: 13–16 mg/kg/day (6.5–8 mg/lb./day)
- more severe infections: 17–25 mg/kg/day (8.5–12.5 mg/lb./day)

The daily dose should be divided into three or four equal doses per day, regardless of severity.

In pediatric patients weighing less than 10 kg (22 lb.), 37.5 mg (0.5 teaspoon) given three times a day should be considered the minimum recommended dose.

Dosing in newborn infants varies depending on age and weight, and the treating physician's instructions should be followed.

Precautions

The FDA-approved package insert includes a boxed warning, which is the highest-level warning the FDA requires. This warning concerns *Clostridium difficile*-associated diarrhea (CDAD), which has been associated with almost all antibacterial agents, including clindamycin. CDAD can range in severity from mild diarrhea to fatal colitis, so clindamycin should be reserved for serious infections that cannot be treated with less toxic agents. Patients with nonbacterial infections should not use clindamycin. If diarrhea occurs either during or after the use of clindamycin, it should be reported to the patient's physician and carefully monitored.

Pediatric

The injectable form of clindamycin also contains benzyl alcohol to act as a preservative. Benzyl alcohol has been associated with serious harmful effects and death in children and newborns. Doctors should monitor the dosage of injectable clindamycin in pediatric patients to avoid reaching toxic levels of benzyl alcohol, particularly because the minimum amount of benzyl alcohol needed to create toxicity is not known.

The oral suspension of clindamycin should not be refrigerated. Refrigeration may cause the suspension to thicken and become difficult to pour.

Geriatric

In patients over the age of 60, adverse reactions may be more frequent and more severe.

Pregnant or breastfeeding

Clindamycin carries the FDA pregnancy category B, meaning that studies in animals have found no risk to the developing fetus. Clinical trials with pregnant women have not shown an increased risk to the fetus during the second and third trimesters. However, clindamycin has not been adequately studied in pregnant women during the first trimester, so if a woman discovers she is pregnant, she should discuss the use of clindamycin with her doctor.

Clindamycin is released in breast milk, and because of the risk of serious adverse reactions in infants, nursing mothers should not take clindamycin.

Side effects

The most common and dangerous side effect associated with clindamycin is the development of diarrhea, which may lead to an inflammation of the large intestine. Although this reaction has been seen with all antibiotics, it is more common with clindamycin. This side effect may appear even months after the conclusion of a course of clindamycin therapy. Symptoms of a reaction to clindamycin include watery or bloody stools, diarrhea, stomach cramps, and fever.

A large number of other side effects have been reported in association with clindamycin. These side effects include:

- digestive problems, including abdominal pain, nausea, diarrhea, vomiting, and heartburn
- inflammation of the esophagus (esophagitis)
- inflammation of the colon (pseudomembranous colitis)
- pain when swallowing
- yellowing of the skin (jaundice)
- rashes
- hives
- severe allergic reactions (e.g., anaphylaxis, Stevens-Johnson syndrome)
- thick, white vaginal discharge
- burning, itching, or swelling of the vagina

Some of these side effects can be serious, so patients who experience side effects should contact the doctor immediately or seek emergency medical help if necessary.

Geriatric

Elderly patients may be more sensitive to gastrointestinal effects of clindamycin than younger patients.

Interactions

Clindamycin has some known interactions with drugs and other substances.

Drugs

Clindamycin interacts most seriously with drugs used in surgery. Patients should discuss the use of clindamycin with the anesthesiologist.

Antibiotics, including clindamycin, may diminish the effectiveness of live vaccines (e.g., bacillus Calmette-Guérin [BCG] and typhoid). Administration of these vaccines should be delayed at least 24 hours after the last dose of antibiotics.

Clindamycin may reduce the effects of estrogen-containing drugs, increasing the risk of oral contraceptive

failure. An alternative contraceptive method should be considered.

Food and other substances

Food may delay a patient's reaching peak blood levels of clindamycin, but it will not significantly reduce them. Clindamycin may be given with food.

Resources

PERIODICALS

- Amin, A. N., et al. "Hospitalist Perspective on the Treatment of Skin and Soft Tissue Infections." *Mayo Clinic Proceedings* 89, no. 10 (2014): 1436–51.
- Bartlett, J. G. "How Important Are Anaerobic Bacteria in Aspiration Pneumonia: When Should They Be Treated and What Is Optimal Therapy." *Infectious Disease Clinics of North America* 27, no. 1 (2013): 149–55.
- Boyanova, L., R. Kolarov, and I. Mitov. "Recent Evolution of Antibiotic Resistance in the Anaerobes as Compared to Previous Decades." *Anaerobe* 31 (February 2015): 4–10. <http://dx.doi.org/10.1016/j.anaerobe.2014.05.004> (accessed January 31, 2015).
- Brook, I., H. M. Wexler, and E. J. C. Goldstein. "Antianaerobic Antimicrobials: Spectrum and Susceptibility Testing." *Clinical Microbiology Reviews* 26, no. 3 (2013): 526–46.
- Deshpande, A., et al. "Community-Associated *Clostridium Difficile* Infection and Antibiotics: A Meta-Analysis." *Journal of Antimicrobial Chemotherapy* 68, no. 9 (2013): 1951–61.
- Kaplan, S. L. "Recent Lessons for the Management of Bone and Joint Infections." *Journal of Infection* 68, suppl. 1 (2014): S51–S56.
- Lynch, T. J. "Choosing Optimal Antimicrobial Therapies." *Medical Clinics of North America* 96, no. 6 (2013): 1079–94.
- Oliver, R. S., and R. F. Lamont. "Infection and Antibiotics in the Aetiology, Prediction and Prevention of Preterm Birth." *Journal of Obstetrics & Gynaecology* 33, no. 8 (2013): 768–75.

WEBSITES

- "Clindamycin Injection." Drugs.com. <http://www.drugs.com/pro/clindamycin-injection.html> (accessed January 31, 2015).
- MedlinePlus. "Clindamycin." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682399.html> (accessed January 31, 2015).
- Pfizer. "Cleocin HCl." Pfizer.com. <http://labeling.pfizer.com/showlabeling.aspx?id=625> (accessed January 31, 2015).
- Pfizer. "Cleocin Pediatric." Pfizer.com. <http://labeling.pfizer.com/showlabeling.aspx?id=628> (accessed January 31, 2015).
- Pfizer. "Cleocin Phosphate." Pfizer.com. <http://labeling.pfizer.com/showlabeling.aspx?id=626> (accessed January 31, 2015).

U.S. Food and Drug Administration. "Cleocin HCL (Clindamycin Hydrochloride) Capsules." <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm194129.htm> (accessed January 31, 2015).

ORGANIZATIONS

Infectious Diseases Society of America, 1300 Wilson Boulevard, Suite 300, Arlington, VA 22209, (703) 299-0200, Fax: (703) 299-0204, <http://www.idsociety.org/>.

National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, MSC 9806, Bethesda, MD 20892-9806, (866) 284-4107, Fax: (301) 402-3573, TTY: (800) 877-8339, ocpostoffice@niaid.nih.gov, <http://www.niaid.nih.gov/>.

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Clindamycin/benzoyl peroxide

Definition

Clindamycin/benzoyl peroxide is a combination of two drugs that together are effective in treating acne.

Purpose

Acne is a common skin condition that causes scaly red skin, blackheads, and pimples. Acne vulgaris is almost universal during adolescence, but there are many other skin conditions that are classified as acne. Most cases of acne are mild and go away by the time people reach their mid-20s. This type of acne can be treated with over-the-counter remedies. There is a more severe type of acne called inflammatory acne, which requires a more powerful treatment.

Description

Benzoyl peroxide and **clindamycin** work by killing the bacteria that cause acne. Clindamycin is an antibiotic that is particularly effective in killing anaerobic bacteria, or bacteria that grow in the absence of air.

In studies of mild to moderate acne, the combination of clindamycin and benzoyl peroxide has no benefit beyond that of benzoyl peroxide used alone, but the combination is more effective than single-drug therapy in treatment of inflammatory acne. Clindamycin/benzoyl peroxide may also have a somewhat faster onset of action than other drugs used for the same purpose.

Clindamycin/benzoyl peroxide. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

U.S. brand names

In the United States, the combination product is sold under several brand names, in varying combinations:

- Acanya: benzoyl peroxide, 2.5%/clindamycin phosphate, 1.2%
- BenzaClin: benzoyl peroxide, 5%/clindamycin phosphate, 1.2%
- Duac: benzoyl peroxide, 5%/clindamycin phosphate, 1.2%
- generic (common formulation): benzoyl peroxide, 5%/clindamycin phosphate, 1.2%

Recommended dosage

Clindamycin/benzoyl peroxide combination products should be applied to affected areas after the skin has been washed thoroughly and patted dry. The recommended application schedules vary for the different brands:

- Acanya: Apply a pea-sized amount once per day.
- BenzaClin: Apply twice a day (every 12 hours).
- Duac: Apply once daily in the evening.
- Clindamycin phosphate and benzoyl peroxide gel: Apply twice daily, once in the morning and once in the evening, or as directed by a physician.

Precautions

Products containing clindamycin and benzoyl peroxide are for dermatological use only. Avoid contact with the eyes and mucous membranes. Other topical acne therapies should be used with caution while using clindamycin/benzoyl peroxide. Many acne products cause dry skin, and skin irritation may be increased with the use of multiple agents or treatments such as chemical peels.

The use of antibiotic agents such as clindamycin may be associated with the overgrowth of nonsusceptible organisms, including fungi. If this occurs, individuals should discontinue the use of this medication and take appropriate measures as directed by their healthcare providers.

In some studies, enough clindamycin has been absorbed through the skin to cause diarrhea, bloody diarrhea, and colitis. If diarrhea occurs, use of clindamycin/benzoyl peroxide should be stopped immediately.

Benzoyl peroxide may cause increased sensitivity to sunlight. Individuals using products that contain benzoyl peroxide should minimize sun exposure (including use of tanning beds or sunlamps) and wear sunscreen or protective clothing. Patients who receive considerable sun exposure due to their jobs and those with inherent sensitivity to the sun should exercise particular caution. They may wish to discuss alternative treatments with their healthcare providers.

Pediatric

The safety and effectiveness of clindamycin/benzoyl peroxide have not been established in patients under the age of 12. Individuals 12 years and older may follow the adult application instructions.

Pregnant or breastfeeding

Clindamycin/benzoyl peroxide is classified as a pregnancy category C drug. This means that its risks to a fetus in pregnancy, if any, are not known. It is also not known whether levels of clindamycin and benzoyl peroxide are excreted in human milk after topical application. Orally and parenterally administered clindamycin have been reported to appear in breast milk. Women should consult with their healthcare provider about using this product while pregnant or nursing.

Other conditions and allergies

Use of clindamycin/benzoyl peroxide combination products should be strictly avoided by patients with an allergy to any component of the formulas. Because

KEY TERMS

Acne—A common skin condition causing pimples on the face and upper torso.

Antibiotic—A drug used to treat infections caused by bacteria and other microorganisms.

Blackhead—An open comedo. A comedo, the primary sign of acne, consists of a widened hair follicle filled with skin debris, bacteria, and oil called sebum. A blackhead has a wide opening to the skin and is capped with a blackened mass of skin debris.

clindamycin/benzoyl peroxide is made by a number of manufacturers who may use different solvents and other products, it may be possible to avoid allergic reactions by switching brands. However, patients who have shown allergic responses to clindamycin, benzoyl peroxide, or lincomycin (an antibiotic closely related to clindamycin) should strictly avoid using this product.

Clindamycin phosphate and benzoyl peroxide gel (1.2%/5%) should be avoided by individuals with a history of regional enteritis, ulcerative colitis, pseudomembranous colitis, or antibiotic-associated colitis.

Side effects

The most common adverse effects caused by clindamycin/benzoyl peroxide gel include skin redness, peeling, burning, and dryness. If these effects become too severe, they may be a reason to discontinue the drug.

Interactions

Individuals should discuss potential drug interactions with their healthcare provider.

Drugs

Clindamycin- and erythromycin-containing products should not be used in combination. This applies whether the **erythromycin**, an antimicrobial, is being used on the skin or is being taken to treat an infection.

Individuals should not use any other skin products to treat acne while using clindamycin- or benzoyl peroxide-containing products, unless advised by their healthcare provider. Since most of these products cause dryness and skin peeling, these effects may combine and cause severe skin irritation.

Resources

PERIODICALS

- Bartlett, K. B., S. A. Davis, and S. R. Feldman. "Tolerability of Topical Antimicrobials in Treatment of Acne Vulgaris." *Journal of Drugs in Dermatology* 13, no. 6 (2014): 658–62.
- Grove, G., C. Zerweck, and J. Gwazdauskas. "Tolerability and Irritation Potential of Four Topical Acne Regimens in Healthy Subjects." *Journal of Drugs in Dermatology* 12, no. 6 (2013): 644–49.
- Harper, J. C. "Gender as a Clinically Relevant Outcome Variable in Acne: Benefits of a Fixed Combination Clindamycin Phosphate (1.2%) and Benzoyl Peroxide (2.5%) Aqueous Gel." *Journal of Drugs in Dermatology* 11, no. 12 (2012): 1440–45.
- Jacobs, A., et al. "Systematic Review on the Rapidity of the Onset of Action of Topical Treatments in the Therapy of Mild-to-Moderate Acne Vulgaris." *British Journal of Dermatology* 170, no. 3 (2014): 557–64.
- Kong, Y. L., and H. L. Tey. "Treatment of Acne Vulgaris During Pregnancy and Lactation." *Drugs* 73, no. 8 (2013): 779–87.
- Pariser, D. M., et al. "An Aqueous Gel Fixed Combination of Clindamycin Phosphate 1.2% and Benzoyl Peroxide 3.75% for the Once-Daily Treatment of Moderate to Severe Acne Vulgaris." *Journal of Drugs in Dermatology* 13, no. 9 (2014): 1083–89.
- Stinco, G., et al. "Efficacy, Tolerability, Impact on Quality of Life and Sebostatic Activity of Three Topical Preparations for the Treatment of Mild to Moderate Facial Acne Vulgaris." *Giornale Italiano di Dermatologia Venereologia*, Sept. 18, 2014.
- Zeichner, J. A., V. Bhatt, and R. Pillai. "In Vitro Percutaneous Absorption of Benzoyl Peroxide from Three Fixed Combination Acne Formulations." *Journal of Clinical Aesthetic Dermatology* 6, no. 8 (2013): 19–22.

OTHER

Center for Drug Evaluation and Research. "Approval Package for: Application Number: ANDA 65-443." FDA.gov. http://www.accessdata.fda.gov/drugsatfda_docs/anda/2009/065443Orig1s000.pdf (accessed January 8, 2015).

WEBSITES

- Physicians' Desk Reference. "Acanya." PDR Health. <http://www.pdrhealth.com/drugs/acanya> (accessed December 9, 2014).
- Physicians' Desk Reference. "BenzaClin." PDR Health. <http://www.pdrhealth.com/drugs/benzaclin> (accessed December 9, 2014).
- Physicians' Desk Reference. "Duac." PDR Health. <http://www.pdrhealth.com/drugs/duac> (accessed December 9, 2014).
- Prasco Laboratories. "Clindamycin—Benzoyl Peroxide." MedLibrary.org. <http://medlibrary.org/lib/rx/meds/clindamycin-benzoyl-peroxide> (accessed January 8, 2015).
- U.S. National Library of Medicine. "Label: Clindamycin—Benzoyl Peroxide—Clindamycin Phosphate and Benzoyl Peroxide Gel." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=23b5c29b-4b63-49e3-80c2-902a9d1bc411> (accessed January 8, 2015).

ORGANIZATIONS

American Academy of Dermatology, 930 E. Woodfield Road, Schaumburg, IL 60173, (847) 240-1280, (866) 503-SKIN (7546), Fax: (847) 240-1859, <https://www.aad.org/>.

Society for Pediatric Dermatology, 8365 Keystone Crossing, Suite 107, Indianapolis, IN 46240, (317) 202-0224, Fax: (317) 205-9481, info@pedsderm.net, <http://www.pedsderm.net/index.php>.

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REVIEWED BY KEVIN GLAZA, RPh

Clomid see **Clomiphene**

Clomiphene

Definition

Clomiphene is a medication used to stimulate ovulation. It is used by women who have been unable to conceive because of failure to release a mature egg (ovum).

Purpose

Clomiphene is used to induce ovulation in women who want to become pregnant but whose bodies are not producing eggs.



Clomiphene, 50 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Clomiphene has also been studied for use in male infertility and as a method of stimulating testosterone production, but results have been inconclusive.

Description

Clomiphene belongs to a medication class called ovulatory stimulants. It acts by blocking the estrogen receptors in the hypothalamus. The hypothalamus weighs about 4 grams (about 0.3% of the average brain) and is the size of a pea. It is located on the undersurface of the brain, close to the brain stem (the part of the brain that connects to the spine). Its function is to coordinate actions of the nervous system and the endocrine system (the glands and the hormones that they produce), including body temperature regulation, blood pressure, and reproduction.

When the estrogen receptors in the hypothalamus are blocked by clomiphene, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are released by the pituitary gland. These two hormones stimulate the ovaries to release an egg.

In women who have very irregular cycles, clomiphene can make it easier to tell when ovulation has occurred in order to increase the chances of conception. Additionally, it may be used to induce ovulation in instances of “male factor” infertility. One approach to male factor infertility is intrauterine insemination, a type of artificial insemination (where sperm are collected, washed, and placed directly into the uterus). In order to perform the procedure at the best time for fertilization, clomiphene may be used to induce ovulation.

Clomiphene is sold in 50 milligram (mg) tablets.

U.S. brand names

Clomiphene is sold in the United States under the brand names of Clomid and Serophene.

Recommended dosage

The initial dose for the first course is 50 mg (one tablet) each day for five days. If ovulation occurs but there is no pregnancy, the same regimen may be repeated for a total of six cycles.

If 50 mg fails to produce ovulation, the dose may be increased to 100 mg. If the first attempt fails to produce ovulation, the 100 mg/day dose may be repeated for two more cycles. If ovulation occurs but there is no pregnancy, the 100 mg dose may be repeated for a total of six cycles. The dose should not be increased beyond 100 mg/day.

The majority of patients who are going to respond to clomiphene will do so on the first course of treatment.

KEY TERMS

Follicle—As part of the female reproductive system, a fluid-filled sac containing an immature egg.

Follicle-stimulating hormone—A hormone produced by the pituitary gland that, in women, stimulates the growth of the ovum-containing follicles in the ovaries.

Luteinizing hormone—A hormone secreted by the pituitary gland that, in women, stimulates ovulation.

Ovulation—The phase of the female monthly cycle when a developed egg is released from the ovary into the fallopian tube for possible fertilization.

Polycystic ovary syndrome—A syndrome seen in women of childbearing age marked by enlarged ovaries. Symptoms include irregular menstrual periods, excess hair, acne, and obesity.

The duration of administration should not go beyond five days in a cycle, and the dose should not be increased above 100 mg/day.

Precautions

Clomiphene is intended for use only to treat ovarian dysfunction, so patients should be carefully examined for other possible causes of infertility.

The rate of unsuccessful pregnancies associated with clomiphene, which includes ectopic pregnancy, spontaneous abortion, stillbirth, and other causes, is around 21%.

Some patients using clomiphene have reported vision disturbances, including seeing spots or having blurred vision. In most cases, these disturbances go away by themselves, but they may be prolonged and in very rare cases are permanent. Patients with these problems may not be able to drive or operate machinery. The risk of vision problems increases with higher doses or longer durations of treatment. Patients should report any changes in vision immediately.

Clomiphene has been associated with hypertriglyceridemia, or the presence of elevated fat in the blood. Since this can lead to problems with the heart and circulatory system, blood tests should be performed regularly.

Clomiphene has also been associated with ovarian hyperstimulation syndrome (OHSS), which has a large number of very serious symptoms. Among them are

bleeding ovaries; difficulty breathing; and anasarca, which is a state of generalized swelling, renal (kidney) failure, and deep venous thrombosis (blood clots inside the veins). To reduce the risk of this syndrome, the dose of clomiphene should be kept as low as possible, and the patient should be alert to any signs of weight gain or abdominal or pelvic pain. The syndrome may not become apparent until several days after the conclusion of a treatment cycle. Patients with polycystic ovaries may be particularly at risk.

Other conditions and allergies

Clomiphene should not be administered to patients with liver disease or a history of liver problems.

Clomiphene should not be administered to patients with hormone-dependent tumors, such as estrogen-sensitive breast cancer. It should not be administered to patients with abnormal uterine bleeding of unknown cause. Additionally, it should not be administered to patients with ovarian cysts or enlarged ovaries that are not related to polycystic ovarian syndrome.

For patients with uterine fibroids (noncancerous growths in the uterus), clomiphene may cause enlargement of the fibroids.

Pregnant or breastfeeding

Clomiphene carries the U.S. Food and Drug Administration (FDA) pregnancy category X, which means that fetal abnormalities have been demonstrated in human or animal studies or there is evidence of risk to a developing fetus based on reports of adverse reactions. The risks involved outweigh potential benefits in pregnant women. Clomiphene should not be administered during pregnancy. To avoid accidental administration during early pregnancy, every patient should have a pregnancy test before each cycle of clomiphene.

There is some evidence that clomiphene may be used to suppress lactation for women who do not wish to breastfeed, but further studies are required.

Side effects

The most common side effects of clomiphene include:

- enlargement of the ovaries
- hot flashes, or vasomotor flushes
- abdominal/pelvic discomfort, including distension, bloating, pain, or soreness
- nausea and vomiting
- breast tenderness and enlargement
- visual symptoms, including blurred vision and spots

- headache
- intermenstrual spotting or abnormally heavy bleeding

Pregnant or breastfeeding

Patients who conceive as a result of clomiphene treatment have an increased chance of multiple births. Almost 7% of pregnancies conceived with the aid of clomiphene are twins, compared to 3% in the general population. In addition, there have been increased numbers of triplets, quadruplets, and, in one case, sextuplets. Families should be aware of the risks to both mother and infants that are associated with multiple pregnancies.

Interactions

There are no documented drug interactions with clomiphene.

Resources

PERIODICALS

- Leanza, V., et al. "Ovulation Induction with Clomiphene Citrate for Infertile Couple." *Minerva Ginecologica* 66, no. 3 (2014): 309–12.
- Luco, S. M., et al. "The Evaluation of Pre and Post Processing Semen Analysis Parameters at the Time of Intrauterine Insemination in Couples Diagnosed with Male Factor Infertility and Pregnancy Rates Based on Stimulation Agent: A Retrospective Cohort Study." *European Journal of Obstetrics & Gynecology and Reproductive Biology* 179 (2014): 159–62.
- Mazzola, C. R., et al. "Predicting Biochemical Response to Clomiphene Citrate in Men with Hypogonadism." *Journal of Sexual Medicine* 11, no. 9 (2014): 2302–7.
- Tomao, F., et al. "Fertility Drugs, Reproductive Strategies, and Ovarian Cancer Risk." *Journal of Ovarian Research* 7 (May 8, 2014). <http://dx.doi.org/10.1186/1757-2215-7-51> (accessed March 2, 2015).
- Weiss, N. S., et al. "How Long Should We Continue Clomiphene Citrate in Anovulatory Women?" *Human Reproduction* 29, no. 11 (2014): 2482–86.

OTHER

- U.S. Food and Drug Administration. "Clomid [prescribing information]." http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/016131s026lbl.pdf (accessed March 2, 2015).

WEBSITES

- "Clomiphene." Drugs.com. <http://www.drugs.com/clomiphene.html> (accessed February 1, 2015).
- MedlinePlus. "Clomiphene." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682704.html> (accessed February 1, 2015).

Sanofi. "Product Information: Clomid." Sanofi.com.au. http://products.sanofi.com.au/aus_pi_clomid.pdf (accessed February 1, 2015).

U.S. National Library of Medicine. "LactMed: Clomiphene." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+634> (accessed February 1, 2015).

U.S. National Library of Medicine. "Clomiphene Citrate—Clomiphene Citrate Tablet." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=be399623-6400-475d-93d3-1dedd4d43017> (accessed February 1, 2015).

ORGANIZATIONS

International Committee Monitoring Assisted Reproductive Technologies, 540 University Avenue, Suite 200, Palo Alto, CA 94301, (408) 647-9809, Fax: (408) 867-4751, secretariat@icmartivf.org, <http://www.icmartivf.org/>.

Society for Assistive Reproductive Technologies, 1209 Montgomery Highway, Birmingham, AL 35216-2809, (205) 978-5000, Fax: (205) 978-5018, kjefferson@asrm.org, <http://www.sart.org/>.

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Clonazepam

Definition

Clonazepam belongs to a group of drugs called benzodiazepines. Benzodiazepines are medications that help relieve nervousness, tension, symptoms of anxiety, and some types of seizures by slowing the central nervous system.

Purpose

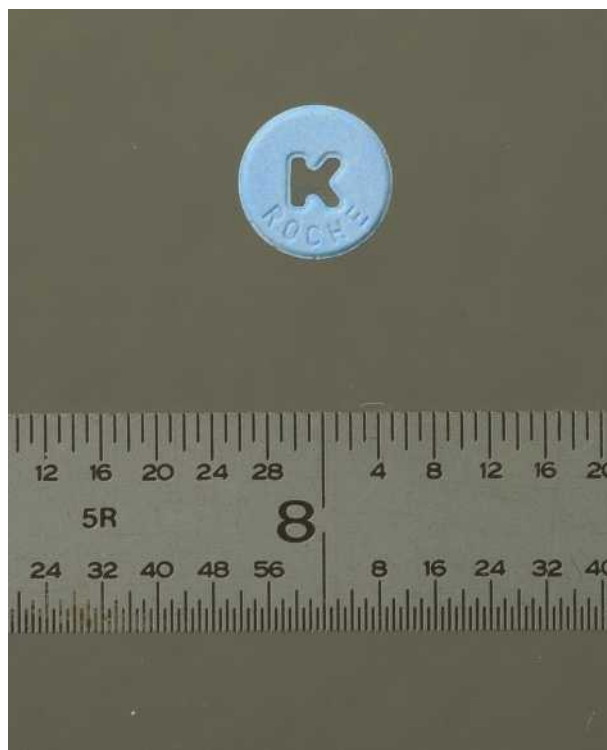
Clonazepam is approved by the U.S. Food and Drug Administration (FDA) for the treatment of panic disorder and some types of epilepsy.

Off-label use

Clonazepam is sometimes used off label to treat social phobia; mania; post-traumatic stress disorder (PTSD); medication-induced movement disorders, which are a side effect of some antipsychotic drugs; and restless legs syndrome. An off-label use is one that is not approved by the FDA, but it is legal for physicians to administer the drug for that purpose.

Description

Clonazepam belongs to a group of drugs called benzodiazepines. Benzodiazepines are sedative-hypnotic



Klonopin (clonazepam), 1 mg. (© Cengage Learning®)

drugs that help to relieve nervousness, tension, anxiety symptoms, and seizures by slowing the central nervous system. To do this, they block the effects of a specific chemical involved in the transmission of nerve impulses in the brain, decreasing the excitement level of the nerve cells.

When clonazepam is used to treat panic disorder, it is more sedating than **alprazolam**, another benzodiazepine drug used to treat panic disorder. However, unlike alprazolam, clonazepam may trigger depressive episodes in patients with a history of depression. In people who experience social phobia, treatment with clonazepam reduces the rate of depression.

Clonazepam comes in 0.5, 1, and 2 milligram (mg) tablets.

U.S. brand names

In the United States, clonazepam is sold under the brand name Klonopin.

Recommended dosage

For panic disorder, the initial recommended dose is 0.25 mg twice daily. This dose can be increased every three days in increments of 0.125–0.25 mg twice daily. The target dose for panic disorder is 1 mg per day, although some people benefit from doses up to a maximum of 4 mg per day. When a person stops taking

clonazepam, the drug should be gradually discontinued by decreasing the dose by 0.125 mg twice daily every three days.

Although clonazepam is not FDA approved for the treatment of PTSD, doses in the range of 0.25–3 mg daily appear to help treat symptoms of this disorder. Daily dosages for the treatment of social phobia range from 1 to 2.5 mg, while the dosage to control mania may be as high as 10 mg daily.

Precautions

Because clonazepam is a nervous system depressant, it should not be taken with other such depressants, such as alcohol, other sedatives and related drugs, sleeping pills, or tranquilizers. People taking clonazepam may feel unusually drowsy and mentally sluggish when they first start taking the drug. They should not drive, operate machinery, or engage in activities that require mental alertness until they see how clonazepam affects them. This excessive sedation usually goes away after a short time on the drug.

People who have underlying depression should be closely monitored while taking clonazepam, especially if they are at risk for attempting suicide. Clonazepam treatment should not be stopped abruptly, as patients may experience withdrawal symptoms such as tremor, insomnia, anxiety, and seizures. Clonazepam can be habit forming.

Geriatric

Because of a loss of coordination, elderly patients are at risk for falls.

Pregnant or breastfeeding

Women who are pregnant should not use clonazepam, because it may harm the developing fetus.

Other conditions and allergies

Clonazepam should never be taken by people who have had an allergic reaction to it or another benzodiazepine drug such as **diazepam** (Valium). People with narrow-angle glaucoma or severe liver disease should not take clonazepam. People who have kidney disease may need to take a reduced dosage of the drug. Saliva production may increase while taking clonazepam. Because of this, people with respiratory disease or an impaired gag reflex should use clonazepam with close physician supervision.

Side effects

The main side effects of clonazepam are sedation, dizziness, impaired coordination, depression, and fatigue.

KEY TERMS

Benzodiazepines—A group of central nervous system depressants used to relieve anxiety or to induce sleep.

Central nervous system depressant—Any drug that lowers the level of stimulation or excitement in the central nervous system.

Epilepsy—A neurological disorder characterized by recurrent seizures. Seizures are caused by a disturbance in the electrical activity in the brain and can lead to loss of consciousness, muscle spasms, rhythmic movements, abnormal sensory experiences, or altered mental states.

Panic disorder—An anxiety disorder in which an individual experiences sudden, debilitating attacks of intense fear.

Social phobia—An anxiety disorder characterized by a strong and persistent fear of social or performance situations.

Some people experience decreased sex drive while taking clonazepam. The drug may also cause short-term memory loss or amnesia and amnesic disorders.

A small number of people develop sinus problems and upper respiratory tract infections while taking clonazepam. One of the side effects of clonazepam may be increased salivation. This may cause some people to start coughing while taking clonazepam. Clonazepam may also cause loss of appetite and dry mouth. It may cause either constipation or diarrhea. There are a few reports of clonazepam causing menstrual irregularities or blurred vision.

Interactions

Several drugs and supplements interact with clonazepam. Patients should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs and herbal or dietary supplements.

Drugs

Clonazepam may increase the sedative effects of other drugs that depress the central nervous system, such as certain strong pain medicines (opiates such as codeine, **oxycodone**, and **hydromorphone**) and antihistamines (found in many cold and allergy medications).

Disulfiram (Antabuse), a medication used to treat alcohol dependence, increases the effect of clonazepam. Medications that make clonazepam ineffective include

phenobarbital, **phenytoin**, carbamazepine, theophylline, **rifampin**, and rifabutin.

Herbs and supplements

The herbal preparations of gotu kola, kava kava, and St. John's wort increase the effects of clonazepam and should not be used.

Food and other substances

The sedative effect of clonazepam is increased if taken with alcohol.

Resources

BOOKS

Lacy, Charles F., Leonard L. Lance, and Laura L. Armstrong. *Lexi-Comp's Drug Information Handbook*. Hudson, OH: Lexi-Comp, 2010.

Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger, 2013.

PERIODICALS

Nardi, A. E., et al. "Clonazepam for the Treatment of Panic Disorder." *Current Drug Targets* 14, no. 3 (May 2013): 353–64.

WEBSITES

AHFS Consumer Medication Information. "Clonazepam." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682279.html> (accessed February 20, 2015).

Micromedex. "Clonazepam (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/clonazepam-oral-route/description/drg-20072102> (accessed February 20, 2015).

NYU Langone Comprehensive Epilepsy Center. "Clonazepam (Klonopin)." <http://epilepsy.med.nyu.edu/treatment/medications/clonazepam> (accessed February 20, 2015).

ORGANIZATIONS

American Academy of Child and Adolescent Psychiatry, 3615 Wisconsin Avenue NW, Washington, DC 20016-3007, (202) 966-7300, Fax: (202) 966-2891, <http://aacap.org/>.

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Clonidine

Definition

Clonidine belongs to a class of drugs called central alpha-adrenergic agonists.

Purpose

Clonidine tablets and patches are approved by the U.S. Food and Drug Administration (FDA) for the treatment of high blood pressure (hypertension). An extended-release form is available to treat attention deficit hyperactivity disorder (ADHD).

Off-label use

In addition to its approved uses, clonidine is prescribed to treat several other conditions. It has been found to be useful in the treatment of alcohol, opiate, and nicotine withdrawal syndromes and in treating Tourette syndrome, which is a type of tic disorder.

Clonidine is also useful in treating neuropathic pain, which is usually characterized as a sensation of tingling, burning, or shooting pain in the limbs that may come and go quickly and erratically. Clonidine gel used topically (on the skin) provides analgesia to the affected painful nerves. There is also an injectable form that is administered directly into the spinal cord for the treatment of postoperative pain.



Clonidine hydrochloride, 0.2 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Other known uses of clonidine include:

- treatment of dysmenorrhea (painful cramps during menstrual period)
- hypertensive crisis
- hot flashes associated with menopause
- as a diagnostic tool in the diagnosis of pheochromocytoma (a tumor of the adrenal glands that may be accompanied by high blood pressure, a fast heart rate, and changes in the endocrine system)

Other indications for and benefits of the use of clonidine may be identified by further research.

Description

Clonidine works on specific nerve cells in the brain that are responsible for lowering blood pressure, slowing heart rate, and decreasing the body's reaction to the withdrawal of chemicals such as alcohol, opiates, and nicotine. Clonidine is beneficial in opiate withdrawal because it treats symptoms commonly associated with that condition (watery eyes and nose, diarrhea, irritability). For opiate withdrawal, clonidine is often used alone. For the treatment of alcohol withdrawal, clonidine is usually combined with benzodiazepine tranquilizers such as **chlordiazepoxide** (Librium), **diazepam** (Valium), **alprazolam** (Xanax), or **lorazepam** (Ativan).

Clonidine tablets are available in 0.1, 0.2, and 0.3 milligram (mg) strengths. Clonidine skin patches are available in 0.1 mg, 0.2 mg, and 0.3 mg strengths. Each patch lasts seven days. The extended-release form is available in 0.1 mg and 0.2 mg tablets. A liquid suspension is also available.

U.S. brand names

In the United States, clonidine tablets are sold under the brand name Catapres, and clonidine skin patches are sold under the brand name Catapres-TTS. The extended-release form is sold under the brand name Kapvay. The tablets are also available generically.

Origins

Clonidine was synthesized in the 1960s and was initially tested as a nasal decongestant. In the United States, clonidine was first used to treat hypertension, although it has also been investigated for treatment of different neuropsychiatric disorders.

Recommended dosage

To treat hypertension, dosages of the tablets start at 0.1 mg taken twice per day but may be adjusted to 0.2–0.6 mg per day. The doses vary for other formulations.

KEY TERMS

Attention deficit hyperactivity disorder (ADHD)—A developmental disorder characterized by distractibility, hyperactivity, impulsive behaviors, and the inability to remain focused on tasks or activities.

Opiate—A drug containing or derived from opium—such as codeine, morphine, and heroin—that alleviates pain and induces sleep.

Tourette syndrome—An abnormal condition that causes uncontrollable facial grimaces and tics and arm and shoulder movements. Tourette syndrome is perhaps best known for uncontrollable vocal tics that include grunts, shouts, and use of obscene language (coprolalia).

Withdrawal—Physical symptoms and psychological discomforts experienced after a person suddenly stops using a drug on which he or she has become dependent.

Dosages of 0.4–0.6 mg have been used for the treatment of alcohol withdrawal. Total daily dosages for the treatment of opiate withdrawal range between 0.5 and 1.4 mg, depending on the stage as well as the severity of withdrawal symptoms. If the clonidine patch is used to treat nicotine withdrawal symptoms, dosages that deliver 0.1–0.2 mg daily are used. For oral therapy (tablets), a total dosage of 0.2–0.4 mg daily is taken in divided doses.

Pediatric

Pediatric doses of clonidine are calculated based on the child's body weight. Clonidine dosage for ADHD in children is 5 micrograms (mcg) per kilogram (kg, or 2.2 lb.) of body weight per day, given orally in four divided doses. Children who require a daily dosage of 0.2 mg usually can use the 0.3 mg dermal patch. If ADHD is associated with sleep disturbances, low to moderate doses of clonidine can be taken at bedtime. Oral doses in children with Tourette syndrome range from 3 to 6 mcg/kg/day, divided into two to four even doses.

Precautions

Clonidine should not be abruptly withdrawn, but rather slowly decreased over several days to avoid withdrawal symptoms. Withdrawal symptoms include an increase in blood pressure, irritability, nervousness, insomnia, and headache. Because of the possibility of withdrawal, clonidine should not be used in patients who are unwilling or unable to follow the prescribing information.

Pregnant or breastfeeding

Clonidine should not be used by pregnant women, except in the rare case where the benefits of taking clonidine outweigh the risks to the developing fetus.

Other conditions and allergies

Clonidine should not be used by people who have a known allergy to this drug. If a person has underlying depression, clonidine should be used with caution and under close physician supervision.

Clonidine should be used only with caution and close physician supervision in patients with chronic renal failure, coronary artery disease, and preexisting eye problems. People with kidney disease may need to take a reduced dosage.

Side effects

The most common side effect associated with clonidine is dizziness accompanying sudden changes in position, such as standing up rapidly. In order to avoid this, patients should stand up slowly. People using the dermal patch may develop rash, hair loss, a burning sensation on the skin, or other skin irritations where the patch is applied. Switching to tablets may not completely eliminate these skin problems.

Clonidine can cause dry mouth, constipation, nausea, daytime sleepiness, weakness, and lethargy. These side effects may take several weeks to disappear. In some cases, these side effects can be eliminated with dosage readjustment. In addition, clonidine may cause eye dryness, loss of sex drive, and decreased sexual activity.

If patients experience weight gain in the beginning of therapy, they can expect this side effect to decline over a period of several days to weeks.

Interactions

Clonidine's blood pressure-lowering effects may be enhanced by other drugs that also lower blood pressure. Conversely, the blood pressure-lowering effects of clonidine may be negated by many antidepressants.

Resources

BOOKS

- American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda, MD: ASHP, 2015.
- Holland, Leland Norman, and Michael Patrick Adams. *Core Concepts in Pharmacology*. 4th ed. New York: Prentice Hall, 2014.
- Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger, 2013.

OTHER

- U.S. Food and Drug Administration. *Highlights of Prescribing Information* (Kapvay). http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022331s0141bl.pdf (accessed February 20, 2015).

PERIODICALS

- Beaulieu, M. J. "Oral Clonidine in the Management of Acquired Opioid Dependency." *Neonatal Network* 32, no. 6 (2013): 419–24.
- Eapen, V., P. Ward, and R. Clarke. "Clonidine in Tourette Syndrome and Sensorimotor Gating." *Psychiatry Research* 215, no. 2 (2014): 494–96.
- Kumar, A., et al. "Clonidine for Management of Chronic Pain: A Brief Review of the Current Evidences." *Saudi Journal of Anaesthesia* 8, no. 1 (2014): 92–96.
- Lambert, P., et al. "Clonidine Premedication for Postoperative Analgesia in Children." *Cochrane Database of Systematic Reviews* 1, art. no. CD009633 (2014). <http://dx.doi.org/10.1002/14651858.CD009633.pub2> (accessed February 20, 2015).

WEBSITES

- AHFS Consumer Medication Information. "Clonidine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682243.html> (accessed February 20, 2015).
- Micromedex. "Clonidine." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/clonidine-oral-route/proper-use/drg-20063252> (accessed February 20, 2015).
- U.S. National Library of Medicine. "Clonidine Hydrochloride." DailyMed. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a842ab83-3531-44dd-a8a8-64dd89_e87026 (accessed February 20, 2015).

ORGANIZATIONS

- American Academy of Clinical Toxicology, 6728 Old McLean Village Drive, McLean, VA 22101, (703) 556-9222, Fax: (703) 556-8729, admin@clintox.org, <http://www.clintox.org/>.
- American Academy of Family Physicians, 11400 Tomahawk Creek Parkway, Leawood, KS 66211-2672, (913) 906-6000, (800) 274-2237, Fax: (913) 906-6075, center@aafp.org, <http://www.aafp.org/>.
- American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.
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Clopidogrel

Definition

Clopidogrel is an anticoagulant, which is a drug that stops blood from clotting.

Purpose

Clopidogrel is used to prevent blood clots. It is used in people with unstable angina or non-ST-segment elevation myocardial infarction (a type of heart attack), referred to collectively as acute coronary syndrome or UA/NSTEMI. These are two closely related conditions that are caused by limited oxygen supply to the heart, usually associated with blocked blood flow.

Clopidogrel is also approved for patients who have had a recent stroke or heart attack or who have peripheral arterial disease (PAD). Studies show that clopidogrel can reduce the risk of having another stroke or heart attack and the risk of death from other causes related to the vascular system (blood vessels).

Description

Blood clotting is a complex mechanism in which platelets group together and encourage the formation of blood clots. Injury or damage to the wall of a blood



Plavix (clopidogrel), 75 mg. (© Cengage Learning®)

vessel or plaque buildup (such as in PAD) can lead to platelet aggregation. Clots inside the blood vessels can block the blood supply to essential organs, which may lead to heart attacks or strokes. If the blood clot is lodged in a leg, it will cause claudication (pain caused by too little blood flow). In the worst case, this can lead to death of the tissues of the limb and gangrene when the large mass of tissue dies. By stopping the platelets from binding to each other, clopidogrel reduces the risk of clot formation.

Clopidogrel itself is not an active drug but must be metabolized by the liver into an active form. The active drug blocks some of the receptors on the surface of the blood platelets so that the platelets cannot bind together and release clotting factors.

Clopidogrel is available in 75 and 300 milligram (mg) tablets.

U.S. brand names

Clopidogrel is marketed under the brand name Plavix.

Recommended dosage

For patients with UA/NSTEMI, clopidogrel is started with one initial 300 mg dose, referred to as a loading dose. The dosage is then continued with one 75 mg tablet every day. Individuals may also be advised to start taking **aspirin**, which may be in the range of 75–325 mg daily.

For patients with ST-elevation myocardial infarction (STEMI), clopidogrel may be started without the loading dose. The normal dose is 75 mg/day in combination with aspirin.

There are a number of alternative dosing regimens, depending on the patient's situation. Individuals should follow the specific instructions of their healthcare provider.

Pediatrics

Safety and efficacy of clopidogrel has not been demonstrated in children.

Geriatric

No dose adjustments are required based on age.

Precautions

Clopidogrel carries a boxed warning on its package insert, which is the highest level of warning that the U.S. Food and Drug Administration (FDA) provides. Clopidogrel is not an active drug—it is a prodrug, or a therapeutic agent that is altered in the body to its active

KEY TERMS

Aggregation—A clumping together of platelets induced by various agents as part of the mechanism leading to clot formation.

Angina—Pain, discomfort, or pressure in the chest that is caused by an insufficient supply of blood (ischemia) to the heart muscle. It is also sometimes characterized by a feeling of choking, suffocation, or crushing heaviness. This condition is also called angina pectoris.

Anticoagulant—A chemical or medication that prevents blood from clotting.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Claudication—Pain and weakness usually in the legs caused by inadequate blood supply.

Clotting factors—Also known as coagulation factors; proteins in the plasma that serve to activate various parts of the blood-clotting process by being transformed from inactive to active form.

Myocardial infarction—Commonly known as a heart attack, a myocardial infarction is an episode in which some of the heart's blood supply is severely cut off or restricted, causing the heart muscle to suffer and die from lack of oxygen.

Myocardium—The middle layer of the heart wall, composed of muscle.

Peripheral arterial disease (PAD)—A disease characterized by plaque buildup in the arteries.

Platelets—Small, disk-shaped bodies in the blood that form the initial clot at the rupture site of a blood vessel.

form. The conversion to the active form occurs in the liver using the enzyme cytochrome P450 2C19 (CYP2C19). Some people produce smaller amounts of this enzyme than others and are thus less capable of producing the active form of clopidogrel. This means that the regular dose of the drug will not show the same anticoagulant effect, and these patients are at greater risk of repeat heart attacks or strokes. Tests are available to identify this population group so that they can switch to a different drug. The condition is more common in individuals of Asian descent.

Pregnant or breastfeeding

Clopidogrel has been classified as a pregnancy category B drug. While there is no evidence from animal studies or clinical reports that clopidogrel causes any harm to a fetus, there have been no controlled studies in humans. The recommendation is that clopidogrel be used during pregnancy only if clearly necessary (i.e., the benefits outweigh the risks).

Animal studies show that clopidogrel is excreted in milk. While there have been no studies in humans, it seems likely that clopidogrel will be excreted, so it is recommended that mothers either discontinue the drug or discontinue nursing, taking into account the importance of the drug to the mother.

Other conditions and allergies

Individuals who are allergic to the drugs ticlopidine and prasugrel may also be sensitive to clopidogrel, as these drugs share the same therapeutic and chemical class.

Side effects

The most important side effect is the risk of bleeding. Generally, the risk of a serious bleeding incident is higher when clopidogrel is taken with aspirin. Bleeding incidents include intracranial bleeding, eye bleeding, and gastrointestinal bleeding.

Interactions

Individuals should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs or supplements.

Drugs

Because clopidogrel is effective only when metabolized, drugs that reduce the levels of the CYP2C19 enzyme will reduce the effectiveness of the anticoagulant. These include **omeprazole** (Prilosec) and **esomeprazole** (Nexium). **Dexlansoprazole**, **lansoprazole**, and **pantoprazole** have effects similar to omeprazole and esomeprazole but have less of an effect on liver enzymes.

Drugs with known anticoagulant effects may have an additive effect to clopidogrel, increasing the risk of bleeding. These drugs include nonsteroidal anti-inflammatory agents and other anticoagulants such as **warfarin**.

Some antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), both alter platelet function. The combination with clopidogrel may increase the risk of bleeding.

Resources

PERIODICALS

- Goldswieg, A. M., et al. "Contemporary Use of Dual Antiplatelet Therapy for Preventing Cardiovascular Events." *American Journal of Managed Care* 20, no. 8 (2014): 659–65.
- Rubboli, A., et al. "The Optimal Management of Patients on Oral Anticoagulation Undergoing Coronary Artery Stenting." *Thrombosis and Haemostasis* 112, no. 6 (2014): 1080–87.
- Tantry, U. S., et al. "Resistance to Antiplatelet Drugs: What Progress Has Been Made?" *Expert Opinion on Pharmacotherapy* 15, no. 17 (2014): 2553–64.
- Winslow, R. "When Plavix May Not Work." *Wall Street Journal*, March 22, 2010.

OTHER

- U.S. Food and Drug Administration. "Medication Guide: Plavix." <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM243349.pdf> (accessed March 3, 2015).

WEBSITES

- AHFS Consumer Medication Information. "Clopidogrel." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601040.html> (accessed March 3, 2015).
- U.S. Food and Drug Administration. "Information on Clopidogrel Bisulfate (Marketed as Plavix)." <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm190836.htm> (accessed March 3, 2015).
- U.S. National Library of Medicine, National Institutes of Health. "Clopidogrel—Clopidogrel Bisulfate Tablet, Film Coated." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=eda8df1-caf9-ff72-1304-5ae8b355f8e7> (accessed March 3, 2015).

ORGANIZATIONS

- American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.
- American Society for Preventative Cardiology (ASPC), 6816 Southpoint Parkway, Suite 1000, Jacksonville, FL 32216, (904) 309-6235, Fax: (904) 998-0855, <https://www.asponline.org/>.

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Clotrimazole/betamethasone

Definition

Clotrimazole/betamethasone is a combination of an antifungal agent with a high potency anti-inflammatory drug (corticosteroid).



Clotrimazole/betamethasone cream. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Purpose

Clotrimazole/betamethasone lotion has been shown to be effective in treating fungal infections of the skin, such as ringworm (tinea corporis), athlete's foot (tinea pedis), and jock itch (tinea cruris).

Description

Clotrimazole/betamethasone is sold as a topical lotion that is applied to the infected area of skin. Each gram (g) of cream contains 10 milligrams (mg) of clotrimazole and 0.643 mg of betamethasone.

U.S. brand names

Clotrimazole/betamethasone is sold under the brand name Lotrisone (0.05% betamethasone/1% clotrimazole). A generic cream and lotion with the same concentrations of active ingredients is also available.

Canadian brand names

In Canada, the cream is sold as Lotriderm.

International brand names

International brand names for clotrimazole/betamethasone include:

- Clotrasone
- Derzid-c

- Gynesten-B
- Lotricomb
- Lotriderm

Recommended dosage

For treatment of fungal infections other than the palms and soles, a thin film of the cream or lotion is applied to the affected area twice a day at 12-hour intervals for one week. If there is no clinical improvement after one week, the treatment should be re-evaluated. Treatment should not be used for more than two weeks. The maximum weekly dosage is 45 g. Individuals should refrain from applying occlusive (airtight and watertight) dressings to the infected areas.

For treatment of fungal infections of the palms and soles, because of the thickness of the skin in these areas, treatment may be extended up to four weeks.

Precautions

Corticosteroids such as betamethasone are associated with adverse effects, the most serious of which is the development of reversible hypothalamic-pituitary-adrenal (HPA) axis suppression. This condition may occur with long-term use of any corticosteroid that is systemically absorbed over a long period of time. It affects the hypothalamus, the pituitary gland, and the adrenal gland. The adrenal gland releases cortisol, which is a natural hormone. When the body detects the presence of steroid hormones, the level of natural cortisol production is reduced. Because cortisol regulates many essential functions, reduction of its production is very serious. At the same time, long-term high levels of cortisol-like drugs can lead to Cushing syndrome, characterized by the development of a fatty hump between the shoulders, facial swelling, stretch marks (striae), high blood pressure, and bone loss. Cushing syndrome occurs either when the body is producing too much cortisol or when the hormone is used for medicinal purposes. Betamethasone is a very potent form of steroid hormone, and enough can be absorbed through the skin to cause both Cushing syndrome and HPA suppression if used for an extended period of time. This is why there is a time limit on how long clotrimazole/betamethasone may be used.

Clotrimazole/betamethasone should not be used to treat diaper dermatitis (diaper rash) in any age group (including patients who require adult incontinence products).

Pediatric

Children are more likely to absorb betamethasone in higher concentrations than adults, which subjects

KEY TERMS

Adrenal gland—An endocrine gland located above each kidney. The inner part of each gland secretes epinephrine (adrenaline), and the outer part secretes steroid hormones.

Corticosteroid—A class of drugs based on hormones formed in the adrenal gland, used to reduce inflammation.

Cushing syndrome—A group of conditions caused by increased production of cortisol hormones or by the administration of glucocorticoid hormones (cortisone-like hormones); symptoms include fat accumulation, high blood pressure, bone loss, and emotional disturbances.

Hypothalamus—A structure within the brain responsible for a large number of normal functions throughout the body, including regulating sleep, body temperature, hunger, and sexual development. The hypothalamus also regulates the functions of the pituitary gland by directing the pituitary to stop or start production of its hormones.

Inflammation—The body's reaction to invasion by foreign matter, particularly infection; characterized by swelling, redness, and pain.

Pituitary gland—A gland located at the base of the brain and controlled by the hypothalamus. It controls most endocrine functions and is responsible for things such as kidney function, lactation, and growth and development.

Tinea corporis—Fungal infection of the body affecting any skin region other than the scalp, groin, palms, and soles; commonly referred to as ringworm.

Tinea cruris—Fungal infection of the groin; commonly referred to as jock itch.

Tinea pedis—Fungal infection of the foot; commonly referred to as athlete's foot.

them to a greater risk of adverse effects. Clotrimazole/betamethasone is not recommended for patients under 17 years of age.

Geriatric

Because of the risk of adverse effects, including skin atrophy and skin ulceration, clotrimazole/betamethasone should be used with extreme care in elderly patients with thinning skin.

Pregnant or breastfeeding

Clotrimazole/betamethasone is categorized as a pregnancy category C drug. Although there have been no reports of fetal abnormalities related to clotrimazole/betamethasone cream, some corticosteroids have been absorbed through the skin and are known to cause fetal abnormalities in test animals. Clotrimazole/betamethasone cream has not been tested in pregnant women.

Corticosteroids can be excreted in human milk and can interfere with infant development. While there is no clear evidence that steroid drugs can be absorbed through the skin at adequate levels to interfere with infant growth and development, extreme caution should be used if clotrimazole/betamethasone is prescribed for a nursing mother.

There is no evidence of fetal toxicity from clotrimazole, which is available by itself for treatment of skin fungus.

Other conditions and allergies

Clotrimazole/betamethasone should not be used by patients who are allergic to any of its components.

Side effects

The most serious effects associated with clotrimazole/betamethasone are the development of HPA suppression and Cushing syndrome. Excessive use of high-potency topical steroids may also cause skin atrophy and localized hair growth.

Other side effects may be relatively minor, such as development of a mild rash, dry skin, and local irritation where the cream or lotion is applied.

Interactions

Although a very large number of drugs may interact with clotrimazole and/or betamethasone, there are no significant interactions when the drugs are used only for short-term application to the skin under proper conditions. Individuals should consult with their healthcare provider before applying any other topical skin products while using clotrimazole/betamethasone.

Resources

PERIODICALS

Balkrishnan, R., et al. "Analysis of Factors Associated with Prescription of a Potentially Inappropriate Combination Dermatological Medication among U.S. Outpatient Physicians." *Pharmacoepidemiology & Drug Safety* 13, no. 3 (2004): 133–38.

El-Gohary, M., et al. "Topical Antifungal Treatments for Tinea Cruris and Tinea Corporis." *Cochrane Database of*

Systematic Reviews 8, art. no. CD009992 (August 4, 2014). <http://dx.doi.org/10.1002/14651858.CD009992.pub2> (accessed March 4, 2015).

Railan, D., et al. "Pediatricians who Prescribe Clotrimazole-Betamethasone Dipropionate (Lotrisone) Often Utilize It in Inappropriate Settings Regardless of Their Knowledge of the Drug's Potency." *Dermatology Online Journal* 8, no. 2 (2002): 3.

OTHER

Merck. "Patient Information: Lotrisone." http://www.merck.com/product/usa/pi_circulars/l/lotrisone_cream/lotrisone_ppi.pdf (accessed March 4, 2015).

U.S. Food and Drug Administration. "Lotrisone." http://www.fda.gov/ohrtms/dockets/ac/03/briefing/3999B1_12_Lotrisone%20Label.pdf (accessed March 4, 2015).

WEBSITES

Micromedex. "Betamethasone and Clotrimazole (Topical Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/betamethasone-and-clotrimazole-topical-route/description/drg-20061704> (accessed March 4, 2015).

Mosby's Drug Consult. "Betamethasone Dipropionate; Clotrimazole (0466)." http://www3.us.elsevierhealth.com/DrugConsult/Top_200/Drugs/e0466.html (accessed March 4, 2015).

Physicians' Desk Reference. "Lotrisone." PDR Health. <http://www.pdrhealth.com/drugs/lotrisone> (accessed March 4, 2015).

U.S. National Library of Medicine, National Institutes of Health. "Lotrisone." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1c18e5fc-bf82-47bc-bfd9-8d3e503569ba> (accessed March 4, 2015).

ORGANIZATIONS

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Clozapine

Definition

Clozapine is an antipsychotic drug used to alleviate the symptoms and signs of schizophrenia—a form of severe mental illness that is characterized by hallucinations, delusions, unusual behavior, and loss of contact with reality.

Purpose

Clozapine is principally used to reduce the signs and symptoms of severe schizophrenic illness. The drug is



Clozapine, 200 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

intended for use in patients with severe schizophrenia who have not responded to any other antipsychotic drug. Clozapine is also used in patients with severe schizophrenia when other antipsychotic medications have caused intolerable side effects. As many as 20%–60% of patients have schizophrenia that is treatment resistant, making the management of schizophrenia a challenge for clinicians. Augmenting clozapine with other drugs such as **risperidone** may further minimize some symptoms associated with schizophrenia.

Description

Clozapine is considered an atypical antipsychotic drug. Atypical antipsychotics differ from typical antipsychotics in their effectiveness in treating schizophrenia and their profile of adverse effects. Clozapine may reduce the signs and symptoms of schizophrenia in a large proportion of patients with treatment-resistant schizophrenia who do not respond to typical antipsychotics. Moreover, the drug is less likely than typical antipsychotics to cause tardive dyskinesia and other extrapyramidal (pertaining to a neural network in the brain) side effects. Tardive dyskinesia is a syndrome of involuntary, uncoordinated movements that may not disappear or may only partially improve after the drug is stopped. Tardive dyskinesia involves involuntary movements of the tongue, jaw, mouth or face, or other groups of skeletal muscles. The appearance of tardive dyskinesia increases with increasing age and with increasing dosage. It may also develop after the use of the antipsychotic has

stopped. Women are at greater risk than men for developing tardive dyskinesia. There is no known effective treatment for this syndrome, although gradual (but rarely complete) improvement may occur over a long period.

The superiority of clozapine in patients resistant to treatment is considered an important advance, but the drug is not without problems. Clozapine is generally considered the most toxic of the antipsychotic drugs. It causes agranulocytosis, a life-threatening depletion of white blood cells, in 1%–2% of patients. It also causes epileptic seizures and adverse effects on the heart and blood pressure more frequently than other antipsychotic medicines. Clozapine is usually reserved for the most severely ill patients with schizophrenia who have not responded to other treatments. Other atypical antipsychotic drugs were developed subsequently and are considered safer to use than clozapine.

The mechanisms of action of antipsychotic drugs are not completely understood. The effect of clozapine is believed to be related to its actions in blocking neurotransmission due to the neurotransmitters dopamine and serotonin in a region of the brain called the limbic system, which is involved with emotions and motivation. The actions of clozapine may target the limbic system more specifically than those of typical antipsychotic drugs.

U.S. brand names

In the United States, the drug is sold under the brand name Clozaril.

Origins

Clozapine was the first atypical antipsychotic drug to be developed. In the late 1980s, clozapine was tested in severely ill patients with schizophrenia who had been treated with a typical antipsychotic drug but had not shown much improvement. A significant proportion of these patients improved as a result of treatment with clozapine.

Recommended dosage

Clozapine is available as 12.5, 25, 100, and 200 milligram (mg) tablets. The usual dosage of clozapine is 300–600 mg per day; however, some patients may require daily dosages of up to 900 mg. To minimize adverse effects, the initial dose of clozapine is 12.5 mg twice a day, and the dose is increased by 25–50 mg each day until the dose reaches 300–450 mg per day. The daily dosage of the drug is then determined based on the individual patient's response, but increases should not exceed 100 mg once or twice a week.

KEY TERMS

Delusions—Irrational beliefs that defy normal reasoning and remain firm even when overwhelming proof is presented to dispute them. Delusions are distinct from culturally or religiously based beliefs that may be seen as untrue by outsiders.

Epilepsy—A disorder associated with disturbed electrical discharges in the central nervous system that cause seizures.

Extrapyramidal symptoms—A group of side effects associated with antipsychotic medications and characterized by involuntary muscle movements, including contraction and tremor.

Neurotransmitter—One of a group of chemicals secreted by a nerve cell (neuron) to carry a chemical message to another nerve cell, often as a way of transmitting a nerve impulse. Examples of neurotransmitters include acetylcholine, dopamine, serotonin, and norepinephrine.

Schizophrenia—A major mental illness marked by psychotic symptoms, including hallucinations, delusions, and severe disruptions in thinking.

Seizure—A convulsion or uncontrolled discharge of nerve cells that may spread to other cells throughout the brain.

Precautions

Clozapine may cause agranulocytosis, a life-threatening depletion of white blood cells. The blood cells affected by clozapine defend the body against infections by bacteria and other microorganisms, and patients with agranulocytosis are subject to severe infections. Clozapine treatment is reserved for the most severely ill patients with schizophrenia who have not responded to other treatments. Clozapine is available only through a distribution system that assures close monitoring of white blood cells. Patients must have white blood cell counts determined before starting treatment, then once every week for the first six months, once every other week after that, and once a week for the first month after clozapine treatment is stopped.

Clozapine may cause epileptic seizures in about 5% of patients. The frequency of seizures goes up as the dosage is increased. Usually, patients who experience seizures on clozapine discontinue the drug or reduce the dose. Neuroleptic malignant syndrome (NMS), a dangerous condition characterized by high fever, muscular rigidity, rapid pulse, sweating, and altered mental state,

may occur with all antipsychotic medications, including clozapine. NMS requires immediate medical treatment.

Clozapine frequently causes sedation and may interfere with driving and other tasks requiring alertness. The drug may increase the effects of alcohol and sedatives and related drugs. Clozapine may cause low blood pressure and sudden drops in blood pressure on standing up, which may cause dizziness or fainting. Elevated heart rate may occur in up to one-fourth of patients; this effect may be a serious risk for patients with heart disease. Clozapine-induced fever, unrelated to any illness, may occur. The fever usually subsides within a few days, but it may require discontinuing the drug.

Clozapine may cause myocarditis (heart inflammation). Symptoms may be similar to the flu and include chest pain, fatigue, fever, joint pain, and leg swelling. If any of these or other unusual side effects develop, patients should contact their physician immediately.

Geriatric

Clozapine and other antipsychotic drugs are associated with an increased risk of death when used in elderly patients with dementia. In June 2008, the U.S. Food and Drug Administration (FDA) announced a requirement for manufacturers of clozapine (and other antipsychotic drugs) to add a warning label to their packaging stating this risk. The reason for the increase was unclear in studies, but most deaths were found to be related to either cardiovascular complications or complications associated with infection. Clozapine is not approved by the FDA for the treatment of behavior problems in older adults with dementia, and patients in this category (or caregivers of patients in this category) should discuss the risks of taking clozapine with their physician. Elderly patients may also be particularly sensitive to sedation, low blood pressure, and other side effects.

Pregnant or breastfeeding

Clozapine should be used in pregnant women only when strictly necessary. Babies born to mothers who took clozapine during their pregnancy may be at risk for extrapyramidal symptoms (EPS) and symptoms of withdrawal, including agitation, trouble breathing, and difficulty feeding. Clozapine may be secreted in breast milk, and breastfeeding may not be advisable. Clozapine has a higher risk of adverse side effects in children and adolescents but may be necessary if other treatments are not effective.

Side effects

Clozapine may cause many side effects. The following side effects are grouped by the body system affected:

- cardiovascular: decreases of blood pressure, especially on arising from a seated or lying position, which may cause dizziness or fainting; rapid heart rate; changes in heart rhythm; abnormal electrocardiogram
- nervous system: sedation, increased seizure tendency
- digestive system: increased appetite, excessive salivation, nausea, constipation, abnormal liver tests, elevated blood glucose
- autonomic: blurred vision; exacerbation of glaucoma; dry mouth; nasal congestion; decreased sweating; difficulty urinating, particularly in men with enlarged prostate
- skin: rashes
- body as a whole: weight gain, fever

Interactions

Clozapine may interact with many other drugs. Patients (or their caregivers) should inform the healthcare provider in charge about all other drugs the patient is taking before the patient starts treatment. Because of the risk of agranulocytosis, clozapine should not be given along with medications that suppress production of blood cells.

Drugs

Clozapine may intensify the effects of drugs causing sedation, including barbiturates, narcotic pain medications, minor tranquilizers, and antihistamines. Similarly, clozapine may cause excessive reductions of blood pressure in patients taking other medicines that lower blood pressure. Clozapine may also intensify side effects of drugs that cause blurred vision, dry mouth, diminished sweating in hot weather, and constipation. Many other antipsychotics and antidepressants cause such side effects.

Clozapine may increase the effects of other medications that also lower seizure threshold (make it more likely to have seizures), such as steroid drugs, the asthma medication theophylline, and many other psychiatric drugs. Patients with epilepsy may require adjustment in their dosage of antiseizure medications. Lithium may increase the risk of seizures and other nervous system adverse effects when given with clozapine.

Certain drugs that are eliminated by the liver may interfere with the elimination of clozapine from the body, causing higher blood levels and increased side effects. Conversely, clozapine may interfere with the elimination of other drugs that are metabolized by the liver. Antidepressants that affect brain serotonin levels may increase blood levels of clozapine, possibly causing increased side effects.

Food and other substances

Clozapine may increase the sedative effect of alcohol.

Resources

BOOKS

- Albers, Lawrence J., Rhoda K. Hahn, and Christopher Reist. *Handbook of Psychiatric Drugs*. Laguna Hills, CA: Current Clinical Strategies, 2010.
- American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda, MD: ASHP, 2015.
- Graham, George. *The Disordered Mind: An Introduction to Philosophy of Mind and Mental Illness*. 2nd ed. New York: Routledge, 2013.
- Holland, Leland Norman, and Michael Patrick Adams. *Core Concepts in Pharmacology*. 4th ed. New York: Prentice Hall, 2014.
- Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger, 2013.

PERIODICALS

- Gogtay, N., and J. Rapoport. "Clozapine Use in Children and Adolescents." *Expert Opinion on Pharmacotherapy* 9, no. 3 (February 2008): 459–65.
- Grant, J. E., et al. "Clozapine Revisited: Impact of Clozapine vs. Olanzapine on Health Care Use by Schizophrenia Patients on Medicaid." *Annals of Clinical Psychiatry* 27, no. 1 (2015): E1–E10.
- Han, M., et al. "Cognitive Differences in Schizophrenia on Long-Term Treatments with Clozapine, Risperidone and Typical Antipsychotics." *International Clinical Psychopharmacology* 30, no. 2 (2015): 89–95.
- McEvoy, J. P., et al. "Effectiveness of Clozapine versus Olanzapine, Quetiapine, and Risperidone in Patients with Chronic Schizophrenia Who Did Not Respond to Prior Atypical Antipsychotic Treatment." *American Journal of Psychiatry* 163, no. 4 (April 2006): 600–10.
- Micoulaud-Franchi, Jean-Arthur, et al. "Effects of Clozapine on Perceptual Abnormalities and Sensory Gating: A Preliminary Cross-Sectional Study in Schizophrenia." *Journal of Clinical Psychopharmacology* (January 13, 2015): e-pub ahead of print. <http://dx.doi.org/10.1097/JCP.0000000000000270> (accessed February 20, 2015).
- Whitney, Z., et al. "Treatment of Clozapine-Associated Weight Gain: A Systematic Review." *European Journal of Clinical Pharmacology* (January 28, 2015): e-pub ahead of print. <http://dx.doi.org/10.1007/s00228-015-1807-1> (accessed February 20, 2015).

WEBSITES

- AHFS Consumer Medication Information. "Clozapine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a691001.html> (accessed February 20, 2015).
- National Alliance on Mental Illness. "Clozaril (Clozapine)." http://www2.nami.org/Template.cfm?Section=About_Medications&Template=/TaggedPage/TaggedPageDisplay.

cfm&TPLID=51&ContentID=20850 (accessed February 20, 2015).

ORGANIZATIONS

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.
 American Psychological Association, 750 First Street NE, Washington, DC 20002-4242, (202) 336-5500, (800) 374-2721, TTY: (202) 336-6123, <http://www.apa.org/>.
 Mental Health America, 2000 N. Beauregard Street, 6th Floor, Alexandria, VA 22311, (703) 684-7722, (800) 969-6642, Fax: (703) 684-5968, <http://www1.nmha.org/>.
 National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.
 National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

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Clozaril see **Clozapine**

Codeine/acetaminophen see **Acetaminophen/codeine**

Cogentin see **Benztropine**

Colchicine

Definition

Colchicine is a medication that is derived from the plant *Colchicum autumnale*.

Purpose

Colchicine is used to prevent attacks of gout. Colchicine is also used to treat and prevent familial Mediterranean fever (FMF), an inherited genetic condition characterized by bouts of fever and peritonitis, or inflammation of the abdomen. In the most severe cases, renal (kidney) failure may result. Colchicine is used to prevent attacks of FMF and is extremely effective for this purpose.

Colchicine has been studied in a number of other conditions, but the studies have been small and have not found strong evidence in support of colchicine.



Colcrys (colchicine), 0.6 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Description

Gout is a condition characterized by joint pain caused by elevated levels of uric acid in the blood. If the uric acid crystallizes, the crystals may be deposited in joints or other tissues. The joint at the base of the big toe is the most common location, but the uric acid crystals may also appear as kidney stones. The preferred treatment for acute attacks of gout is high-dose nonsteroidal anti-inflammatory drugs (NSAIDs) such as **ibuprofen** (Motrin), **indomethacin** (Indocin), naproxen (Naprosyn), or others. However, because all NSAIDs can cause serious stomach upset and even ulcers, not all patients can tolerate these drugs. For those patients, colchicine remains available as a treatment option.

U.S. brand names

Colchicine is marketed as 0.6 milligram (mg) tablets sold under the brand name Colcrys and 0.6 mg capsules sold under the brand name Mitigare. Colcrys is the only form that is labeled as indicated for treatment of familial Mediterranean fever. It is also available as a generic.

International brand names

Colchicine is available internationally, but it is usually marketed under its generic name. Brand names include but are not limited to:

- Articol (Mediline, Peru)
- Artrichine (ECU, Ecuador)

- Colchysat Bürger (Ysatfabrik, Germany)
- Degout (Chin Teng, Taiwan)
- Goutnil (Inga, India)
- Suyuni (Tai Yu, Taiwan)

Origins

Colchicine has been in medical use for centuries. It is derived from the fall flowering crocus *Colchicum autumnale*. The plant is popular as a decorative plant that produces flowers in the autumn as other plants are starting to fade. But because of the presence of colchicine, the plant may be ill suited for homes with young children or pets. The active principle, the alkaloid colchicine, was first isolated in 1820.

Recommended dosage

For treatment of an acute gout flare-up, 1.2 mg (two tablets or capsules) is taken at the first sign of a flare, then 0.6 mg (one tablet or capsule) 1 hour later. The total dosage should not exceed 1.8 mg in a one-hour period. Doses greater than 1.8 mg/day do not increase pain relief and increase the risk of toxicity. Once administered, the activity of colchicine does not begin for 18–24 hours. The peak effect is reached in 48–72 hours.

For gout prevention, one tablet or capsule may be taken once or twice a day, with a maximum of two doses a day.

Pediatric

Colchicine is not recommended for the treatment of gout in patients under the age of 18 years.

Recommended dosages for treating familial Mediterranean fever in children are as follows:

- younger than 4 years: safety and efficacy not established
- 4–6 years: 0.3–0.8 mg/day by mouth in a single daily dose or divided into two doses every 12 hours
- 6–12 years: 0.9–0.8 mg/day by mouth in a single daily dose or divided into two doses every 12 hours
- older than 12 years: 1.2–0.4 mg/day by mouth in single daily dose or divided into two doses every 12 hours

Because commercial dosage forms come only in 0.6 mg, parents or caregivers may wish to consider asking the pharmacist to prepare powders or capsules in pediatric doses.

Precautions

Colchicine is extremely toxic. It should be used with care and kept out of reach of children. Colchicine is not a

KEY TERMS

Acute—Having a sudden onset and lasting a short time.

Alkaloid—A naturally occurring compound that contains both nitrogen and carbon and acts as a base, which means it takes a hydrogen ion from an acid. Well-known alkaloids include morphine, ephedrine, and nicotine.

Familial Mediterranean fever—A hereditary disorder characterized by recurring fevers and inflammation.

Gout—A type of arthritis in which uric acid, a waste product that normally passes out of the body in urine, collects in the joints and the kidneys, resulting in swollen, painful joints and possibly kidney stones.

Uric acid—A compound resulting from the body's breakdown of purine, a white crystalline substance that is one of the building blocks of DNA. It is normally present in human urine only in small amounts.

general analgesic (pain reliever) and should not be used to treat pain other than that from gout.

Pediatric

Colchicine is very toxic and should be kept away from children. It is not approved for treatment of gout in children under the age of 18 or to treat familial Mediterranean fever in children under the age of 4.

Pregnant or breastfeeding

Colchicine is classified as a pregnancy category C drug. This means that there have been no adequate human studies of the drug's effects on a fetus, but animal reproductive studies of colchicine have found some evidence of adverse fetal effects. Colchicine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Colchicine is excreted into human milk. While there are no published reports of adverse effects in breastfeeding infants of mothers taking colchicine, colchicine may affect development of the gastrointestinal tract. Caution should be exercised, and breastfeeding infants should be observed for adverse effects when colchicine capsules are administered to a nursing woman.

Side effects

The most common adverse effects of colchicine are gastrointestinal problems such as nausea and vomiting, diarrhea, and abdominal pain. These adverse effects may be the first signs of drug toxicity and may indicate the need for a dose adjustment or discontinuation of treatment.

Muscle pain is much more common among patients with liver or kidney problems and elderly patients, but it has been reported among healthy patients as well. Colchicine-induced muscle pain is usually reversible when the drug is discontinued, but loss of pain may take up to several months.

Some studies have reported fertility impairment among patients, both male and female, taking colchicine, but no direct relationship has been demonstrated.

Interactions

Individuals should discuss all medications they are currently taking, including over-the-counter drugs and supplements, with their healthcare provider before taking colchicine.

Drugs

Colchicine is metabolized in the liver by an enzyme called cytochrome P3A4 (CYP3A4). A large number of other drugs inhibit the production of this enzyme, which means that colchicine is not eliminated as quickly as it should be, and blood levels of colchicine may increase. Drugs that inhibit the production of CYP3A4 include antibiotics (e.g., **clarithromycin**), antifungals (e.g., **ketoconazole**), and antiretrovirals (e.g., indinavir).

Cholesterol-lowering drugs (statins) may increase the risk of muscle pain and weakness when used with colchicine.

Food and other substances

Colchicine concentrations may be elevated by grapefruit juice ingestion, increasing the risk of toxicity and muscle weakness. Patients taking colchicine should not consume grapefruit juice.

Resources

PERIODICALS

- Abramson, S. B. "Treatment of Gout and Crystal Arthropathies and Uses and Mechanisms of Action of Nonsteroidal Anti-inflammatory Drugs." *Current Opinion Rheumatology* 4, no. 3 (1992): 295–300.
- Hamuryudan, V., et al. "Colchicine in Behçet Syndrome: a Long-Term Survey of Patients in a Controlled Trial." *Journal of Rheumatology* 41, no. 4 (2014): 735–38.
- Krishnan, E., and L. Chen. "Trends in Physician-Diagnosed Gout and Gout Therapies in the US: Results from the

National Ambulatory Health Care Surveys 1993 to 2009." *Arthritis Research & Therapy* 15, no. 6 (2013): R181.

Lange, U., C. Schumann, and K. L. Schmidt. "Current Aspects of Colchicine Therapy—Classical Indications and New Therapeutic Uses." *European Journal of Medical Research* 6, no. 4 (2001): 150–60.

OTHER

U.S. Food and Drug Administration. "Medication Guide: Mitigare Capsules." <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM417495.pdf> (accessed January 10, 2015).

WEBSITES

- "Colchicine." Drugs.com. <http://www.drugs.com/international/colchicine.html> (accessed January 8, 2015).
- Merck Manuals. "Familial Mediterranean Fever." The Merck Manual Professional Edition. http://www.merckmanuals.com/professional/pediatrics/hereditary_periodic_fever_syndromes/familial_mediterranean_fever.html?qt=colchicine&alt=sh (accessed January 10, 2015).
- Takeda Pharmaceuticals U.S.A. Colcrys.com. <https://www.colcrys.com/default.aspx> (accessed January 10, 2015).
- U.S. National Library of Medicine. "Colchicine." MedlinePlus. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682711.html> (accessed January 10, 2015).
- U.S. National Library of Medicine. "Label: Colchicine—Colchicine Capsule." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ee1583ac-c308-4beb-b602-9ecac4977026#section-8.1> (accessed January 10, 2015).

ORGANIZATIONS

American College of Rheumatology, 2200 Lake Boulevard, Atlanta, GA 30319, (404) 633-3777, Fax: (404) 633-1870, acr@rheumatology.org, <https://www.rheumatology.org/default.aspx>.

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Colcrys see **Colchicine**

Colesevelam

Definition

Colesevelam is one of a class of drugs known as bile acid sequestrants.

Purpose

Colesevelam is a bile acid sequestrant prescribed to reduce low-density lipoprotein (LDL) cholesterol levels in adults with high cholesterol or high triglyceride levels (triglyceridemia). It may be prescribed on its own or in



Welchol (colesevelam), 625 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

combination with a statin drug. It is used along with suggested dietary and other lifestyle changes, such as engaging in regular physical activity. Colesevelam is also used to improve blood glucose levels in adults with type 2 diabetes mellitus.

Colesevelam may be used to reduce LDL levels in boys and postmenarchal girls ages 10 to 17 with heterozygous familial hypercholesterolemia, which is a genetic disorder characterized by high cholesterol and LDL levels. The drug may be prescribed on its own in combination with a statin if dietary changes and exercise do not help to lower cholesterol.

Off-label use

Due to its propensity for causing constipation, colesevelam has been studied for control of Crohn's disease. Although initial results were favorable, there has not been enough research to justify this as an off-label use.

Description

Colesevelam binds to bile acids in the intestine. The drug combines with bile salts that cannot be reabsorbed by the body, which results in the elimination of LDLs that are bound to the bile salts.

U.S. brand names

Colesevelam is sold under the brand name Welchol in the United States. However, its patent expires June

2015, so the generic form may be available shortly after the patent lapses.

Canadian brand names

In Canada, colesevelam is sold as Lodalis.

International brand names

Other brand names include Cholestagel.

Origins

Colesevelam was developed by GelTex Pharmaceuticals and later acquired by Genzyme. It is marketed in the United States by Daiichi Sankyo.

Recommended dosage

The recommended dose of colesevelam tablets is six tablets daily, either as a single dose or two three-tablet doses. This applies whether the drug is being used in combination with another lipid-lowering agent or not, and whether the primary use is for lowering lipid levels or controlling blood glucose levels.

Because the tablets are quite large, patients who have trouble swallowing tablets may wish to use the oral suspension. The appropriate dose is one 3.75-gram packet once daily or one 1.875-gram packet twice daily. To prepare, the entire contents of one packet may be mixed with 0.5–1 cup (4 to 8 ounces) of water, fruit juice, or diet soft drink.

Colesevelam should be taken with meals and a drink; it should not be taken on an empty stomach.

Pediatric

The dose for children age ten and above is the same as the adult dose. Colesevelam has not been studied in children younger than ten or in girls who have not yet had their first menstrual period.

Precautions

Although colesevelam has been shown to lower LDL levels, it has not been shown to reduce cardiovascular events (e.g., heart disease) associated with high cholesterol. Only the statins—atorvastatin (Lipitor), **simvastatin** (Zocor), **lovastatin** (Mevacor), **pravastatin** (Pravachol), **rosuvastatin** (Crestor), and others—have been demonstrated to reduce the number of cardiovascular events.

Colesevelam can sometimes increase triglyceride levels, particularly when used with insulin or sulfonylureas. Marked hypertriglyceridemia can cause acute pancreatitis.

KEY TERMS

Bile acid—A detergent that is made in the liver and excreted into the intestine to aid in the absorption of fats.

Blood glucose—The main sugar that the body makes from the food in the diet; also referred to as blood sugar.

Crohn's disease—A chronic inflammatory disease of unknown cause, involving any part of the gastrointestinal tract from mouth to anus, but commonly involving the large intestine, with scarring and thickening of the bowel wall. Crohn's disease frequently leads to intestinal obstruction and has a high rate of recurrence after treatment.

Heterozygous—Possessing two different forms of a particular gene, one inherited from each parent.

Hypercholesterolemia—High blood cholesterol.

Lipids—A group of fats and fat-like substances that are not soluble in water, are stored in the body, and serve as a source of fuel for the body.

Low-density lipoprotein (LDL)—A type of lipoprotein that consists of about 50% cholesterol and is associated with an increased risk of coronary artery disease; it is also referred to as the "bad" cholesterol.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Pancreatitis—Inflammation of the pancreas.

Postmenarchal—After menstrual function begins.

Statins—A group of medications given to lower blood cholesterol levels that work by inhibiting an enzyme involved in cholesterol formation. Statins are also known as HMG-CoA reductase inhibitors.

Sulfonylureas—Class of drugs used to treat type 2 diabetes mellitus.

Triglycerides—Substances formed in the body from fat in the diet. Triglycerides are the main fatty materials in the blood. Together with protein, they make up high- and low-density lipoproteins (HDLs and LDLs).

Other conditions and allergies

Colesevelam is not recommended for use in patients with current bowel obstructions or who are at risk of bowel obstruction. It is also not recommended for use in patients with a history of hypertriglyceridemia-induced pancreatitis (inflammation of the pancreas caused by high triglyceride levels).

Geriatric

There are no special precautions for geriatric patients; however, because elderly people may take a number of different drugs, extra care should be taken to avoid drug interactions. Colesevelam binds with many other drugs and affects their absorption, which could in turn alter their effectiveness.

Pregnant or breastfeeding

Colesevelam is considered a category B pregnancy drug. This means that although there are no adequate studies of colesevelam use in pregnant women, animal reproduction studies have revealed no evidence of fetal harm.

Colesevelam hydrochloride is considered safe for nursing mothers. It is not expected to be excreted in human milk because it is not absorbed from the gastrointestinal tract.

Side effects

The most common side effect of colesevelam is constipation. Other side effects include upset stomach and nausea. Muscle discomfort and weakness have been reported.

Interactions

Only a small number of drugs have been shown not to interact with colesevelam. Most drugs, including herbs and supplements, need to be administered at least four hours prior to colesevelam to ensure proper absorption.

Drugs

Drugs that have been reported to be compatible with colesevelam include:

- aspirin
- atenolol
- cephalexin
- ciprofloxacin
- digoxin
- enalapril
- fenofibrate

- lovastatin
- metoprolol
- pioglitazone
- rosiglitazone
- quinidine
- repaglinide
- sitagliptin
- statins (**atorvastatin**, fluvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin etc.)
- valproic acid
- verapamil

Herbs and supplements

Colesevelam may effect the absorption of fat-soluble vitamins (A, D, E, and K). This is especially significant during pregnancy, when requirements for vitamins and other nutrients are increased. Women taking colesevelam should consult with their healthcare providers about whether or not they should take supplemental vitamins or adjust their intakes to avoid deficiencies.

Resources

PERIODICALS

- Bays, H. E. "Lowering Low-Density Lipoprotein Cholesterol Levels in Patients with Type 2 Diabetes Mellitus." *International Journal of General Medicine* 7 (2014): 355–64.
- Beigel, F., et al. "Colesevelam for the Treatment of Bile Acid Malabsorption-Associated Diarrhea in Patients with Crohn's Disease: A Randomized, Double-Blind, Placebo-Controlled Study." *Journal of Crohn's and Colitis* 8, no. 11 (2014): 1471–79.
- Fonseca, Vivian A., et al. "Colesevelam HCl Improves Glycemic Control and Reduces LDL Cholesterol in Patients with Inadequately Controlled Type 2 Diabetes on Sulfonylurea-Based Therapy" *Diabetes Care* 31, no. 8 (2008): 1479–84.
- Goldberg, R. B., et al. "Efficacy and Safety of Colesevelam in Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control Receiving Insulin-Based Therapy." *Archives of Internal Medicine* 168, no. 14 (2008): 1531–40.
- Rosenstock, J., et al. "Efficacy and Safety of Colesevelam in Combination with Pioglitazone in Patients with Type 2 Diabetes Mellitus." *Hormone and Metabolic Research* 46, no. 13 (2014): 943–49.
- Tenenbaum, A., et al. "Optimal Management of Combined Dyslipidemia: What Have We Behind Statins Monotherapy?" *Advances in Cardiology* 45 (2008): 127–53.

WEBSITES

AHFS Consumer Medication Information. "Colesevelam." American Society of Health-System Pharmacists.

Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699050.html> (accessed March 2, 2015).

MedlinePlus. "Cholesterol." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/cholesterol.html> (accessed March 2, 2015).

Physicians' Desk Reference. "Welchol." PDR Health. <http://www.pdrhealth.com/drugs/welchol> (accessed February 27, 2015).

Welchol.com. <http://www.welchol.com/pi.htm> (accessed January 25, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org/>.

American Society for Preventive Cardiology, 6816 Southpoint Parkway, Suite 1000, Jacksonville, FL 32216, (904) 309-6235, <http://www.aspconline.org/>.

Samuel D. Uretsky, PharmD

REVIEWED BY KEVIN GLAZA, RPh

Combivir see **Lamivudine/zidovudine**

Concerta see **Methylphenidate**

Conjugated estrogens

Definition

Conjugated estrogens are mixtures of estrogenic substances (different molecules that all act as female sex hormones).

Purpose

Conjugated estrogens are prescribed as oral tablets, as an injection, or as a vaginal cream for a number of purposes:

- The most common use of the oral tablets is to relieve symptoms of menopause, including moderate to severe hot flashes and vaginal irritation. They are also used for treatment of low estrogen levels (hypoestrogenism), whether caused by a natural condition (such as ovarian failure) or by surgery (such as surgical removal of the ovaries).
- Tablets may be used to treat some forms of breast cancer in both women and men and to relieve some symptoms of advanced androgen-dependent prostate cancer.
- The tablets are approved for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause, but for this purpose alone, the vaginal cream is the preferred choice. The tablets

are appropriate if the vulvar and vaginal atrophy are accompanied by hot flashes that require treatment.

- The tablets may be used to prevent osteoporosis in postmenopausal women.
- The injection is used to treat abnormal uterine bleeding caused by a hormonal imbalance.
- The vaginal cream is used for atrophy and shrinkage of the skin of the vagina and vulva.

Off-label use

Conjugated estrogens should never be taken to prevent dementia, heart attack, heart disease, or stroke.

Description

Conjugated estrogens are available in three formulations:

- oral tablets in 0.3, 0.45, 0.625, 0.9, or 1.25 milligrams (mg)
- injection (for intramuscular or intravenous administration), 25 mg
- vaginal cream, 0.625 mg/gram (g)

U.S. brand names

Conjugated estrogens are marketed under the brand name Premarin. According to the U.S. Food and Drug Administration (FDA), Premarin is a natural product that cannot be standardized sufficiently to permit the approval of a generic equivalent. Other products are allowed to use the term “conjugated estrogens,” but they are not equivalent to Premarin. Most nations have products labeled as conjugated estrogens, but their composition may not be precisely the same.

Origins

In 1997, two companies petitioned the FDA to approve synthetic preparations of estrogenic substances. The FDA refused on the ground that since Premarin may vary in the quantities of estrogenic hormones, it would be impossible to create a synthetic generic. However, the FDA ended up approving synthetic mixtures of estrogenic hormones, first as synthetic conjugated estrogens A (no longer being produced) and synthetic conjugated estrogens B.

Recommended dosage

The recommended dosage varies depending on the condition being treated.

Dosages include:

- For alleviating symptoms of menopause, initiate treatment at 0.3 mg, either as a daily dose or in a cyclic regimen (25 days on, 5 days off).



Premarin (a type of conjugated estrogen), 0.625 mg.
(© Cengage Learning®)

- For low estrogen levels caused by female hypogonadism, start treatment at 0.3–0.625 mg once daily in a cyclic regimen (3 weeks on, 1 week off), adjusting dosage as needed every 6 to 12 months. Progestin treatment should be added to maintain bone mineral density once skeletal maturity is achieved.
- To treat low estrogen levels caused by female castration or primary ovarian failure, 1.25 mg may be taken once daily in a cyclic regimen (25 days on, 5 days off).
- To prevent osteoporosis, start treatment at 0.3 mg once daily in cyclic regimen (25 days on, 5 days off), adjusted as necessary. The drug may be given daily if needed.
- To help relieve symptoms in men with prostate cancer, 1.25–2.5 mg may be taken every 8 hours.
- For injections used to treat abnormal uterine bleeding, 25 mg may be administered intramuscularly (into a muscle) or intravenously (into a vein) every 6 to 12 hours as needed, or 25 mg intravenously every 24 hours. If there is no response after two doses, other treatment options should be evaluated. Alternately, the drug can be given by mouth, with 10–20 mg daily doses divided into 4-hour intervals.

- When using the vaginal cream for vulvar or vaginal atrophy, the starting dose is 0.5 g, applied daily for 21 days and then stopped for 7 days. The starting dose should be 0.5 g, but dose adjustments may be made.
- The cream may also be used for dyspareunia (painful intercourse); 0.5 g is applied intravaginally in a twice-weekly (e.g., Monday and Thursday) continuous regimen or in a cyclic regimen (21 days of therapy followed by 7 days off).

Individuals should always use the lowest dose that controls their symptoms.

Precautions

The Premarin packaging contains a boxed warning, which is the most serious warning issued by the FDA. Estrogen used in hormonal therapy is often combined with a progesterone. When used alone, conjugated estrogens may increase the risk of endometrial cancer. However, taking conjugated estrogens in combination with **medroxyprogesterone**, a progesterone-like hormone, carries an increased risk of invasive breast cancer. Women filling prescriptions for conjugated estrogens must be issued patient data sheets discussing the uses and risks. Because of the severity of the risks associated with conjugated estrogens, the information should be carefully studied and discussed with a healthcare professional.

A Women's Health Initiative study, conducted by the National Heart, Lung, and Blood Institute, reported that women taking estrogens alone had an increased risk of stroke and deep vein thrombosis (a blood clot in the veins of the leg). Women taking estrogens in combination with progesterone had a higher risk of heart attack, stroke, and pulmonary embolism (blood clot in the lung). Both estrogen alone and in combination with a progesterone increased the risk of dementia.

Premarin vaginal cream may weaken latex condoms.

Pediatric

Conjugated estrogens are not indicated for use in children.

Pregnant or breastfeeding

Conjugated estrogens should not be used during pregnancy. Use while breastfeeding may reduce both the quantity and quality of milk.

Other conditions and allergies

Premarin may cause rare instances of allergy and may make several conditions worse, including asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic

KEY TERMS

Atrophy—The wasting away or decrease in size of an organ or tissue in the body.

Dementia—Loss of brain function that occurs with certain diseases. It affects memory, thinking, language, judgment, and behavior.

Estradiol—The primary human female sex hormone; it is the most physiologically active form of estrogen.

Estrogen—A female hormone produced by the ovaries that stimulates the growth of the lining of the uterus.

Hypoestrogenism—Low levels of estrogen. This may be caused by failure of the ovaries to produce enough hormones or to surgical removal of the ovaries.

Menopause—The end of a woman's menstrual periods, when a woman no longer can conceive a child.

Osteoporosis—The excessive loss of calcium from the bones, causing the bones to become fragile and break easily. Postmenopausal women are especially vulnerable to this condition because estrogen, a hormone that protects bones against calcium loss, decreases drastically after menopause.

lupus erythematosus, and hepatic hemangiomas (a type of liver tumor that is not cancerous).

Side effects

Individuals taking conjugated estrogens should contact a healthcare provider immediately if any of the following symptoms occur:

- breast changes, including lumps or nipple discharge
- coughing up blood (hemoptysis)
- severe vomiting
- dizziness or faintness
- shortness of breath
- pain or heaviness in the chest
- loss of vision or double vision
- severe headache
- mental confusion, including problems with memory or learning
- speech problems
- weakness or numbness in an arm or leg
- pain, tenderness, or redness in the leg

Other potential side effects include:

- fluid retention
- constipation or diarrhea
- hair loss or growth
- nervousness
- vaginal irritation
- changes in libido (sexual desire)

Patients should discuss any concerning side effects with their healthcare provider.

Interactions

Individuals should consult with their healthcare provider about all potential drug interactions, including reactions between conjugated estrogens and over-the-counter drugs or supplements.

Drugs

There are no absolute contraindications to the use of any drugs with conjugated estrogens; however, conjugated estrogens are metabolized in the liver by an enzyme called CYP450, and many drugs either increase or decrease the production of this enzyme. This may affect the speed in which conjugated estrogens are eliminated from the body, either reducing their effectiveness or increasing the risk of adverse effects.

Food and other substances

Grapefruit juice may raise blood levels of estrogens, increasing the risk of adverse reactions.

Resources

PERIODICALS

- Bhupathiraju, S. N., and J. E. Manson. "Menopausal Hormone Therapy and Chronic Disease Risk in the Women's Health Initiative: Is Timing Everything?" *Endocrine Practice* 20, no. 11 (2014): 1201–13.
- Cannoletta, M., and A. Cagnacci. "Modification of Blood Pressure in Postmenopausal Women: Role of Hormone Replacement Therapy." *International Journal of Women's Health* 6 (August 11, 2014): 745–57.
- Collins, J. A., J. M. Blake, and P. G. Crosignani. "Breast Cancer Risk with Postmenopausal Hormonal Treatment." *Human Reproductive Update* 11, no. 6 (2005): 545–60.
- Isaac, Elizabeth. "It's All in the Name: Cenestin®, Premarin®, and the Conjugated Estrogen Saga." *Mass General* (newsletter) 9, no. 10 (1999). <http://www2.massgeneral.org/pharmacy/Newsletters/1999/October%201999/Conjugated%20Estrogen%20Saga.htm> (accessed March 5, 2015).
- Lundin, J. I., et al. "Formulations of Hormone Therapy and Risk of Parkinson's Disease." *Movement Disorders* 29, no. 13 (2014): 1631–36.

Mattison, D. R., et al. "Pharmacokinetics and Toxicokinetics of Selected Exogenous and Endogenous Estrogens: A Review of the Data and Identification of Knowledge Gaps." *Critical Reviews in Toxicology* 44, no. 8 (2014): 696–724.

Prentice, R. L. "Postmenopausal Hormone Therapy and the Risks of Coronary Heart Disease, Breast Cancer, and Stroke." *Seminars in Reproductive Medicine* 32, no. 6 (2014): 419–25.

WEBSITES

- AHFS Consumer Medication Information. "Estrogen." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682922.html> (accessed March 5, 2015).
- Goldman, Bruce. "Estradiol, but Not Premarin, Preserves Key Brain Regions in Postmenopausal Women at Risk for Dementia, Study Shows." *Stanford Medicine*, March 12, 2014. <http://med.stanford.edu/news/all-news/2014/03/estradiol-but-not-premarin-preserves-key-brain-regions-in-postmenopausal-women-at-risk-for-dementia-study-shows.html> (accessed March 5, 2015).
- Healthwise. "Conjugated Estrogens (Oral)." Cigna. <http://www.cigna.com/healthwellness/hw/medications/conjugated-estrogens-d00541a1> (accessed March 5, 2015).
- National Heart, Lung, and Blood Institute. "Women's Health Initiative." U.S. National Institutes of Health. <https://www.nhlbi.nih.gov/whi/> (accessed March 5, 2015).
- Project AWARE (Association of Women for the Advancement of Research and Education). "Premarin—Facts & Opinions." http://www.project-aware.org/Managing/Hrt/PremarinFacts_Opinion.shtml (accessed March 5, 2015).
- PubMed Health. "Conjugated Estrogens." U.S. National Library of Medicine, National Institutes of Health. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0000474/> (accessed March 5, 2015).
- U.S. Food and Drug Administration. "Conjugated Estrogens." <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm092884.htm> (accessed March 5, 2015).

ORGANIZATIONS

- American Congress of Obstetricians and Gynecologists, 409 12th Street SW, Washington, DC 20024-2188, (202) 638-5577, (800) 673-8444, resources@acog.org, <http://www.acog.org/>.
- National Heart, Lung, and Blood Institute (NHLBI), PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbinfo@nhlbi.org, <http://www.nhlbi.nih.gov/>.

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Contraceptives see **Oral contraceptives**

Copaxone see **Glatiramer**

Coreg see **Carvedilol**

Cosopt see **Dorzolamide/timolol**

Coumadin see **Warfarin**

Cozaar see **Losartan**

Crestor see **Rosuvastatin**

Cutivate see **Fluticasone**

Cyclobenzaprine

Definition

Cyclobenzaprine is a skeletal muscle relaxant that relieves muscle pain and discomfort caused by sprains, strains, or other injuries to the muscle. It should be used in conjunction with rest, physical therapy, and other methods of relieving muscle pain.

Purpose

Cyclobenzaprine and other skeletal muscle relaxants have been widely used for the treatment of strains and sprains, especially athletic injuries. Cyclobenzaprine is not effective in treating pain caused by central nervous system problems and has been ineffective in treating other kinds of pain.

A 2008 paper that appeared in *American Family Physician* recommended using simple analgesics such as acetaminophen or nonsteroidal anti-inflammatory drugs

(NSAIDs) as the first-line therapy for strains and sprains. The authors recommended cyclobenzaprine for the treatment of lower back pain and fibromyalgia. Studies seem to show the greatest benefit from cyclobenzaprine over the first day or two, with reduced effectiveness over a two-week period. Skeletal muscle relaxants are particularly useful when there is tenderness at specific spots in the muscle. Although both pain relievers (such as **ibuprofen**, naproxen, and others) and skeletal muscle relaxants such as cyclobenzaprine have been effective in treating some forms of back pain, combinations of the two do not seem to offer any benefit.

Off-label use

Two companies market kits so that dispensing pharmacists or healthcare providers can prepare a cyclobenzaprine cream. This topical form has not been approved by the U.S. Food and Drug Administration (FDA) but may be used with a prescription.

Description

In its generic form, cyclobenzaprine is available as 5, 7.5, and 10 milligram (mg) tablets.

While there are a limited number of published studies comparing the effectiveness of different skeletal muscle relaxants, cyclobenzaprine may be preferred to similar drugs—namely **carisoprodol** and diazepam—as a matter of patient safety. Carisoprodol, another skeletal muscle relaxant, is metabolized in the body as meprobamate (better known as Miltown), which is a Schedule III controlled drug. **Diazepam** (Valium), a member of the benzodiazepine drug class, is a Schedule II drug. Schedule II drugs have a known medical use but also a high potential for abuse and dependence; Schedule III drugs have a moderate risk of abuse and dependence. While all three drugs are effective for similar uses, cyclobenzaprine is less likely to cause long-term dependence.

U.S. brand names

In the United States, cyclobenzaprine is sold under the brand names Fexmid as a 7.5 mg tablet and Amrix as an extended-relief capsule in 15 mg and 30 mg strengths.

Cyclobenzaprine was previously sold under the brand name Flexeril. However, its manufacturer, McNeil Pharmaceuticals, discontinued production of the drug, and the brand name rights have not yet been transferred to another company.

Canadian brand names

In Canada, cyclobenzaprine is sold under the brand name Apo-Cyclobenzaprine.



Cyclobenzaprine, 10 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

KEY TERMS

Analgesic—Pain reliever.

Anticholinergic—A drug that blocks the effects of acetylcholine. There are several kinds of anticholinergic drugs, but in general these drugs have a relaxing effect, particularly on the muscles of the stomach, intestine, and bladder. They can be used to prevent nausea, vomiting, and motion sickness. Anticholinergics can be used for painful menstruation and runny nose and to prevent urination during sleep.

Central nervous system—The brain and spinal cord.

Dependence—A state in which a person requires a steady concentration of a particular substance in order to avoid withdrawal symptoms.

Drug schedule—A classification system for drugs, including narcotics, sedatives, hallucinogens, and other drugs, that are restricted under federal and state laws in the United States. Schedule I substances have no approved medical use, while drugs in Schedules II, III, and IV have approved uses. The higher the schedule, the lower the degree of restriction.

Fibromyalgia—A condition characterized by widespread musculoskeletal pain accompanied by fatigue, sleep, memory, and mood issues.

Sprain—An injury to the ligaments around a joint. Ligaments are strong, flexible fibers that hold bones together. When a ligament is stretched too far or tears, the joint will become painful and swell.

Strain—An injury to a muscle in which overstretching makes the muscle fibers tear.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

Recommended dosage

For the treatment of muscle spasms, patients may take one 5 mg tablet every eight hours, increasing the dose to 7.5–10 mg every eight hours if necessary.

The extended-release capsule is usually prescribed in doses of 15 mg to be taken each day, although some patients may require two capsules daily.

Precautions

The manufacturer warns of the possibility of withdrawal symptoms if cyclobenzaprine is discontinued

abruptly after long-term use. These may include nausea and headache.

Cyclobenzaprine causes drowsiness in a high percentage of patients. Individuals taking cyclobenzaprine should avoid driving or operating machinery until they have a better understanding of how the drug affects them.

Pediatric

Cyclobenzaprine immediate-release tablets are not indicated for patients under the age of 15, and the sustained-action capsules are not indicated for patients under the age of 18.

Geriatric

Cyclobenzaprine is eliminated more slowly in elderly patients (over the age of 65) than in younger patients. Because this may lead to drug accumulation within the body, the sustained-action capsules should not be administered to elderly patients.

Pregnant or breastfeeding

Cyclobenzaprine is considered a pregnancy category B drug, which means that although there are no comparable human studies, adverse fetal effects have not been observed in animal reproduction studies. Still, due to potential risks, the drug manufacturer recommends avoiding use during pregnancy unless clearly needed.

The U.S. National Library of Medicine's LactMed database states that breastfeeding is not a reason to discontinue cyclobenzaprine, but because of a lack of clinical studies in breastfeeding women, it may be advisable to switch to another drug that has been proven safe when nursing.

Other conditions and allergies

Cyclobenzaprine should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, or increased intraocular pressure (pressure in the eyes), and in patients taking anticholinergic medications.

Cyclobenzaprine should not be given to any patient recovering from a recent heart attack or who has an arrhythmia (irregular heartbeat), heart block, or any form of conduction disturbance. It should also not be used in patients with hyperthyroidism.

Cyclobenzaprine should not be given to patients who may be allergic to any of the drug's components.

Side effects

The most commonly reported adverse effects of cyclobenzaprine are drowsiness and dry mouth. Other side effects include headache and fatigue.

Less common adverse effects include abdominal pain, acid reflux, constipation, diarrhea, dizziness, nausea, irritability, lack of concentration, nervousness, upper respiratory infection, and pharyngitis (sore throat).

Interactions

Cyclobenzaprine interacts with several hundred drugs. Patients should make sure that their healthcare providers are aware of all the drugs they are taking, including over-the-counter drugs and vitamin or herbal supplements.

Drugs

Cyclobenzaprine should not be given to patients using monoamine oxidase inhibitors (MAOIs, a type of antidepressant drug) or within 14 days after their discontinuation.

Cyclobenzaprine should not be used at the same time or within 14 days after discontinuing isocarboxazid, phenelzine, or tranylcypromine.

Cyclobenzaprine is closely related to the tricyclic antidepressants and should not be used at the same time as drugs in this class or with any other antidepressant drug.

Herbs and supplements

Cyclobenzaprine has been known to interact with eucalyptus and sage. Patients taking cyclobenzaprine should avoid use of any products containing these herbs.

Resources

PERIODICALS

- Alencar, F. G. Jr., et al. "Patient Education and Self-Care for the Management of Jaw Pain upon Awakening: A Randomized Controlled Clinical Trial Comparing the Effectiveness of Adding Pharmacologic Treatment with Cyclobenzaprine or Tizanidine." *Journal of Oral & Facial Pain and Headache* 28, no. 2 (2014): 119–27.
- Beebe, F. A., R. L. Barkin, and S. Barkin. "A Clinical and Pharmacologic Review of Skeletal Muscle Relaxants for Musculoskeletal Conditions." *American Journal of Therapeutics* 12, no. 2 (2005): 151–71.
- Childers, M. K., et al. "Low-Dose Cyclobenzaprine Versus Combination Therapy with Ibuprofen for Acute Neck or Back Pain with Muscle Spasm: A Randomized Trial." *Current Medical Research and Opinion* 21, no. 9 (2005): 1485–93.

- Chou, R., and L. H. Huffman. "Medications for Acute and Chronic Low Back Pain: A Review of the Evidence for an American Pain Society/American College of Physicians Clinical Practice Guideline." *Annals of Internal Medicine* 147, no. 7 (2007): 505–14.
- Richards, B. L., S. L. Whittle, and R. Buchbinder. "Muscle Relaxants for Pain Management in Rheumatoid Arthritis." *Cochrane Database of Systematic Reviews* 1, art. no. CD008922 (January 18, 2012). <http://dx.doi.org/10.1002/14651858.CD008922.pub2> (accessed March 3, 2015).
- See, Sharon, and Regina Ginzburg. "Choosing a Skeletal Muscle Relaxant." *American Family Physician* 78, no. 3 (2008): 365–70.
- Turturro, M. A., C. R. Frater, and F. J. D'Amico. "Cyclobenzaprine with Ibuprofen versus Ibuprofen Alone in Acute Myofascial Strain: A Randomized, Double-Blind Clinical Trial." *Annals of Emergency Medicine* 41, no. 6 (2003): 818–26.

OTHER

"Amrix Prescribing Information." Amrix.com. <http://www.amrix.com/PDF/prescribing-information.pdf> (accessed January 25, 2015).

WEBSITES

- Amrix.com. <http://www.amrix.com/hcp/Default.aspx> (accessed January 25, 2015).
- MedlinePlus. "Cyclobenzaprine." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682514.html> (accessed January 25, 2015).
- U.S. National Library of Medicine. "LactMed: Cyclobenzaprine." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+517> (accessed March 3, 2015).

ORGANIZATIONS

American Pain Society, 8735 W. Higgins Road, Suite 300, Chicago, IL 60631, (847) 375-4715, Fax: (847) 375-6479, info@americanpainsociety.org, <http://www.americanpainsociety.org/>.

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Cyclosporine

Definition

Cyclosporine is an immunosuppressant drug used to prevent rejection of kidney, liver, and heart transplants; to prevent graft-versus-host disease in patients receiving allogeneic bone marrow transplants; and for severe autoimmune diseases that are resistant to corticosteroids and other therapy.



Cyclosporine, 25 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Purpose

Cyclosporine is best known as a drug used to prevent the rejection of organ transplants and bone grafts.

Description

Cyclosporine suppresses (prevents the activity of) the cells in the lymphatic system, known as T cells, that would otherwise mount an immune response. This suppression makes cyclosporine useful in conjunction with organ transplants. In a transplant, the patient receiving a donated organ can react to the organ as though it were a foreign substance, rejecting it; cyclosporine helps prevent this response. Cyclosporine is also used to treat severe rheumatoid arthritis, and it is being used investigatively as a drug that may help to temper multidrug resistance in cancer patients.

The drug is available in several forms, including an intravenous (IV) solution, an oral solution, and an oral capsule. Cyclosporine is broken down in the liver.

U.S. brand names

Cyclosporine, also spelled as cyclosporin and ciclosporin, takes several brand names in the United States, including Neoral, Sandimmun, Sandimmune, and Sang Cya. It is also known in slight variant forms, such as cyclosporin A, CsA, and CyA. The Neoral and Sang Cya brand name products are interchangeable, but the Sandimmune brand name product cannot be used interchangeably for those other two products.

Origins

Cyclosporine was discovered in 1972. It was first isolated from a fungus.

Recommended dosage

The dosage varies depending on the reason for use and the patient, and the dosage is also often adjusted by the physician. The dosage is based on the patient's ideal body weight, and the oral dose is approximately three times higher than the intravenous dose. IV use is reserved for patients who cannot take the oral dose, and it is recommended that patients who can be switched to the oral form be switched as soon as possible.

The usual initial oral dose is 14–18 milligrams (mg) per kilogram (kg, or 2.2 lb.) of body weight per day, beginning 4–12 hours before organ transplantation. After the transplantation, the dose is decreased and then usually tapered to 3–10 mg/kg per day.

Precautions

Because cyclosporine suppresses the immune system, it can lead to infections and possibly lymphoma, and it is toxic to the kidneys. Crowds of people should be avoided, and no live vaccines should be administered without consulting the patient's doctor. The use of this drug along with other drugs that are toxic to the kidneys must be closely monitored. It should be ingested and swallowed in its capsule without breaking the capsule. The liquid solution should only be mixed in a glass container.

Geriatric

This drug has not been specifically studied for use with the elderly.

Pregnant or breastfeeding

Pregnant or nursing women should not take this drug.

Other conditions and allergies

Patients should inform their doctor of any hypersensitivities or drug allergies they have before taking this drug. Cyclosporine in both liquid and capsule form has some castor oil components in it, which could cause an allergic reaction for some. Some allergic reactions to the IV solution may be severe.

Side effects

More than 10% of patients taking this drug experience the following:

KEY TERMS

Allogeneic—Referring to bone marrow transplants between two different, genetically dissimilar people.

Intravenous line—A tube that is inserted directly into a vein to carry medicine directly to the bloodstream, bypassing the stomach and other digestive organs that might alter the medicine.

Kilogram (kg)—Metric measure that equals 2.2 pounds.

Lymphatic system—The system that collects and returns fluid in tissues to the blood vessels and produces defensive agents for fighting infection and invasion by foreign bodies.

Milligram (mg)—One-thousandth of a gram. A gram is the metric measure that equals about 0.035 ounces.

- high blood pressure
- unusual hair growth
- kidney toxicity
- tremors
- thickening of the gums

Other, less common side effects include seizures, headache, acne, abdominal pain, nausea and vomiting, leg cramps, and some endocrine/metabolic conditions known as hypomagnesemia, hypokalemia, hyperkalemia, and hyperlipidemia.

Interactions

Cyclosporine interacts with a long list of other drugs. A physician should be informed about each and every drug a person eligible for treatment with cyclosporine is taking. **Vaccinations** should not be given while a person is taking cyclosporine.

Drugs that may make cyclosporine less effective include carbamazepine, phenobarbital, **phenytoin**, and others.

Drugs that may increase cyclosporine's toxicity include **acyclovir**; amphotericin B; corticosteroids; **erythromycin**; certain antibiotics; and some antifungals, including **fluconazole**, itraconazole, and ketoconazole.

Food and other substances

Cyclosporine should not be taken with grapefruit or related juices because the combination can make it more toxic.

Resources

BOOKS

Chu, Edward, and Vincent T. DeVita Jr. *Physicians' Cancer Chemotherapy Drug Manual 2014*. Burlington, MA: Jones & Bartlett Learning, 2014.

Wilkes, Gail M., and Margaret Barton-Burke. *2013 Oncology Nursing Drug Handbook*. Burlington, MA: Jones & Bartlett Learning, 2013.

PERIODICALS

Muellenhoff, M. W., and J. Y. Koo. "Cyclosporine and Skin Cancer: An International Dermatologic Perspective over 25 Years of Experience: A Comprehensive Review and Pursuit to Define Safe Use of Cyclosporine in Dermatology." *Journal of Dermatology Treatment* 23, no. 4 (2012): 290–304.

WEBSITES

AHFS Consumer Medication Information. "Cyclosporine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601207.html> (accessed February 21, 2015).

American College of Rheumatology. "Cyclosporine." [https://www.rheumatology.org/Practice/Clinical/Patients/Medications/Cyclosporine_\(Neoral_Sandimmune_Gengraf\)/](https://www.rheumatology.org/Practice/Clinical/Patients/Medications/Cyclosporine_(Neoral_Sandimmune_Gengraf)) (accessed February 21, 2015).

ORGANIZATIONS

National Foundation for Transplants, 5350 Poplar Avenue, Suite 430, Memphis, TN 38119, (901) 684-1697, (800) 489-3863, Fax: (901) 684-1128, info@transplants.org, <http://www.transplants.org/>.

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REVIEWED BY KEVIN GLAZA, RPh

Cymbalta see **Duloxetine**

Cyproheptadine

Definition

Cyproheptadine is a first-generation H₁ antihistamine. First generation means that it enters into the central nervous system, as compared with newer, nondrowsy antihistamines. H₁ means that cyproheptadine is effective in treating allergic reactions such as itch and rash.

Purpose

Cyproheptadine is indicated for the treatment of mild allergic reactions, including seasonal allergies, marked by sneezing, itching, and eye inflammation (allergic conjunctivitis). It may also be used to treat urticaria (hives) and



Cyproheptadine, 4 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

dermatographism, a type of hives in which firm stroking of the skin causes dilation of the blood vessels.

Off-label uses

The mild anticholinergic, antiserotonergic, and local anesthetic properties of cyproheptadine are responsible for a large number of adverse effects, but attempts have been made to use them to treat other conditions. Cyproheptadine has been widely used to stimulate appetite. Lack of appetite leading to inadequate nutrition is seen in a number of diseases including many cancers, human immunodeficiency virus (HIV), and cystic fibrosis. While it requires further study, it has the advantage of being safer than other drugs used to stimulate appetite.

Cyproheptadine has been used to prevent migraine headaches, but reports have concluded that based on current evidence, cyproheptadine is at best “possibly” effective, while other remedies have proven effectiveness.

Description

Cyproheptadine is available by prescription. It is marketed as oral tablets containing 4 milligrams (mg) cyproheptadine each and as a liquid containing 2 mg per 5 milliliters (mL). A single dose of cyproheptadine reaches peak activity in six to nine hours.

U.S. brand names

Cyproheptadine was formerly marketed as Periactin, but the brand name has since been abandoned by the

manufacturer, although it is still widely used as a common name for the drug.

International brand names

International brand names include:

- Cypromin
- Cypromine
- Cyprosian
- Cyprotol
- Cytidine
- Decamin
- Earmin
- Ennamax
- Glocy
- Heptasan
- Huavine

Recommended dosage

Treatment is started with 4 mg given every eight hours. The dose may be adjusted upward to 32 mg per day, divided into doses given every eight hours.

Pediatric

Cyproheptadine has not been studied in children under the age of 2 years. For children ages 2–6, 2 mg may be given every 8–13 hours. The maximum dosage should not exceed 12 mg/day. For ages 7–14, 4 mg may be given every 8–12 hours, with a maximum dosage of 16 mg/day.

Precautions

The anticholinergic activity of cyproheptadine results in a large number of adverse effects when the drug is used for its primary purpose, which is treatment of hypersensitivity allergic reactions. Other antihistamines without anticholinergic effects should be tried first.

Pediatric

Children are particularly sensitive to the toxic effects of antihistamines, and the drug should never be administered to newborns. Overdoses can produce hallucinations and convulsions. Antihistamines may reduce mental alertness, although in some cases they may produce excitation.

Geriatric

Cyproheptadine should be used with extreme care in elderly patients. The drug’s anticholinergic effects may cause problems in patients with urinary tract conditions or prostate enlargement, which are common

KEY TERMS

Anticholinergic—A drug that opposes the action of acetylcholine, the neurotransmitter of the parasympathetic nervous system. These drugs reduce spasms of smooth muscle, such as the bladder. Their side effects include dry mouth and blurred vision.

Antihistamine—A drug that combats the effects of histamine. Histamine H₁ causes allergic reactions while histamine H₂ causes secretion of stomach acid, but the term normally applies only to H₁ inhibitors, which cause sneezing and rash. Older antihistamines enter the central nervous system and cause sleepiness. Newer drugs do not get into the central nervous system and are called “nonsedating.”

Cystic fibrosis—A genetic condition leading to abnormal transport of chloride and sodium across cell membranes. Among other effects, it leads to frequent lung infections and difficulty breathing.

Parasympathetic—Referring to the portion of the nervous system that is concerned with normal maintenance functions, including digestion and normal heart rate.

Serotonergic—Containing, activating, or otherwise involving serotonin, a chemical that occurs throughout the body with numerous effects, including neurotransmission in the brain.

Urticaria—Hives; raised, itchy areas of skin that usually indicate an allergic reaction.

in older patients. If a patient has not responded to other antihistamines and cyproheptadine is the only possibility, the patient should be started at the lowest dose possible.

Pregnant or breastfeeding

Cyproheptadine is in pregnancy category B, which means that although there are no comparable human studies, animal reproduction studies have found no adverse effects on a fetus.

Nursing mothers should not use cyproheptadine. There is no current information regarding whether cyproheptadine is excreted in human milk, but the toxicity to newborn infants is too great to justify any risk.

Other conditions and allergies

Because cyproheptadine has atropine-like effects, it should be used with caution in patients with a history of

bronchial asthma, increased intraocular pressure (glaucoma), hyperthyroidism, heart disease, or high blood pressure. Cyproheptadine should not be used in patients with enlarged prostate glands, constriction of either the intestines or bladder neck, or angle-closure glaucoma.

Side effects

Because of the anticholinergic effects of cyproheptadine, the drug is associated with a large number of side effects—more than are typically expected with antihistamines.

Some central nervous system side effects are common among first-generation antihistamines, including sedation and sleepiness, dizziness, loss of coordination, confusion, restlessness, excitation, nervousness, tremor, and irritability. While sleepiness is common, insomnia has also been reported. In overdoses, convulsions and hallucinations have been reported.

Side effects related to the drug's atropine-like properties include dry eye, dry mouth, blurred vision, and constipation. Dryness of the nose and throat with thickening of bronchial secretions are also common.

Other reported side effects include allergic reactions such as rash and itch. Increased appetite and weight gain are common, but some patients have had loss of appetite. Low blood pressure and irregular heartbeat have also been reported.

Additional side effects are possible. Patients should consult their healthcare providers for additional information.

Interactions

Individuals should ensure that their healthcare provider and pharmacist are aware of all drugs they are currently taking, including over-the-counter medications and supplements.

Drugs

Cyproheptadine interacts with other drugs or substances that cause sedation. These include sedatives, muscle relaxants, and tranquilizers. The effect is additive, leading to increased sleepiness.

Monoamine oxidase inhibitors (MAOIs)—a class of antidepressant drugs that includes isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate)—will increase and prolong the atropine-like effects and should not be used with cyproheptadine. A period of up to two weeks may be needed between stopping MAOIs and taking cyproheptadine.

In addition to its primary antihistamine effect, cyproheptadine acts as a sedative and an anticholinergic drug. Any drug or diet supplement that shares these activities will have an additive effect when given at the same time as cyproheptadine. The severity of this interaction depends on the dose of each drug as well as the individual response. In most cases these interactions are mild, but for safety's sake, individuals should take caution and see how the drug affects them before driving or performing delicate tasks.

Herbs and supplements

Many herbal remedies have either an atropine-like effect or a sedative property that can interact with cyproheptadine. While it is unlikely that these would have a clinically significant interaction at common dose levels, many natural products are poorly standardized or are standardized in terms of weight of product and not concentration of active component. Individuals should discuss the use of herbs and supplements with their prescriber or pharmacist, including:

- hawthorn
- shepherd's purse
- St. John's wort
- valerian

Food and other substances

Many common foods contain small amounts of atropine, including tomatoes and potatoes, but the quantities are so small that they do not present a risk in normal dietary quantities. Alcohol increases the sedative effect of cyproheptadine.

Resources

PERIODICALS

Chinuck, R., et al. "Appetite Stimulants for People with Cystic Fibrosis." *Cochrane Database of Systematic Reviews* 27, art. no. CD008190 (July 27, 2014). <http://dx.doi.org/10.1002/14651858.CD008190.pub2> (accessed March 3, 2015).

Couluris, M., et al. "The Effect of Cyproheptadine Hydrochloride (Periactin) and Megestrol Acetate (Megace) on Weight in Children with Cancer/Treatment-Related Cachexia." *Journal of Pediatric Hematology/Oncology* 30, no. 11 (2008): 791–97.

Holland, S., et al. "Evidence-Based Guideline Update: NSAIDs and Other Complementary Treatments for Episodic Migraine Prevention in Adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society." *Neurology* 78, no. 17 (2012): 1346–53.

OTHER

California Poison Control System. "Anticholinergic Plants." <http://toxicology.ucsd.edu/Newsletters/CPCS%20Newsletter%20Anticholinergic%20Plants.pdf> (accessed January 30, 2015).

WEBSITES

International Programme on Chemical Safety. "Management of Poisoning—A Handbook for Health Care Workers." Health Library for Disasters. <http://helid.digicollection.org/en/d/Js13469e/5.5.1.html> (accessed January 30, 2015).

MedlinePlus. "Cyproheptadine." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682541.html> (accessed January 30, 2015).

U.S. National Library of Medicine. "Cyproheptadine Hydrochloride—Cyproheptadine Hydrochloride Tablet." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f90faaa3-f40f-4653-8fb8-144d61c6b1d4> (accessed March 3, 2015).

ORGANIZATIONS

American Academy of Allergy, Asthma & Immunology (AAAAI), 555 East Wells Street, Suite 1100, Milwaukee, WI 53202-3823, (414) 272-6071, <http://www.aaaai.org/>.

American Academy of Family Physicians, 11400 Tomahawk Creek Parkway, Leawood, KS 66211-2680, (913) 906-6000, Fax: (913) 906-6075, (800) 274-2237, contactcenter@aafp.org, <http://www.aafp.org/>.

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D

Dabigatran

Definition

Dabigatran (dabigatran etexilate mesylate) is an oral anticoagulant, also called an antithrombotic (“blood thinner”). It belongs to the class of direct thrombin inhibitors, which means that it inhibits the formation of thrombin, an integral component in blood coagulation (clotting).

Purpose

Dabigatran is approved by the U.S. Food and Drug Administration (FDA) for use in reducing the risk of stroke and the formation of blood clots (embolisms) anywhere in the body, especially blood clots that may form in the veins (known as deep venous thrombosis) and blood clots that may travel to the lungs (pulmonary embolism). The drug is most often given to patients with atrial fibrillation (abnormal heartbeat) due to non-heart-valve causes, a condition that places them at greater risk of developing blood clots. It is also used to reduce the risk of recurrence of deep venous thrombosis and pulmonary embolism in patients who have already been treated for these coagulation disorders.

Dabigatran may sometimes be prescribed for people who require anticoagulants for other reasons, including use as a “blood thinner” in patients with coronary artery disease. In such cases, it provides greater convenience than other anticoagulants, such as heparin and **warfarin**, because it does not require frequent blood tests to monitor coagulation factors. In Canada and the United Kingdom, dabigatran is approved for use in preventing blood clots in patients who have undergone hip and knee surgery. Clinical trials are under way to investigate new indications for the use of dabigatran.

Description

The body’s system of coagulation involves a complex process of events called the “coagulation cascade.” This

involves the actions of several important coagulation factors, including fibrinogen, fibrin, thrombin, and platelets, among others. When bleeding occurs anywhere in the body as a result of injury, surgery, or illness of some kind, the coagulation cascade is activated, and thrombin promotes the conversion of fibrinogen into fibrin. It also causes the clumping (aggregation) of platelets, which together with fibrin results in the formation of potentially dangerous blood clots.

Direct thrombin inhibitors such as dabigatran prevent the formation of a blood clot or thrombus by stopping the activity of thrombin. This is only necessary when an individual has a tendency to form clots that may block blood vessels in the heart, lungs, or brain, resulting in heart attacks, pulmonary embolism, or stroke. Blood clots formed in the limbs can also travel to the major organs and have the same damaging effect. Dabigatran has been shown to be effective in preventing clots in both of these clinical conditions.

Dabigatran is formulated in capsules as a mesylate salt in the form of a yellowish powder. The capsules include other inactive ingredients and are available in 75 and 150 milligram (mg) strengths.

U.S. brand names

In the United States, dabigatran is sold under the brand name Pradaxa.

Canadian brand names

In Canada, dabigatran is sold under the brand name Pradaxa.

International brand names

Internationally, dabigatran is sold under the brand name Pradaxa.

Origins

Dabigatran was developed at the pharmaceutical firm Boehringer Ingelheim when it was discovered that



Pradaxa (dabigatran), 150 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

a panel of chemicals with a structure similar to a benzamidine-based thrombin inhibitor called alpha-NAPAP was able to stop the activity of thrombin and trypsin, which both function in human coagulation. Early clinical trials also determined that the drug could be readily absorbed when taken orally.

The FDA approved dabigatran in 2010 for use in the prevention of stroke in patients with non-heart-valve-related atrial fibrillation, and it was approved for use in Canada and Europe at about the same time for the same purpose. It has also been used to reduce the risk of recurrence of deep venous thrombosis and pulmonary embolism in patients who have previously experienced these blood-clotting problems.

Recommended dosage

As an oral anticoagulant, dabigatran is available only in capsules to be taken by mouth. The standard dosage for reducing the risk of stroke and embolism is 150 mg twice a day. Patients with kidney disease and associated renal impairment will be given 75 mg per day and may be given other drugs (e.g., dronedarone or **ketoconazole**) at the same time to help reduce kidney exposure to dabigatran. The standard dosage for treating and reducing risk of recurrence of deep vein thrombosis and pulmonary embolism is 150 mg twice a day after receiving five to ten days of parenteral anticoagulation.

At these recommended doses, dabigatran is rapidly distributed within two hours of administration, reaching a peak level of between eight and ten hours per single dose.

Other conditions and allergies

No dosing recommendations are available for treating and reducing risk of recurrence of deep vein thrombosis and pulmonary embolism in patients with severe renal impairment or those on dialysis. Dabigatran is eliminated primarily in urine. Therefore, it must be cleared by the kidneys, which can place a strain on kidneys that are already compromised by disease.

Precautions

Dabigatran should not be given to patients who have had artificial heart valves implanted. Studies conducted in patients who had undergone replacement of the aortic or mitral valves of the heart within three months prior to taking dabigatran showed that the rates of thromboembolic and bleeding complications were increased, indicating an increased risk in these patients.

The risk of thrombotic (clotting) events is increased if dabigatran is abruptly discontinued. When discontinued for any reason other than serious bleeding or scheduled completion of anticoagulant therapy, another anticoagulant must be given to prevent clot formation.

Since the 2010 approval of dabigatran, it has been associated with bleeding in patients using the drug. However, the FDA conducted investigations to determine whether bleeding events had occurred more often than would be expected with a drug that acted on coagulation. A clinical trial comparing dabigatran with warfarin, the most commonly used anticoagulant drug worldwide, showed that dabigatran had a lower risk of death, stroke, and bleeding in the brain (cerebral vascular accident) than warfarin. The FDA clinical investigators concluded that dabigatran has a favorable risk/benefit ratio. Physicians generally monitor patients closely when they are taking dabigatran, and patients at increased risk of bleeding are not candidates for the drug.

Patients who are receiving spinal anesthesia, who are undergoing spinal surgery or spinal puncture, or who have an indwelling spinal (epidural) catheter are at increased risk of developing hematomas in the spine if they are given dabigatran, which can result in long-term or permanent paralysis. Such patients are not candidates for use of dabigatran, and the risk must be considered when patients taking dabigatran are being scheduled for spinal procedures. If dabigatran use and spinal procedures are combined in the same patient, any signs of neurological impairment (e.g., tingling or loss of sensation

KEY TERMS

Antithrombotic—A type of drug that prevents the development of blood clots.

Atrial fibrillation—An irregular and usually rapid heart rate that results in poor blood flow to body organs.

Cerebrovascular accident—A stroke, or the loss of brain function due to interrupted blood flow to the brain. Such loss of blood flow is often caused by a blood clot or piece of a blood clot called a thromboembolism.

Coagulation cascade—The sequence of biochemical activities, involving clotting factors, that stop bleeding by forming a clot.

Deep vein thrombosis (DVT)—A blood clot in a deep vein (most often in the legs). This frequently leads to pulmonary embolism if untreated.

Embolism—A piece of a blood clot or thrombus that has broken away from the thrombus and traveled to another location through the body's network of blood vessels. An embolism can travel to the lungs, heart, or brain or can lodge in veins or arteries anywhere in the body.

Fibrin—The protein formed as the end product of the blood-clotting process when fibrinogen interacts with thrombin.

Hematoma—A collection of blood forming outside of blood vessels within tissue. It appears as a “black-and-blue” or deep-red area. A hematoma can form after a specific injury or may form when bleeding occurs under the skin for other reasons.

Parenteral—Administered inside the body but outside the digestive tract.

Thrombin—An enzyme in blood plasma that plays a role in the blood-clotting process.

Thrombus—A blood clot formed as a solid mass of platelets and fibrin.

in the arms, legs, or face or loss of consciousness) require immediate emergency treatment.

Before taking dabigatran, patients are advised to tell their physicians about any allergies or previous allergic reactions to drugs. It is also important to inform the treating physician about prior history of heart valve surgery, kidney or liver disease, bleeding disorders (e.g., bleeding of stomach/intestines, brain, or other organs) or blood disorders (e.g., anemia, hemophilia, low platelet

count, or thrombocytopenia), stroke, major surgery, and falls or other injuries. Any of these disorders can carry risk of developing bleeding or clotting problems, and each patient's individual risk must be evaluated before taking dabigatran.

It is also critically important that patients report the use of dabigatran to any healthcare provider who may provide the patient with any kind of medical or dental treatment.

Side effects

Patients taking dabigatran are at increased risk of bleeding because of the anticoagulant characteristics of the drug itself. Bleeding can be major, occurring in an organ such as the brain, spine, stomach, or intestines, or it may develop in joints (intra-articular) or intramuscularly. Bleeding can be life threatening, reducing blood pressure significantly and requiring multiple transfusions. Certain types of bleeding may require surgery, especially bleeding under the skull (intracranial bleeding), hemorrhagic stroke, or spinal bleeding. Although all anticoagulant drugs (e.g., warfarin, heparin) can cause bleeding, the incidence is somewhat higher with dabigatran, especially in patients aged 75 and older.

Gastrointestinal reactions may include upper abdominal pain or discomfort (dyspepsia), gastroesophageal reflux, esophagitis, gastric hemorrhage, and gastric ulcer.

Hypersensitivity or allergic reactions to dabigatran may include hives (urticaria), rash and itching (pruritus), allergic swelling (edema), or anaphylactic reaction or shock.

Geriatric

The incidence of bleeding as a result of dabigatran is higher than other anticoagulant drugs, particularly for patients older than 75.

Interactions

Dabigatran has known interactions with some drugs, herbs, and supplements.

Drugs

Certain drugs may react with dabigatran and increase risk of bleeding or bleeding complications, including:

- aspirin, low strength
- celecoxib (Celebrex)
- duloxetine (Cymbalta)
- escitalopram (Lexapro)
- warfarin or other anticoagulants
- antiplatelet medications such as clopidogrel, prasugrel, ticagrelor, ticlopidine

PATIENT PROFILE

Dabigatran (Pradaxa) was prescribed to help prevent blood clots and stroke or other clot-related events (thrombosis) in a 60-year-old woman who had been diagnosed with atrial fibrillation. Atrial fibrillation is an irregular, rapid heart rate that results in poor blood flow to body organs; it is associated with abnormal blood clotting. Dabigatran is an oral anticoagulant, also called an antithrombotic, in the drug class of direct thrombin inhibitors. It works by stopping the formation of thrombin, an integral component in the body's blood-coagulation system. Dabigatran is used to treat patients with atrial fibrillation and without heart valve disorders to reduce the risk of developing blood clots (emboli) anywhere in the body. Clots can develop in blood vessels that may carry the clots to the brain, causing stroke, or to the lungs, causing pulmonary embolism. This patient had previously developed clots in her legs after undergoing surgery to remove varicose veins. At that time, a type of mesh trap was surgically placed in a major artery to keep clots from traveling to her upper body. Now, because atrial fibrillation placed her at increased risk of blood clots, medication was needed to stop clot formation that could block blood vessels in the heart, lungs, or brain, resulting in heart attack, pulmonary embolism, or stroke.

Dabigatran is available in capsules to be taken by mouth. For this patient, the doctor prescribed a 150 mg tablet to be taken orally twice a day. She was urged to maintain her dosage carefully and to not stop taking the medication on her own, since risk of clot formation actually increases if dabigatran is stopped suddenly.

She was also advised to report any unusual symptoms or possible reactions to the drug.

Although the patient reported no symptoms or reactions within the first four weeks of dabigatran therapy, at her first follow-up visit to the doctor she said she was suffering from abdominal discomfort, indigestion or heartburn, and regurgitation of stomach acid after eating and when lying down. The patient had thought this was a digestive problem and not related to blood coagulation or dabigatran use. However, although laboratory tests showed that her red blood cell count was normal, a stool examination revealed a trace of blood (occult) in the stool, a possible sign of slight gastrointestinal bleeding. All anticoagulant drugs carry the risk of bleeding, but dabigatran is more strongly associated with gastrointestinal issues such as erosive gastritis, ulcer, and bleeding than other more commonly used anticoagulants such as warfarin. The doctor felt that the dabigatran should be stopped in order to decrease the patient's bleeding risk and the gastrointestinal symptoms, and that another drug should be substituted to prevent stroke. Warfarin (Coumadin), which works differently than dabigatran to stop blood clot formation, was prescribed for the patient. Based on results of a specific test of kidney function (creatinine clearance), warfarin therapy was started one day before discontinuing dabigatran, so that there would be no gap in protection or risk of clotting from discontinuing dabigatran. The patient continued with warfarin therapy without incident, and her gastrointestinal disturbance subsided within ten days. No occult blood was found in repeat stool examinations.

- nonsteroidal anti-inflammatory drugs (NSAIDs such as **ibuprofen**)
- **rivaroxaban**
- sulfinpyrazone
- thrombolytics such as alteplase
- tirofiban

Other drugs that may react unfavorably with dabigatran include:

- **diltiazem** hydrochloride, which may increase the blood levels and anticoagulation effects of dabigatran
- milk of magnesia (magnesium hydroxide), which may interfere with dabigatran absorption and reduce its effectiveness
- dronedarone, ketoconazole, and quinidine, which may increase risk of side effects
- enzalutamide and **rifampin**, which may decrease the effectiveness of dabigatran

Herbs and supplements

Certain herbs and supplements may also react negatively with dabigatran, including:

- fish oil (omega-3 polyunsaturated fatty acids), which can increase risk of bleeding when combined with dabigatran
- St. John's wort, which may decrease the effectiveness of dabigatran

Resources

BOOKS

American Society of Health-System Pharmacists. *AHFS Drug Information 2011*. Bethesda, MD: ASHP, 2011.

PERIODICALS

Eikelboom, J. W., et al. "Dabigatran vs. Warfarin in Patients with Mechanical Heart Valves." *New England Journal of Medicine* 369, no. 1 (2013): 1206–14.

Moore, T. J., M. R. Cohen, and D. R. Mattison. "Dabigatran, Bleeding, and the Regulators." *British Medical Journal* 349 (2014): 4517.

Wann, L. S., et al. "2011 ACCF/AHA/HRS Focused Update on the Management of Patients with Atrial Fibrillation (Update on Dabigatran): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines." *Circulation* 123, no. 10 (2011): 1144–50.

WEBSITES

AHFS Consumer Medication Information. "Dabigatran." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a610024.html> (accessed February 9, 2015).

"Dabigatran." RxList.com. <http://www.rxlist.com/tegretol-drug.htm> (accessed February 5, 2015).

ORGANIZATIONS

American Society for Clinical Pharmacology and Therapeutics, 528 N Washington Street, Alexandria, VA 22314, (703) 836-6981, info@ascpt.org, <http://www.ascpt.org>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Demadex see **Torsemide**

Depakene see **Valproic acid**

Depakote see **Valproic acid**

Depo-Provera see **Medroxyprogesterone**

Desipramine

Definition

Desipramine is an antidepressant drug used to elevate mood and promote recovery of a normal range of emotions in patients with depressive disorders. In addition, desipramine has uses in treating a number of other psychiatric and medical conditions.

Purpose

Desipramine is known principally as an antidepressant drug used to promote recovery of depressed patients. It also has therapeutic uses in panic disorder, pain management, attention deficit hyperactivity disorder, sleep attacks (narcolepsy and cataplexy), binge eating, and drug addiction.



Desipramine, 25 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Description

Desipramine is one of the tricyclic antidepressants, so-called because of the three-ring chemical structure common to these drugs. Until the late 1980s, desipramine and other tricyclic antidepressants, such as **imipramine**, formed the mainstay of the pharmacological treatment of depressive disorders.

The therapeutic action of antidepressants is not completely understood. It is known that these drugs boost the levels of certain messenger chemicals, called neurotransmitters, which are involved in transmitting signals between nerve cells in the brain. This action may help to restore normal emotional feelings by counteracting abnormalities of nerve signal transmission that occur in depressive disorders.

Desipramine is one of a large number of tricyclic antidepressant compounds. Each was developed for somewhat differing pharmacological effects and side-effect profiles. The effects of desipramine are similar to those of other tricyclics, although some patients may find one drug of this group more effective or more tolerable than another. It is typically available as 10, 25, 50, 75, 100, and 150 milligram (mg) tablets.

U.S. brand names

In the United States, the drug is also known by its brand name, Norpramin.

KEY TERMS

Antidepressant—Any of a group of medications given to relieve mood disorders, including anxiety disorders as well as major depression. Antidepressants include monoamine oxidase inhibitors (MAOIs), tricyclic (TCAs) and tetracyclic (TeCAs) antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs).

Cataplexy—A symptom of narcolepsy marked by a sudden episode of muscle weakness triggered by strong emotions. The muscle weakness may cause the person's knees to buckle or the head to drop. In severe cases, the patient may become paralyzed for a few seconds or minutes.

Epilepsy—A neurological disorder characterized by the onset of seizures. Seizures are caused by a disturbance in the electrical activity in the brain and can cause loss of consciousness, muscle spasms, rhythmic movements, abnormal sensory experiences, or altered mental states.

Neurotransmitter—A chemical in the brain that transmits messages between neurons, or nerve cells.

Recommended dosage

For adults, desipramine is usually administered in dosages of 100–200 mg per day. Doses ranging from 75 mg to 300 mg per day are sometimes prescribed. The initial daily dose is usually low to avoid side effects, but it is usually increased, as necessary, until a therapeutic effect is achieved. Desipramine may be administered in divided doses or a single daily dose.

Geriatric patients, children, and adolescents are more sensitive to the side effects and toxicities of tricyclic antidepressants than other people.

Pediatric

For children 6–12 years old, the recommended dose ranges from 10 mg to 30 mg per day in divided doses. For adolescents, daily dosages range from 25 mg to 50 mg but may be increased up to 100 mg, if needed.

Geriatric

For geriatric patients, the dose may range from 25 mg to 100 mg per day.

Precautions

Because desipramine and other tricyclic antidepressants may cause drowsiness, activities requiring alertness, such as driving, may be impaired. Patients should avoid such activities until they understand how the drug affects them. Dizziness or light-headedness may occur when standing due to sudden decreases in blood pressure. Fainting may also occur.

Studies have found that some antidepressant drugs, including desipramine, may increase the chances of suicidal thoughts in children and adults up to age 24. Patients taking desipramine should be monitored, regardless of age, for worsening depression or other adverse changes in behavior.

Pregnant or breastfeeding

It has not been determined whether desipramine is safe to take during pregnancy, and the patient's need for this medicine should be balanced against the possibility of harm to the fetus. Tricyclic antidepressants may be secreted in breast milk and may cause sedation and depressed breathing in a nursing infant.

Other conditions and allergies

Patients with glaucoma may find their condition aggravated. Among patients with epilepsy, seizures may become more frequent. Persons with heart disease should use tricyclic antidepressants with caution due to a possibility of adverse effects on heart rhythm.

Side effects

Desipramine may cause many side effects. Initially, the side effects of tricyclic drugs may be more pronounced, but sensitivity to the drug may decrease with continued treatment. Some of the more common side effects include fatigue, confusion, nervousness, restlessness, sleep difficulties, numbness, tingling sensations, tremors, blurred vision, difficulty urinating (especially in men with prostate enlargement), constipation, rashes, and weight gain. Sensitivity to ultraviolet light may be increased, and sunburns may occur more easily. Sweating may be reduced, causing sensitivity to heat and hot weather. Patients may also develop dry mouth due to decreased saliva, possibly contributing to the development of tooth decay, gum disease, and mouth infections. Patients should avoid sweets, sugary beverages, and chewing gum containing sugar.

Less commonly, tricyclic drugs may cause adverse effects on almost any organ or system of the body, particularly the blood, hormones, kidney, and liver.

Patients should consult their physicians if symptoms develop or bodily changes occur.

Interactions

Tricyclic antidepressants such as desipramine may interact with many other drugs. Patients should inform their physicians about all other drugs they are taking, including supplements.

Tricyclic drugs may intensify the effects of drugs causing sedation, including barbiturates, narcotic pain medications, minor tranquilizers, and antihistamines. Tricyclics may cause excessive drops in blood pressure in patients taking blood pressure medicine, especially upon sitting up or standing. Conversely, these drugs may interfere with the pressure-reducing effects of certain other blood pressure medicines. Tricyclics may interact with thyroid medications to produce heart rhythm abnormalities. Also, they may increase seizure tendency in patients with epilepsy, requiring adjustment of antiepileptic medications. Concurrent use of tricyclic antidepressants with other antidepressants or other psychiatric medicines may result in intensification of certain side effects.

Certain drugs may interfere with the elimination of tricyclic antidepressants from the body, causing higher blood levels and increased side effects. This effect may occur with cimetidine (Tagamet), other antidepressants, **methylphenidate** (Ritalin, Concerta), and some antipsychotic medications. Patients taking monoamine oxidase inhibitors (MAOIs) should tell their physicians before starting desipramine (or vice versa). They will likely need to wait a period of at least 14 days after their last MAOI dosage before beginning treatment with desipramine.

Food and other substances.

Desipramine and other tricyclic antidepressants may enhance the sedative effect of alcohol. Grapefruit juice or grapefruit can increase the concentration and toxicity of desipramine.

Resources

BOOKS

Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger, 2013.

PERIODICALS

Amitai, Yona, and Henri Frischer. "Excess Fatality from Desipramine in Children and Adolescents." *Journal of the American Academy of Child and Adolescent Psychiatry* 45, no. 1 (January 2006): 54–60.

Ghanizadeh, A. "A Systematic Review of the Efficacy and Safety of Desipramine for Treating ADHD." *Current Drug Safety* 8, no. 3 (2013): 169–74.

Hearn, L., et al. "Desipramine for Neuropathic Pain in Adults." *Cochrane Database of Systematic Reviews* 9, art. no. CD011003 (2014). <http://dx.doi.org/10.1002/14651858.CD011003.pub2> (accessed February 20, 2015).

Mohkber, N., et al. "Comparison of Sertraline, Venlafaxine and Desipramine Effects on Depression, Cognition and the Daily Living Activities in Alzheimer Patients." *Pharmopsychiatry* 47, nos. 4–5 (2014): 131–40.

WEBSITES

AHFS Consumer Medication Information. "Desipramine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682387.html> (accessed February 21, 2015).

Florida Hospital. "Tricyclic Antidepressants (TCAs)." <https://www.floridahospital.com/tricyclic-antidepressants-tcas> (accessed February 21, 2015).

Healthwise. "Desipramine." University of Michigan Health System. <http://www.uofmhealth.org/health-library/d00145a1> (accessed February 21, 2015).

ORGANIZATIONS

American Academy of Child and Adolescent Psychiatry, 3615 Wisconsin Avenue NW, Washington, DC 20016-3007, (202) 966-7300, Fax: (202) 966-2891, <http://aacap.org/>.

American College of Neuropsychopharmacology, 5034-A Thoroughbred Lane, Brentwood, TN 37027, (615) 324-2360, Fax: (615) 523-1715, acnp@acnp.org, <http://www.acnp.org/default.aspx>.

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Desvenlafaxine

Definition

Desvenlafaxine is a prescription drug used to treat depression. This medication belongs to a class of drugs known as serotonin-norepinephrine reuptake inhibitors (SNRIs), which affect the neurotransmitters serotonin and norepinephrine. These chemicals are involved in normal brain function, and low levels are associated with clinical depression.



Pristiq (desvenlafaxine), 50 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Purpose

Desvenlafaxine is prescribed to treat clinical depression. The drug is a synthetic form of a metabolite of the antidepressant drug **venlafaxine**. It was developed based on the theory that a significant portion of the therapeutic benefits of venlafaxine come from this metabolite. Desvenlafaxine is expected to have fewer interactions with other medications than venlafaxine due to differences in how it is processed in the body. Whether there is an advantage in taking desvenlafaxine instead of venlafaxine is debated.

Other potential uses were being explored as of 2015.

Description

Desvenlafaxine works by acting on the neurotransmitters serotonin and norepinephrine, which are chemicals in the body that help regulate normal brain and body functioning. When a nerve cell is triggered, it releases a neurotransmitter that carries the nerve impulse across a gap to the next nerve cell. The neurotransmitter is then reabsorbed by the releasing cell. It is believed that desvenlafaxine works by slowing the reabsorption of the neurotransmitters norepinephrine and serotonin, thus increasing their levels in the brain. Desvenlafaxine has a larger impact on serotonin than norepinephrine.

Individual response to each SNRI varies greatly. Whether an individual will benefit from taking an SNRI drug may have a genetic component. The initial trial of

an SNRI can be difficult, because adverse side effects can occur before the patient begins to see the benefits of the medication. This may be discouraging to the patient. A drug that works best for one patient may not work for another patient, and having no success with one SNRI does not mean that a patient will experience the same results with another SNRI. Finding which SNRI will work for a patient may require a trial of multiple drugs until an effective agent is identified. Generally, a drug is used for four to six weeks before a decision is made regarding its effectiveness. If the drug has shown some benefit, but the healthcare provider thinks that it could be enhanced, the dosage may be increased if the patient is able to tolerate it.

Desvenlafaxine is available as a 50-milligram (mg) tablet and as a 50 mg or 100 mg extended-release tablet.

U.S. brand names

In the United States, desvenlafaxine is sold under the brand names Pristiq and Khedezla.

Canadian brand names

In Canada, desvenlafaxine is sold under the brand name Pristiq.

International brand names

Internationally, desvenlafaxine is sold under the brand names Fapris, Pristiq, and Zyven-OD.

Origins

Desvenlafaxine was approved by the U.S. Food and Drug Administration (FDA) for the treatment of major depression in February 2008.

Recommended dosage

Desvenlafaxine is a tablet taken by mouth. The dosage varies depending on how an individual patient responds, and it is usually increased gradually. If side effects develop that are not tolerable, the patient may require a lower dose. Desvenlafaxine is usually dosed at 50 mg daily. Higher doses rarely result in better therapeutic effects, and they increase the risk of adverse side effects.

Slowly increasing the dose may help minimize side effects, and some side effects may abate with continued use. Patients are periodically reassessed to determine whether there is a need for continued treatment with desvenlafaxine.

SNRIs, including desvenlafaxine, need to be slowly tapered if discontinued to avoid withdrawal symptoms.

KEY TERMS

Bipolar disorder—A mood disorder marked by alternating episodes of extremely low mood (depression) and exuberant highs (mania).

Depression—A mental state characterized by excessive sadness and loss of interest in life; other symptoms may include altered sleep or eating patterns, loss of concentration, agitation, lack of energy, and, in severe cases, attempts at self-harm or suicide.

Glaucoma—A condition involving increased pressure within the eye that may cause damage and blindness.

Mania—A physiological state of hyperactivity experienced by patients with certain psychiatric illnesses involving inappropriate elevated mood, pressured speech, poor judgment, and sometimes psychotic episodes superimposed on the state of mania.

Metabolite—A chemical compound that occurs as a result of a parent drug being broken down and metabolized in the body. A metabolite may be a medically active or inactive compound, depending on the drug in question.

Monoamine oxidase inhibitor (MAOI)—A type of antidepressant medication that affects various kinds of neurotransmitters, including serotonin.

Neurotransmitter—One of a group of chemicals secreted by a nerve cell (neuron) to carry a chemical message to another nerve cell, often as a way of transmitting a nerve impulse. Examples of

neurotransmitters include acetylcholine, dopamine, serotonin, and norepinephrine.

Norepinephrine—Also called noradrenaline, a chemical messenger in the brain that regulates attention and that powers the “fight-or-flight” stress response; precursor of epinephrine.

Serotonin-norepinephrine reuptake inhibitors (SNRIs)—A drug class that acts to specifically inhibit the reuptake of serotonin and norepinephrine in the neuronal synapse with little effect on other types of neurotransmitters, thereby decreasing side effects associated with broader-acting drugs.

Selective serotonin reuptake inhibitors (SSRIs)—A drug class that acts to specifically inhibit the reuptake of serotonin only in the neuronal synapse with little effect on other types of neurotransmitters, thereby decreasing side effects associated with broader-acting drugs.

Serotonin—A type of neurotransmitter involved in the regulation of the blood vessels, brain processes, and disease states such as depression.

Serotonin syndrome—A potentially life-threatening drug reaction involving an excess of the neurotransmitter serotonin, usually occurring when too many medications that increase serotonin are taken together, such as antimigraine triptans and certain antidepressants.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

Geriatric

Elderly patients tend to develop side effects more easily and may be more sensitive to the effects of the medication. Elderly individuals may require dosing every other day.

Other conditions and allergies

Patients with impaired liver or kidney function affecting drug metabolism require lower doses or less frequent dosing to avoid toxicity.

Precautions

Antidepressant drugs, including desvenlafaxine, have been associated with an increased risk of suicidal

thoughts and behaviors in children and adults up to age 24. Any patient taking an antidepressant drug should be monitored for changes in behavior and worsening depression.

If treatment with desvenlafaxine is stopped, it should be slowly discontinued to avoid the development of SNRI discontinuation syndrome. Such withdrawal symptoms include:

- flulike symptoms
- anxiety or agitation
- vivid or bizarre dreams
- insomnia, nausea
- vomiting or diarrhea
- sense of imbalance

- chills
- fatigue
- dizziness
- headache
- numbness and tingling of the extremities
- other sensory disturbances

Discontinuation syndrome may be avoided if the dose is properly reduced over time.

SNRI overdose may result in a condition known as serotonin syndrome. Serotonin overdose may also be caused by taking multiple drugs that increase the amount of serotonin signaling in the body. Symptoms of serotonin overdose range from mild to life threatening, depending on the individual situation. Symptoms may include:

- high blood pressure
- high fever
- nausea or diarrhea
- headache
- sweating
- increased heart rate
- tremor
- muscle twitching
- delirium
- shock
- coma

Serotonin overdose can also result in death.

Kidney and liver function, as well as blood pressure and behavioral changes, may be monitored while patients are taking desvenlafaxine.

Pediatric

Desvenlafaxine is not indicated for use in pediatric patients.

Pregnant or breastfeeding

Desvenlafaxine is in the FDA pregnancy category C, which means either that there are no adequate human or animal studies of the drug during pregnancy, or that adverse fetal effects were found in animal studies, but there is no available human data. The decision about whether to use category C drugs in pregnancy is generally based on weighing the critical needs of the mother against the risk to the fetus. Other, lower-category agents are used whenever possible. The safety of desvenlafaxine use during breastfeeding is unknown; therefore, its use is not recommended.

Other conditions and allergies

Desvenlafaxine may be contraindicated (should not be used) or may require caution in use in patients with uncontrolled hypertension (high blood pressure), liver function impairment or liver disease, kidney function impairment, seizure disorder, bleeding disorders, glaucoma, dehydration, or a history of alcohol abuse.

SNRIs such as desvenlafaxine are discouraged for use in patients with bipolar disorder, as the drugs can induce a state of mania in these individuals. There are selective conditions under which a doctor may prescribe an SNRI such as desvenlafaxine to a bipolar patient, but only for a short period and under careful monitoring.

Side effects

SNRIs tend to have fewer side effects than other types of older antidepressant medications, but side effects may still occur. Common side effects of desvenlafaxine include:

- nausea and vomiting
- headache
- dizziness
- fatigue
- constipation or diarrhea
- sexual dysfunction
- sweating
- dry mouth
- shakiness
- tremor
- palpitations
- loss of appetite
- weight changes
- hot flashes or chills
- elevated blood pressure
- vision changes
- ringing in the ears
- anxiety
- abnormal dreams
- insomnia

Rare but serious potential side effects include mania, worsened depression and suicidality, seizures, serotonin syndrome, discontinuation syndrome, electrolyte imbalances, lung damage or disease, urinary retention, skin reactions, abnormal bleeding, liver damage, and glaucoma.

Interactions

Patients should make their doctor aware of all drugs, herbs, and supplements they are taking before using desvenlafaxine. Drugs that affect the liver may alter the metabolism of desvenlafaxine, which can result in too much or too little of the drug in the body.

Drugs

SNRIs should not be used with other drugs that inhibit the absorption of serotonin, such as selective serotonin reuptake inhibitors (SSRIs). Antidepressants called monoamine oxidase inhibitors (MAOIs) also increase the amount of serotonin and should not be used concurrently with desvenlafaxine. Patients taking an MAOI should stop and wait at least 14 days before starting treatment with desvenlafaxine. Switching from desvenlafaxine to an MAOI may require a waiting period of up to five weeks.

Other drugs that increase serotonin in the body include sumatriptan (Imitrex), used to treat migraine headaches, and the antipsychotics chlorpromazine and fluphenazine. Diuretics (water pills) such as **hydrochlorothiazide**, diet pills such as sibutramine (Meridia), certain diabetes drugs such as sulfonylureas, mood stabilizers such as valproic acid, and antipsychotics such as **haloperidol** and **clozapine** should not be used with desvenlafaxine to avoid potentially toxic effects. There is increased risk of internal bleeding when desvenlafaxine is used with anticoagulant drugs such as **aspirin** and **warfarin** (Coumadin).

Herbs and supplements

The herbal supplements yohimbe and St. John's wort increase serotonin in the body and should not be used with SNRIs.

Large doses of the herbal supplements red clover, dong quai, ginkgo biloba, feverfew, and concentrated green tea increase the risk of internal bleeding when used with desvenlafaxine.

Food and other substances

Using alcohol or caffeine while taking desvenlafaxine may create toxic reactions and should be avoided.

Resources

BOOKS

Sadock, Benjamin, J., Virginia A. Sadock, and Norman Sussman. *Kaplan & Sadock's Pocket Handbook of Psychiatric Drug Treatment*. 6th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2014.

Wegmann, Joseph. *Psychopharmacology: Straight Talk on Mental Health Medications*. 2nd ed. Eau Claire, WI: Premier Publishing & Media, 2012.

PERIODICALS

Mitchell, Ann M., et al. "Antidepressant Use in Children, Adolescents, and Young Adults: 10 Years after the Food and Drug Administration Black Box Warning." *Journal for Nurse Practitioners* 10, no. 3 (2014): 149–56.

OTHER

U.S. Food and Drug Administration. "Highlights of Prescribing Information: Pristiq." http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021992s033s0361bl.pdf (accessed March 2, 2015).

WEBSITES

AHFS Consumer Medication Information. "Desvenlafaxine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a608022.html> (accessed March 2, 2015).
National Alliance on Mental Illness. "Pristiq® (Desvenlafaxine)." http://www2.nami.org/Template.cfm?Section=court_watch1&template=/ContentManagement/ContentDisplay.cfm&ContentID=168470 (accessed March 2, 2015).

ORGANIZATIONS

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.
Depression and Bipolar Support Alliance, 55 E. Jackson Boulevard, Suite 490, Chicago, IL 60604, (800) 826-3632, Fax: (312) 642-7243, <http://www.dbsalliance.org/>.
Mental Health America, 2000 N. Beauregard Street, 6th Floor, Alexandria, VA 22311, (703) 684-7722, (800) 969-6642, Fax: (703) 684-5968, <http://www1.nmha.org/>.
National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.
National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.
U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Desyrel see **Trazodone**

Detrol see **Tolterodine**

Dexamethasone/ciprofloxacin see
Ciprofloxacin/dexamethasone

Dexamethasone/tobramycin see
Tobramycin/dexamethasone

Dexedrine see **Dextroamphetamine**

Dexilant see **Dexlansoprazole**

Dexlansoprazole

Definition

Dexlansoprazole is a proton pump inhibitor (PPI) and is the counterpart of **lansoprazole** (Prevacid). Lansoprazole, like many other drugs, is a mixture of two molecules that are mirror images of each other, rather like the left and right hand are mirror images. In many cases, the R (right hand) and S (left hand) versions of the drug have differences in their actions or activity. Sometimes one version of the drug will have most of the desired activity, while the other may cause unwanted side effects. Dexlansoprazole has the same chemical composition as lansoprazole but is its “right-hand” version (r-enantiomer).

Purpose

Proton pump inhibitors reduce the level of stomach acid by blocking enzymes in the stomach wall that help create the acid. They are useful for treatment of ulcers, gastroesophageal reflux disease (GERD), and Zollinger-Ellison syndrome.



Dexilant (dexlansoprazole), 60 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

Description

Dexlansoprazole is marketed as a hard gelatin (two-piece) capsule. The 60 milligram (mg) capsules are solid blue and are imprinted with the number 60. The 30 mg capsules have a blue cap and a grey body and are imprinted with the number 30.

The commercial product has a dual-release formulation. The initial release produces peak blood levels in one to two hours after taking the capsule, and the secondary release peaks four to five hours after a dose.

U.S. brand names

Dexilant (formerly marketed as Kapidex) is available as 30 and 60 mg capsules. The name was changed because the old name could be confused with Casodex, which is used to block androgen, the male sex hormone.

Canadian brand names

In Canada, dexlansoprazole is also sold under the brand name Dexilant.

Recommended dosage

The initial dose for treating erosive esophagitis is 60 mg taken once a day for up to eight weeks. After that, the dose may be reduced to 30 mg a day for maintenance and the prevention of heartburn.

To treat gastroesophageal reflux disease, 30 mg/day is taken for four weeks.

For patients who have difficulty swallowing capsules, dexlansoprazole capsules may be opened and sprinkled on applesauce. If this is done, the applesauce must be eaten immediately and the granules must not be chewed. The granules may also be administered through a nasogastric tube or an oral syringe.

Dexlansoprazole may be taken on an empty stomach.

Other conditions and allergies

No dose adjustment is required for patients with mild liver function problems. For patients with moderate liver function problems, the dose should be limited to 30 mg/day. The safety of dexlansoprazole has not been established in patients with severe liver function problems.

Precautions

Proton pump inhibitors have been associated with the possible development of *Clostridium difficile*-associated diarrhea (CDAD). Physicians should consider this possibility if a patient who is being treated with a PPI develops diarrhea that does not improve. The risk of

KEY TERMS

Clostridium difficile—A type of bacteria that occurs normally in the human intestine. *C. difficile* becomes a problem if treatment with antibiotics kills the other intestinal bacteria, allowing the *C. difficile* to grow. *C. difficile* produces a toxin that damages the lining of the intestine. Symptoms of *C. difficile* infection include frequent watery diarrhea, severe abdominal pain, and fever. Treatment requires special antibiotics.

Copolymers—Chains of molecules formed from two or more types of molecule. If a single type of molecule binds with others of the same type to form a chain, it is called a polymer. If two or more molecules form a chain with each other, it is a copolymer.

Enteric-coated drug—A drug that has a coating that breaks apart only in the intestine, not the stomach. Enteric coatings may be used for drugs that would cause stomach irritation, as a way of delaying the release of the drug into the bloodstream, or for drugs that would be harmed by stomach acid.

Esophagitis—Inflammation of the esophagus, the tube that connects the throat with the stomach.

Gastroesophageal reflux disease (GERD)—Occurs when stomach acid or, occasionally, stomach content, flows backward into the esophagus. This backflow (reflux) irritates the lining of the esophagus.

Proton—A hydrogen atom that has been stripped of its electron. Solutions that contain an excess of protons (H^+) are acids.

other infections, including infection with *Salmonella* and *Campylobacter*, may also increase.

Long-term use of more than one year may cause low magnesium levels, which can result in seizures and irregular heartbeat. In clinical reports, magnesium supplements were not always effective in restoring normal levels, and the proton pump inhibitor had to be discontinued.

Pediatric

Dexlansoprazole has not been shown to be safe and effective in patients under the age of 18. Another PPI called **esomeprazole** (Nexium) has been studied in infants and children and may be used instead of dexlansoprazole.

Pregnant or breastfeeding

Proton pump inhibitors have been used during pregnancy to treat GERD with no observed harm to the mother or fetus. Dexlansoprazole is considered a pregnancy category B drug, which means that animal studies have not shown the drug to have adverse effects on a fetus, despite a lack of human studies.

It is not known if dexlansoprazole is excreted into breast milk. Due to the potential for adverse reactions in the breastfeeding infant, the manufacturer recommends a decision be made whether to discontinue breastfeeding or the drug, taking into account the importance of treatment to the mother.

Other conditions and allergies

Dexlansoprazole should not be administered to patients who are allergic to the drug or to any of its components.

Side effects

Dexlansoprazole is generally well tolerated. The most common side effects are:

- diarrhea
- abdominal pain
- nausea
- upper respiratory tract infections
- vomiting
- flatulence

More serious effects are usually related to long-term use (more than one year).

Interactions

Drugs

Because proton pump inhibitors reduce the amount of acid in the stomach, they should not be taken with other drugs that depend on an acidic environment for their activity. These drugs include erlotinib (used to treat an advanced form of lung cancer) and ribavirin and nelfinavir (both used for treatment of human immunodeficiency virus [HIV] infection).

Mesalamine (used for ulcerative colitis) and itraconazole and **ketoconazole** (antifungals) are also likely to interact with dexlansoprazole. Patients should make sure that their healthcare providers are aware of all drugs they are currently taking, including over-the-counter drugs and supplements.

Herbs and supplements

There is a possibility that iron supplements, including ferrous sulfate and gluconate, may interact with

dexlansoprazole, reducing the amount of iron available to the body.

Rose hip, St. John's wort, blessed thistle, devil's claw, and phytoestrogens (plant products, such as soy, that act like female hormones) all have the potential for producing mild interactions with dexlansoprazole.

Resources

PERIODICALS

Fass, R., et al. "Maintenance of Heartburn Relief after Step-Down from Twice-Daily Proton Pump Inhibitor to Once-Daily Dexlansoprazole Modified Release." *Clinical Gastroenterology and Hepatology* 10, no. 3 (2012): 247–53.

Metz, D. C., et al. "Clinical Trial: Dexlansoprazole MR, a Proton Pump Inhibitor with Dual Delayed-Release Technology, Effectively Controls Symptoms and Prevents Relapse in Patients with Healed Erosive Oesophagitis." *Alimentary Pharmacology and Therapeutics* 29, no. 7 (2009): 742–54.

Parekh, P. J., E. C. Oldfield IV, and D. A. Johnson. "Treatment of Gastroesophageal Reflux Disease: Two New Oral Formulations Dexlansoprazole MR and Esomezol (Esomeprazole Strontium)." *Expert Opinion on Pharmacotherapy* 15 no. 9 (2014): 1215–22.

Park, C. H., et al. "The Association Between the Use of Proton Pump Inhibitors and the Risk of Hypomagnesemia: A Systematic Review and Meta-Analysis." *PLOS One*, 9 no. 11 (2014): e112558.

Shin, J. M., and N. Kim. "Pharmacokinetics and Pharmacodynamics of the Proton Pump Inhibitors." *Journal of Neurogastroenterology and Motility* 19, no. 1 (2013): 25–35.

Solem, C., et al. "Mealtime-Related Dosing Directions for Proton-Pump Inhibitors in Gastroesophageal Reflux Disease: Physician Knowledge, Patient Adherence." *Alimentary Pharmacology and Therapeutics* 38, no. 2 (2013): 190–201.

Wu, M. S., S. C. Tan, and T. Xiong. "Comparative Efficacy of Dexlansoprazole vs. Esomeprazole in the Treatment of Gastro-oesophageal Reflux Disease." *Alimentary Pharmacology and Therapeutics* 38, no. 2 (2013):190–201.

OTHER

U.S. Food and Drug Administration. "Gastrointestinal Drugs Advisory Committee Meeting: Lansoprazole, Dexlansoprazole." <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/gastrointestinal-drugsadvisorycommittee/ucm232031.pdf> (accessed February 10, 2015).

WEBSITES

MedlinePlus. "GERD." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/gerd.html> (accessed February 10, 2015).

Physicians' Desk Reference. "Dexilant." PDR Health. <http://www.pdrhealth.com/drugs/dexilant> (accessed January 25, 2015).

U.S. Food and Drug Administration. "Proton Pump Inhibitor Information." <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm213259.htm> (accessed February 10, 2015).

U.S. National Library of Medicine. "Dexilant." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9819f033-3bbe-442e-8e92-45fec77b237d> (accessed February 10, 2015).

ORGANIZATIONS

American Gastroenterological Association, 4930 Del Ray Avenue, Bethesda, MD 20814, (301) 654-2055, Fax: (301) 654-5920, member@gastro.org, <http://www.gastro.org/>.

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Dexmethylphenidate

Definition

Dexmethylphenidate (Focalin) is a medication used to treat attention deficit hyperactivity disorder (ADHD). It belongs to the class of drugs known as central nervous system (CNS) stimulants and acts on the neurological signaling chemicals norepinephrine and dopamine. Norepinephrine and dopamine are types of neurotransmitters involved in normal brain function and have an effect on mood, concentration, and impulse control.

Purpose

Dexmethylphenidate is used to treat some of the symptoms of ADHD in both adults and children six years old and older. It is a CNS stimulant that improves memory, concentration, and impulse control, and it belongs to the category of drug that remains the mainstay of ADHD therapy. The first drug chosen for ADHD is often **methylphenidate** (Ritalin), but patients who do not respond well to methylphenidate are usually given dexmethylphenidate as a second-choice drug. Dexmethylphenidate is available as an extended-release medication, which reduces the need for re-dosing through the school day or workday. Dexmethylphenidate may have some antidepressant properties and may be useful for patients who have both ADHD and depression. However, dexmethylphenidate has not officially been approved for use in treating depression.



Focalin XR (dexmethylphenidate XR, 20 mg. *(Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)*

Description

Dexmethylphenidate has a therapeutic mechanism of action that is focused on the modulation of the natural body chemicals norepinephrine and dopamine. Norepinephrine and dopamine are types of neurotransmitters in the nervous system, chemicals that neurons use to signal one another in complex pathways for normal brain and body functioning. Neurotransmitter signaling pathways are responsible for many regulatory processes, including mood, concentration, and impulse control. It is believed that a decrease in norepinephrine signaling contributes to disorders such as ADHD and depression. It is thought that dexmethylphenidate increases signaling of norepinephrine and dopamine, which has an impact on areas of the brain that involve attention span, judgment, response to external stimuli, memory, motor function, mental focus, and impulse control.

Recommended dosage

Dexmethylphenidate is given as an oral medication in pill form, but it may be sprinkled on food as well. Doses are taken early in the day with a full glass of water; doses are not taken in the evening. Patients are frequently reassessed for the need for treatment, as drugs for ADHD are often avoided unless absolutely necessary. The dose chosen depends on individual patient response to the medication regarding its effectiveness and regarding side effects. Patients are dosed at the lowest possible effective

dose to avoid the development of adverse effects. Slowly increasing the dose over time helps with minimizing side effects.

The dose of dexmethylphenidate in both adults and children six years old and greater is started at 2.5 milligrams (mg) taken twice a day. The dose is increased by 5 mg or 10 mg increments every week for a maximum of 20 mg a day.

The extended-release formulation of dexmethylphenidate is given orally once a day at a dose of 10–30 mg. The dose is started low at 5 mg once a day taken in the morning and increased in increments of 5 mg a day over seven days to the desired dose. The maximum dose for the extended-release form is 30 mg per day.

Dosing of both the regular and extended-release form is altered if the patient was previously taking methylphenidate and is switching to dexmethylphenidate. In this scenario, the patient starts taking dexmethylphenidate at 50% of the current methylphenidate daily dose and increases as needed from there. Doses are given at least four hours apart. Doses are lowered if side effects become intolerable.

Precautions

Dexmethylphenidate is a potentially habit-forming medication and should not be used for longer periods or at higher doses than prescribed. Patients are often given “drug holidays”—for example, when school is over for the summer—during which they forgo medication to avoid the development of adverse effects. Caution is used in patients with a history of substance abuse and related disorders.

There is an association between ADHD and Tourette syndrome. Patients with Tourette syndrome often have involuntary movements or vocalizations known as tics. Patients who have Tourette syndrome and ADHD may find that the stimulant medications used to treat ADHD worsen their tics. Caution must be used in treating patients with motor tics, Tourette syndrome, or a family history of the disorder. Dexmethylphenidate may not be appropriate for use in these patients.

Some patients taking dexmethylphenidate develop increased aggressiveness, psychosis, mania, or suicidal behavior in the first weeks of use. Children are especially at risk for these behavioral side effects. Patients taking dexmethylphenidate should be monitored closely for behavioral changes, especially when starting treatment or after dose changes. Dexmethylphenidate is discouraged from use in patients with bipolar disorder, as it is more likely to induce a state of mania in these individuals than in those without bipolar disorder.

Cardiac function, heart rate, and blood pressure may be monitored while taking dexmethylphenidate.

Pediatric

Blood cell parameters and growth progression (in pediatric patients) may need to be monitored with prolonged use, as growth retardation may occur with prolonged use.

Pregnant or breastfeeding

Dexmethylphenidate is classified as category C for pregnancy, which means that either there are no adequate human or animal studies, or adverse fetal effects were found in animal studies, but there is no available human data. The decision whether to use category C drugs in pregnancy is generally based on weighing the critical needs of the mother against the risk to the fetus. Other, lower-category agents are used whenever possible. The safety of dexmethylphenidate use during breastfeeding is listed as probably safe, but data are limited and caution is advised.

Other conditions and allergies

Dexmethylphenidate may lower seizure threshold in some patients and may not be appropriate for use in patients with seizure disorder. Dexmethylphenidate may be contraindicated or may require caution in use in patients with hyperthyroidism, high blood pressure, liver function impairment or liver disease, kidney function impairment, heart conditions or abnormalities, and glaucoma.

Side effects

Dexmethylphenidate has many adverse effects. Sensitivity to dexmethylphenidate varies among patients, and some patients may find even lower doses are more than their body system can tolerate. Common reactions include abdominal discomfort or pain, dizziness, insomnia, anxiety, headache, decreased appetite, changes in blood pressure and heart rate, weight loss, and visual disturbances. Dry mouth and throat pain are especially likely with the extended-release formulation.

Rare but serious reactions include toxic skin reactions, blood disorders, heart arrhythmias, heart attack, stroke, seizures, and sudden death.

Interactions

Patients should make their doctor aware of all medications and supplements they are taking before using dexmethylphenidate.

KEY TERMS

Attention deficit hyperactivity disorder—A condition characterized by lack of concentration, impulsive or inappropriate behavior (relative to age level), and hyperactivity.

Cytochrome P450 (CYP450)—Enzymes present in the liver that metabolize drugs.

Dopamine—A type of neurotransmitter involved in regulation of concentration, impulse control, judgment, mood, attention span, psychostimulation, and disease states such as addiction, ADHD, and depression.

Mania—Physiological state of hyperactivity experienced by patients with certain psychiatric illnesses involving inappropriate elevated mood, pressured speech, poor judgment, and sometimes psychotic episodes superimposed on the state of mania.

Monoamine oxidase inhibitors (MAOIs)—Type of antidepressant medication that affects various kinds of neurotransmitters including serotonin.

Neurotransmitter—A chemical messenger that travels through the body and acts in the nervous system. Neurotransmitter signaling is responsible for a wide range of bodily processes and is often the target of medications involving the brain and cardiovascular system.

Norepinephrine—A type of neurotransmitter involved in regulation of concentration, impulse control, judgment, mood, attention span, psychostimulation, and disease states such as ADHD and depression.

Tic—Involuntary movements (such as twitching or facial grimacing) or vocalizations (such as throat clearing or barking) associated with Tourette syndrome.

Tourette syndrome—An inherited neuropsychiatric disorder characterized by the development of both motor and vocal tics. The tics are preceded by a feeling of tension or urgency in the affected individual until the tic behavior is performed and relieves the perceived feeling of tension.

Drugs

Dexmethylphenidate is metabolized by a set of liver enzymes known as cytochrome P450 (CYP450), and it may interact with other drugs that are also metabolized through these enzymes. For example, dexmethylphenidate

may inhibit the metabolism of the anticonvulsant medication phenytoin and the anticoagulant medication **warfarin**, causing increased levels of these drugs in the blood and toxicity. The anticonvulsant medication **carbamazepine** may lower levels of dexamethylphenidate present in the blood by inducing its metabolism, causing lower levels of dexamethylphenidate and reducing its effectiveness.

Certain drugs may cause toxicity when used with dexamethylphenidate. There have been rare reports of sudden cardiac death when dexamethylphenidate was used with the blood pressure drug **clonidine**. Use of the antipsychotic pimozide with dexamethylphenidate increases the risk of motor tics as a side effect of medication. Many antidepressants interact with dexamethylphenidate. The antidepressant **bupropion** increases the risk of seizures when used with dexamethylphenidate. The antidepressant **venlafaxine** may cause greater than expected weight loss when used with dexamethylphenidate. Antidepressants called monoamine oxidase inhibitors (MAOIs) also increase the amount of norepinephrine and dopamine released and cannot be used with dexamethylphenidate, as it may cause overstimulation of the CNS and toxicity. Switching drug treatment for an individual patient from an MAOI to dexamethylphenidate may require a waiting period of up to two weeks between drugs. Many diet drugs, such as sibutramine, may have additive effects with dexamethylphenidate that cause toxicity.

Herbs and supplements

It is unknown which herbal supplements interact with dexamethylphenidate. Patients should consult with their healthcare provider before taking any herbs or dietary supplements.

Food and other substances

Using alcohol while taking dexamethylphenidate may create toxic reactions in the body and should be avoided. Caffeine may cause toxicity with dexamethylphenidate by increasing the risk of heart rhythm abnormalities and excess nervous system stimulation.

Resources

BOOKS

- Brunton, Laurence L., et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill Medical, 2011.
- Stargrove, Mitchell Bebel, et al. *Herb, Nutrient, and Drug Interactions: Clinical Implications and Therapeutic Strategies*. St. Louis: Mosby, 2007.

PERIODICALS

- Santisteban, J. A., et al. "Effect of Extended-Release Dexamethylphenidate and Mixed Amphetamine Salts on Sleep: A Double-Blind, Randomized, Crossover Study in Youth with Attention-Deficit Hyperactivity Disorder." *CNS Drugs* 28, no. 9 (2014): 825–33.
- Silva, R. R., et al. "Extended-Release Dexamethylphenidate 30 mg/d versus 20 mg/d: Duration of Attention, Behavior, and Performance Benefits in Children with Attention-Deficit/Hyperactivity Disorder." *Clinical Neuropharmacology* 36, no. 4 (2013): 117–21.
- Sugrue, D., R. Bogner, M. J. Ehret. "Methylphenidate and Dexamethylphenidate Formulations for Children with Attention-Deficit/Hyperactivity Disorder." *American Journal of Health System Pharmacy* 71, no. 14 (2014): 1163–70.

OTHER

- U.S. Food and Drug Administration. "Medication Guide (Focalin)." <http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088600.pdf> (accessed February 22, 2015).

WEBSITES

- AHFS Consumer Medication Information. "Dexamethylphenidate." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a603014.html> (accessed February 22, 2015).

ORGANIZATIONS

- American College of Neuropsychopharmacology, 5034-A Thoroughbred Lane, Brentwood, TN 37027, (615) 324-2360, Fax: (615) 523-1715, acnp@acnp.org, <http://www.acnp.org/default.aspx>.
- American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.
- Mental Health America, 2000 N. Beauregard Street, 6th Floor, Alexandria, VA 22311, (703) 684-7722, (800) 969-6642, Fax: (703) 684-5968, <http://www1.nmha.org/>.

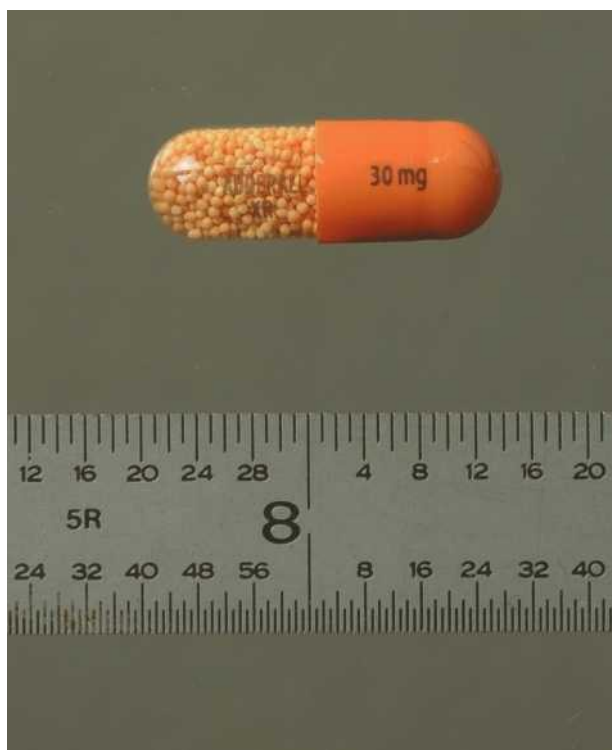
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Dextroamphetamine

Definition

Dextroamphetamine is a medication used to treat attention deficit hyperactivity disorder (ADHD) and the sleep disorder narcolepsy. It belongs to the class of drugs known as central nervous system (CNS) stimulants and works by altering levels of the neurotransmitters norepinephrine and dopamine.



Adderall XR (extended-release amphetamine/dextroamphetamine), 30 mg. (© Cengage Learning®)

Purpose

Dextroamphetamine is used to treat some of the symptoms of ADHD in both adults and children six years of age and older. This CNS stimulant improves memory, concentration, and impulse control and belongs to the category of drugs that remain the mainstay of ADHD therapy.

Dextroamphetamine has also been approved for use in treating narcolepsy, a condition where patients experience uncontrollable sleep attacks during the day. It is one of the main treatments for this disorder. Dextroamphetamine is available as an extended-release medication, which reduces the need for redosing throughout the school day or workday. It is also available with the drug amphetamine in a combination pill (Adderall). The choice of using dextroamphetamine alone or in combination with other drugs depends on the medical profile of the patient.

Off-label use

For individuals with ADHD who also have coexisting depression, dextroamphetamine may have some antidepressant properties, although it has not been approved by the U.S. Food and Drug Administration (FDA) for this purpose.

Description

Dextroamphetamine works by affecting the neurotransmitters norepinephrine and dopamine. Neurotransmitters are chemicals that neurons (nerve cells) use to communicate with one another. Norepinephrine and dopamine are types of neurotransmitters involved in normal brain function that have an effect on mood, energy level, concentration, appetite, and impulse control. It is believed that lower levels of norepinephrine and dopamine contribute to disorders such as ADHD and depression.

When a nerve cell is triggered, it releases a neurotransmitter that carries the nerve impulse across a gap to the next nerve cell. The neurotransmitter is then reabsorbed by the releasing cell. Dextroamphetamine slows the reabsorption of these neurotransmitters. The increase in norepinephrine and dopamine has an impact on areas of the brain that involve attention span, judgment, response to external stimuli, memory, motor function, mental focus, and impulse control.

U.S. brand names

In the United States, dextroamphetamine is sold under the brand names Dexedrine, Dexedrine Spansule, and ProCentra. Dexedrine 5-milligram (mg) tablets are orange, shield-shaped tablets with "SKF E19" imprinted on the front of the pill. Dexedrine Spansule 5 mg is a brown capsule with "5 mg" printed on the front and "3512 SB" printed on the back. Dexedrine Spansule 10 mg is a brown capsule with "10 mg" printed on the front and "3513 SB" printed on the back. Dexedrine Spansule 15 mg is a brown-and-clear capsule with "15 mg" printed on the front and "3514 SB" printed on the back.

Dextroamphetamine combined with amphetamine is sold under the brand names Adderall and Adderall XR (extended release).

Canadian brand names

In Canada, dextroamphetamine is sold under the brand name Dexedrine.

International brand names

Internationally, dextroamphetamine is sold under the brand name Dexedrine.

Recommended dosage

Dextroamphetamine is given as a tablet. A liquid formulation is also available. Doses should be taken early in the day with a full glass of water; doses are not taken in the evening as they may cause difficulty sleeping.

KEY TERMS

Attention deficit hyperactivity disorder (ADHD)—A condition characterized by lack of concentration, impulsive or inappropriate behavior (relative to age level), and hyperactivity.

Dopamine—A type of neurotransmitter involved in regulation of concentration, impulse control, judgment, mood, attention span, psychostimulation, and disease states such as addiction, ADHD, and depression.

Mania—A physiological state of hyperactivity experienced by patients with certain psychiatric illnesses involving inappropriate elevated mood, pressured speech, poor judgment, and sometimes psychotic episodes superimposed on the state of mania.

Monoamine oxidase inhibitor (MAOI)—A type of antidepressant medication that affects various kinds of neurotransmitters, including serotonin.

Narcolepsy—A condition involving increased daytime sleepiness in the form of uncontrollable sleep attacks that interfere with normal functioning.

Neurotransmitter—One of a group of chemicals secreted by a nerve cell (neuron) to carry a chemical message to another nerve cell, often as a way of transmitting a nerve impulse. Examples of

neurotransmitters include acetylcholine, dopamine, serotonin, and norepinephrine.

Norepinephrine—A type of neurotransmitter involved in regulation of concentration, impulse control, judgment, mood, attention span, psychostimulation, and disease states such as ADHD and depression.

Serotonin—5-Hydroxytryptamine; a substance that occurs throughout the body with numerous effects, including neurotransmission. Low serotonin levels are associated with mood disorders, particularly depression and obsessive-compulsive disorder.

Tics—Involuntary movements (such as twitching or facial grimacing) or vocalizations (such as throat clearing or barking) associated with Tourette syndrome.

Tourette syndrome—An inherited neuropsychiatric disorder characterized by the development of both motor and vocal tics. The tics are preceded by a feeling of tension or urgency in the affected individual until the tic behavior is performed and relieves the perceived feeling of tension.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

Patients are frequently reassessed for the need for treatment, as stimulant medications like dextroamphetamine are generally avoided unless absolutely necessary. The dose chosen depends on individual patient response to the medication regarding its effectiveness and response to side effects. Patients are dosed at the lowest possible effective dose to avoid adverse side effects, and slowly increasing the dose may help with minimizing side effects.

The dose of dextroamphetamine for treating ADHD in both adults and children six years old and older is started at 5 mg taken once or twice a day. The dosage is increased slowly after the first week, as needed, up to 40 mg per day, divided throughout the day. Extended-release tablets may be used to minimize the frequency of dosing. The maximum allowable dosage is 60 mg per day.

Similar dosages are used to treat narcolepsy in adults and children greater than six years old. If multiple doses are needed during the day, they should be taken at least four hours apart. If adverse side effects occur, dosage may be lowered.

Pediatric

Dextroamphetamine is not recommended for children younger than six years of age.

Precautions

Dextroamphetamine is a potentially addictive medication and should never be used for longer periods or at higher doses than prescribed. Patients are often given drug “holidays”—for example, when school is over for the summer—during which they forgo medication to help avoid developing a dependence on the drug. Because of its addictive potential, caution is used in patients with a history of substance abuse.

Dextroamphetamine causes withdrawal symptoms when stopped abruptly. When discontinuing use, the dosage should be gradually reduced under physician supervision.

Rare but serious reactions include severe elevations in blood pressure, heart arrhythmias, heart attack, stroke, seizures, and sudden death. Some patients develop

increased aggressiveness, psychosis, mania, or suicidality in the first weeks of use. Patients taking dextroamphetamine are monitored closely for behavioral changes, especially when starting treatment or after dose changes.

Other conditions and allergies

There is an association between ADHD and Tourette syndrome. Patients with Tourette syndrome often have involuntary movements or vocalizations known as tics. Patients who have Tourette syndrome with ADHD may find that the stimulant medications used to treat ADHD worsen their tics. Caution must be used in treating patients with motor tics, Tourette syndrome, or a family history of the disorder. Dextroamphetamine may not be appropriate for use in these patients.

Dextroamphetamine may be contraindicated or may require caution in use in patients with high blood pressure, blood vessel disease, heart rhythm abnormalities, heart conditions or structural abnormalities, certain thyroid disorders, liver function impairment or liver disease, kidney function impairment, or glaucoma. Dextroamphetamine may lower seizure threshold in some patients and may not be appropriate for use in patients with seizure disorder. Cardiac function, heart rate, and blood pressure may be monitored while taking dextroamphetamine. Dextroamphetamine is discouraged from use in patients with bipolar disorder, as it is more likely to induce a state of mania in these individuals than in those without bipolar disorder.

Pediatric

Children are especially at risk for the behavioral side effects possible when taking dextroamphetamine, including increased aggressiveness, psychosis, mania, or suicidality.

Growth retardation may also occur with prolonged use in children.

Pregnant or breastfeeding

Dextroamphetamine is in the FDA pregnancy category C, which means either that there are no adequate human or animal studies on its effects during pregnancy, or that adverse fetal effects were found in animal studies, but there is no available human data. The decision of whether to use category C drugs in pregnancy is generally based on weighing the critical needs of the mother against the risk to the fetus. Other, lower-category agents are used whenever possible. Some data suggest that dextroamphetamine can enter the breast milk of a lactating mother. Use of the drug while breastfeeding may be unsafe for the infant and is not recommended.

Side effects

Sensitivity to dextroamphetamine varies among patients, and some patients may find that even lower doses are more than their bodies can tolerate. Common reactions include dizziness, insomnia, anxiety, restlessness, euphoria, headache, decreased appetite, weight loss, changes in blood pressure and heart rate, palpitations, tremor, dry mouth, unpleasant taste, diarrhea or constipation, tic exacerbation, impotence, sexual dysfunction, and visual disturbances.

Interactions

Patients should make their doctor aware of all prescription and nonprescription drugs, supplements, and herbal medicines that they are taking before using dextroamphetamine. Drugs that affect the liver may alter the metabolism of dextroamphetamine, resulting in too much or too little dextroamphetamine in the body. This could lead to increased side effects or even toxic doses. Likewise, dextroamphetamine may affect the metabolism of other drugs, leading to higher or lower doses than therapeutically desired.

Drugs

Certain drugs used in combination with dextroamphetamine may cause serious heart rhythm abnormalities, excess nervous system stimulation, or blood pressure changes. Such substances include the obesity drug sibutramine, some migraine medications such as ergotamines, and decongestants such as phenylephrine. Use of the antipsychotic pimozide with dextroamphetamine increases the risk of motor tics as a side effect of medication. Use of certain other antipsychotics, such as fluphenazine, increases risk of psychosis. Antacids and the glaucoma and diuretic drug acetazolamide decrease the excretion of dextroamphetamine from the body and may cause toxic levels to accumulate.

Many antidepressants interact with dextroamphetamine. The antidepressant **bupropion** increases the risk of seizures when used with dextroamphetamine. **Venlafaxine** may cause greater than expected weight loss when used with dextroamphetamine. Antidepressants called monoamine oxidase inhibitors (MAOIs) also increase the levels of norepinephrine and dopamine in the brain and should not be used with dextroamphetamine, as the combination may cause overstimulation of the central nervous system and toxicity. Patients taking MAOIs will need to stop taking the MAOI for at least 14 days before starting treatment with dextroamphetamine (or vice versa).

Herbs and supplements

Many herbal supplements may also interact with dextroamphetamine and cause toxicity, including green tea and ginseng.

Food and other substances

Using alcohol while taking dextroamphetamine may create toxic reactions in the body and should be avoided. Caffeine and marijuana derivatives may cause excessive stimulation when used with dextroamphetamine and should be avoided.

Resources

BOOKS

- Berry, Richard B., and Mary H. Wagner. *Sleep Medicine Pearls*. 3rd ed. Philadelphia: Elsevier/Saunders, 2015.
- Charles, Parker, and Lyza Poulin, eds. *The New ADHD Medication Rules: Paying Attention to the Meds for Paying Attention*. Garden City, VA: Morgan James, 2013.
- Stahl, Stephen M. *Stahl's Essential Psychopharmacology: Prescriber's Guide*. 5th ed. New York: Cambridge University Press, 2014.

PERIODICALS

- Ramtevedt, Bjørn E., H. S. Aabech, and K. Sundet. "Minimizing Adverse Events While Maintaining Clinical Improvement in a Pediatric Attention-Deficit/Hyperactivity Disorder Crossover Trial with Dextroamphetamine and Methylphenidate." *Journal of Child and Adolescent Psychopharmacology* 24, no. 3 (2014): 130–39.

OTHER

- Amedra Pharmaceuticals LLC. "Medication Guide: Dextroamphetamine." U.S. Food and Drug Administration. <http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088583.pdf> (accessed February 6, 2015).

WEBSITES

- Mayo Clinic staff. "Dextroamphetamine (Oral Route)." Mayo Clinic.org. <http://www.mayoclinic.org/drugs-supplements/dextroamphetamine-oral-route/description/drg-20071795> (accessed February 6, 2015).
- MedlinePlus. "Dextroamphetamine." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a605027.html> (accessed February 6, 2015).

ORGANIZATIONS

- American Academy of Sleep Medicine, 2510 North Frontage Road, Darien, IL 60561, (630) 737-9700, Fax: (630) 737-9790, inquiries@aasmnet.org, <http://www.aasmnet.org/>.
- Attention Deficit Disorder Association, PO Box 7557, Wilmington, DE 19803-9997, (800) 939-1019, info@adda.org, <http://www.adda.org/>.
- Children and Adults with Attention Deficit Disorder (CHADD), 4601 Presidents Drive, Suite 300, Lanham, MD 20706,

(301) 306-7070, (800) 233-4050, Fax: (301) 306-7090, <http://www.chadd.org/>.

National Center on Sleep Disorders Research, 6701 Rockledge Drive, Bethesda, MD 20892, (301) 435-0199, Fax: (301) 480-3451, twery@nih.gov, <http://www.nhlbi.nih.gov/about/ncsdr/index.htm>.

National Sleep Foundation, 1010 N. Glebe Road, Suite 310, Arlington, VA 22201, (703) 243-1697, nsf@sleepfoundation.org, <http://www.sleepfoundation.org/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Revised by Tish Davidson, AM

REVIEWED BY JAMES E. WAUN, MD, RPh

Diabeta see **Glyburide**

Diazepam

Definition

Diazepam is a tranquilizer in the class of drugs known as benzodiazepines.

Purpose

Diazepam is used on a short-term basis to treat patients with mild to moderate anxiety. It is also used to



Diazepam, 5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

treat some types of seizures (epilepsy), muscle spasms, nervous tension, and symptoms relating to alcohol withdrawal.

Description

Diazepam is one of many chemically related tranquilizers in the class of drugs called benzodiazepines. Benzodiazepines are sedative-hypnotic drugs that help to relieve nervousness, tension, and other anxiety symptoms by slowing the central nervous system. To do this, they block the effects of a specific chemical involved in the transmission of nerve impulses in the brain, decreasing the excitement level of the nerve cells. All benzodiazepines, including diazepam, cause sedation, drowsiness, and reduced mental and physical alertness.

Diazepam is usually taken as a pill, but an injectable form is sometimes used when a serious seizure is in progress or when muscle spasms are severe. There is a liquid oral form of the drug available, and diazepam is also available as a rectal gel, marketed as Diastat AcuDial.

U.S. brand names

Diazepam is most commonly sold in the United States under the brand name Valium. The generic form of this drug is also available.

Recommended dosage

The typical dose of diazepam used to treat anxiety or seizures in healthy adults ranges from a total of 6 to 40 milligrams (mg) per day, given in three or four doses. For acute treatment of seizures, a higher dose of diazepam is given intravenously (directly into the vein) only in a controlled medical setting such as a hospital or emergency room. For alcohol withdrawal, the typical dose is a total of 30–40 mg per day, divided into three or four doses.

Pediatric

The typical dose for a child over age six months with anxiety or seizures is a total of 3–10 mg per day, divided into several doses. In general, children receive lower doses of diazepam even when they have a body weight equivalent to that of a small adult.

Geriatric

People over age 60 are usually given lower doses, in the range of 4–10 mg per day, to treat anxiety or nervous tension.

KEY TERMS

Anterograde amnesia—The inability to form new memories.

Anxiety—An emotion that can be experienced as a troubled feeling, sense of dread, fear of the future, or distress over a possible threat to a person's physical or mental well-being.

Benzodiazepines—A group of central nervous system depressants used to relieve anxiety or to induce sleep.

Epilepsy—A disorder associated with disturbed electrical discharges in the central nervous system that cause seizures.

Seizure—A convulsion or uncontrolled discharge of nerve cells that may spread to other cells throughout the brain.

Withdrawal effects—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

Precautions

The elderly, children, and those with significant health problems need to be carefully evaluated before receiving diazepam.

The sedative effects of diazepam are cumulative and long lasting. People taking diazepam should not drive, operate dangerous machinery, or engage in hazardous activities that require mental alertness, because diazepam can cause drowsiness. Alcohol and any drugs that treat mental illness should not be used when taking this medication.

The prescribing physician should be consulted regularly if diazepam is taken consistently for more than two weeks. Diazepam and other drugs in this class can be habit forming. Diazepam can become a drug of abuse and should be used with caution in patients with a history of substance abuse and related disorders. People taking diazepam should not stop taking the drug abruptly. Doing so can lead to withdrawal effects such as shaking, stomach cramps, nervousness, and irritability.

Diazepam may carry the risk of anterograde amnesia.

Individuals using diazepam in the form of rectal gel should check the prefilled syringe applicator tip (without removing the cap) for cracks. The U.S. Food and Drug Administration (FDA) issued an alert in 2006 addressing this concern; cracks in the applicator tip have been known to occur, allowing medication to leak out and compromising the amount of medication in the syringe.

PATIENT PROFILE

Diazepam (Valium) was prescribed for a 35-year-old woman with muscle spasms of unknown origin. She had no known diseases that would cause muscle problems, but as a child, she had had mild rheumatic fever and had continued to experience frequent aches and pains in her legs, which she relieved with aspirin. Nevertheless, the muscle spasms remained unexplained. They occurred either as sudden cramping of one leg, from the groin to her foot, or from her upper arm down to her hand and fingers. The spasms developed at any time, seemingly without reason, and were extremely painful and hard to relax. She was consistently embarrassed when spasms occurred in a social setting, at work or in public. Her doctor felt that these short-lived but frequent skeletal muscle spasms could be controlled by medication until a possible source, such as an imbalance in serum electrolytes or neurotransmitters in the brain, was discovered.

Diazepam is in the drug family of benzodiazepines, which are controlled substances with sedative-hypnotic effects. Such drugs can cause drowsiness, dizziness, or loss of balance. Diazepam works by promoting the effects of a neurotransmitter in the brain that carries nerve impulses and is able to relieve anxiety, tremors, and muscle spasms. The patient was given an initial dosage of 2.5 mg tablets to be taken orally twice a day, with or without food. She was advised that she could take up to four tablets a day if she continued to experience muscle spasms but to watch carefully for dizziness or over-sedation. She was instructed to avoid alcohol while using the drug and to report any unusual symptoms that might occur. In addition, the doctor advised the patient to drink

plenty of water and to begin doing some regular form of gentle exercise such as yoga to stretch her muscles.

At her follow-up visit two weeks later, the patient reported that diazepam twice a day effectively reduced the number and frequency of painful muscle spasms. However, she also reported that she was often dizzy and had nearly lost consciousness twice. Her doctor evaluated her dietary habits more closely, revealing that she skipped breakfast regularly, drank copious amounts of coffee at work, and ate fast-food hamburgers and fries or pizza for lunch. She also ate prepared foods for supper during the week because she arrived home so late in the evening. Her blood work had revealed elevated hemoglobin and red blood cell count and imbalances in sodium-potassium and other electrolytes, indicating dehydration. Her urine was also highly concentrated, confirming both dehydration and the source of muscle spasms. Although the dizziness and loss of balance could be attributed to diazepam, it was compounded by poor nutrition and dehydration caused by excess coffee and a high-sodium diet. She was advised to continue with the diazepam but not to exceed two tablets a day, and she was urged to follow a basic healthy diet of whole foods, not prepared foods, using guidelines provided by her doctor. The doctor emphasized that better nutrition, drinking sufficient water, and reducing coffee would be essential to prevent muscle spasms. A daily multivitamin was suggested and a single 99 mg potassium tablet was provided to help correct imbalances. Implementing these lifestyle measures was difficult for the patient but eventually resulted in alleviating the muscle spasms and discontinuing the use of diazepam.

This situation could result in the syringe not containing enough medication to treat a seizure. Cracks can occur over time, so it is important to check syringes on a regular basis to ensure they are acceptable for use.

Pediatric

Children under the age of six months should not take diazepam.

Pregnant or breastfeeding

Diazepam should not be used during pregnancy. It has been found to have adverse effects on a fetus. The drug also passes into breast milk.

Other conditions and allergies

People with a history of liver disease or kidney disease or those with low levels of a protein in the blood

called albumin need to be carefully assessed before starting this drug.

People who have previously had an allergic reaction to any dosage level of diazepam or any other benzodiazepine drug should not take diazepam. People with acute narrow-angle glaucoma should not take diazepam.

Individuals who rely on urine tests to monitor blood sugar should know that this drug can produce false results with tests using Clinistix and Diastix; they should instead use TesTape for urine testing of sugar.

Side effects

Anxiety, irregular heartbeat, forgetfulness, mental depression, and confusion are side effects that could require prompt medical attention. However, these side effects are not common when taking diazepam. Even more unusual but serious events are behavior changes, low blood pressure, muscle weakness, and jaundice

(yellowing of the eyes or skin). More common but less serious side effects include drowsiness, clumsiness, slurred speech, constipation, and dizziness. Rare among these less serious side effects are stomach cramps, headache, muscle spasm, nausea, vomiting, and dry mouth.

Once a person stops taking diazepam, the following side effects could occur from withdrawal: sleeping difficulties, nervousness, and irritability. Less common side effects from withdrawal include:

- confusion
- abdominal cramps
- mental depression
- sensitivity to light
- nausea
- shaking
- increased sweating

Rarely seen side effects include seizures, hallucinations, and feelings of distrust in the patient.

Interactions

Diazepam interacts with a long list of other medications. Individuals who are starting this drug should review the other medications they are taking with their physician and pharmacist for possible interactions. Patients should always inform all their healthcare providers, including dentists, that they are taking diazepam.

Drugs

Diazepam can add to the depressive effects of other central nervous system depressant drugs (for example, alcohol, other tranquilizers, or sleeping pills) when taken together. In severe cases, this effect can result in death.

Several drugs reduce the ability of diazepam to be broken down and cleared from the body, which results in higher levels of the drug in the blood and increases the probability that side effects will occur. These drugs include several antibiotics, such as **erythromycin**; antistomach acid drugs, such as cimetidine (Tagamet); and antifungal drugs, such as **fluconazole**. Other drugs that are used to treat mental disorders should not be combined with diazepam unless the patient is under the careful supervision and monitoring of a doctor.

Food and other substances

Alcohol should not be used when taking diazepam and other benzodiazepine drugs. There may also be an interaction between this drug and grapefruit juice.

Resources

BOOKS

- Albers, Lawrence J., Rhoda K. Hahn, and Christopher Reist. *Handbook of Psychiatric Drugs*. Laguna Hills, CA: Current Clinical Strategies, 2011.
- American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda, MD: ASHP, 2015.
- Aminoff, Michael J., and S. Andrew Josephson, eds. *Neurology and General Medicine*. 5th ed. London: Academic Press/Elsevier, 2014.
- Holland, Leland Norman, and Michael Patrick Adams. *Core Concepts in Pharmacology*. 4th ed. New York: Prentice Hall, 2014.
- Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger, 2013.

WEBSITES

- Children's Hospital and Clinic of Minnesota. "Diazepam (Valium), Rectal." <http://www.childrensmn.org/Manuals/PFS/Med/042157.pdf> (accessed February 23, 2015).
- Roche Pharmaceuticals. "Valium [prescribing information]." U.S. Food and Drug Administration. http://www.access-data.fda.gov/drugsatfda_docs/label/2008/013263s0831bl.pdf (accessed February 23, 2015).
- Micromedex. "Diazepam (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/diazepam-oral-route/description/drg-20072333> (accessed February 23, 2015).
- NYU Langone Comprehensive Epilepsy Center. "Diazepam (Valium, Diastat)." <http://epilepsy.med.nyu.edu/treatment/medications/diazepam#sthash.QFQJoOoC.dpbs> (accessed February 23, 2015).

ORGANIZATIONS

- American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.
- Anxiety Disorders Association of America, 8701 Georgia Avenue, Suite 412, Silver Spring, MD 20910, (240) 485-1001, Fax: (240) 485-1035, <http://www.adaa.org/>.
- Mental Health America, 2000 N. Beauregard Street, 6th Floor, Alexandria, VA 22311, (703) 684-7722, (800) 969-6642, Fax: (703) 684-5968, <http://www1.nmha.org/>.
- National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.
- National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

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Diclofenac

Definition

Diclofenac is one of a large group of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs). These drugs all have similar functions, which are pain relief, reduction of inflammation, and reduction of fever. Although there are several different chemical classes of these drugs, they all appear to work the same way, with the same effects and side effects. They are called nonsteroidal because their chemical structures are not related to cortisone, which is the natural anti-inflammatory hormone in the body.

Purpose

Diclofenac is available in a number of different dosage forms, and they may have different uses. The following are the labeled indications for each dosage form, but additional uses may be prescribed off label.

- capsules: mild to moderate pain relief (analgesia), osteoarthritis (Zorvolex brand only)
- immediate-release tablets: mild to moderate pain relief, dysmenorrhea (painful menstruation), osteoarthritis, rheumatoid arthritis
- extended-release tablets: osteoarthritis, rheumatoid arthritis
- delayed-release tablets: osteoarthritis, rheumatoid arthritis, ankylosing spondylitis



Diclofenac sodium ER (extended release), 100 mg.
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- oral solution (sold as a powder): migraine headache
- topical products: pain relief of various types, including minor muscle strains, sunburn, and osteoarthritis
- eyedrops: inflammation or pain in patients undergoing eye surgery

Description

The effects of NSAIDs are essentially the same as **aspirin**. The difference is that aspirin has anti-inflammatory properties only when the drug reaches toxic levels in the bloodstream. NSAIDs can be used to treat inflammation at lower dose levels. Individuals may respond to different NSAIDs differently and may need to try different drugs before finding the one that works best for them.

When using diclofenac, the oral solution reaches peak effectiveness in 10–30 minutes. Immediate-release tablets normally reach peak within one hour, while delayed-release tablets take approximately two hours. Capsules peak in approximately 30 minutes. The extended-release tablets remain effective for 24 hours.

U.S. brand names

Brand names sold in the United States include:

- Flector (1.3% topical patch)
- Pennsaid (1.5% topical solution)
- Rexaphenac (1% topical cream)
- Solaraze (3% topical gel)
- Voltaren (1% topical gel)
- Voltaren ER (100 milligram [mg] extended-release tablets)
- Zipsor (25 mg liquid-filled capsules)
- Zorvolex (18 and 35 mg capsules)

Delayed-release tablets are available in 25, 50, and 75 mg strengths.

Canadian brand names

In Canada, diclofenac is sold under the brand name Voltaren.

International brand names

Diclofenac is widely distributed under both generic and branded names, alone and in combination. Cataflam is one of the most common brand names. The drug misoprostol is frequently combined with diclofenac to reduce the risk of gastric ulcers.

Recommended dosage

Recommended dosages vary depending on the condition being treated. Most forms of diclofenac should be taken

KEY TERMS

Ankylosing spondylitis—A form of arthritis that affects the bones at the base of the spine where it connects to the pelvis.

Anti-inflammatory drug—A drug that reduces inflammation.

Arthritis—A condition characterized by damage to a joint. There are a number of different types of arthritis, but the primary two are rheumatoid arthritis, which is marked by inflammation, and osteoarthritis.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Inflammation—Redness, swelling, and pain; may indicate illness or injury.

Nonsteroidal anti-inflammatory drugs (NSAIDs)—A class of drugs that is used to relieve pain and symptoms of inflammation, such as ibuprofen and aspirin.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

with food or a full glass of water to prevent stomach upset. There are two exceptions: Zorvolex-brand capsules should be taken on an empty stomach, and the powder for oral solution should be mixed only with water. Food may also reduce the effectiveness of the solution.

Some common dosages include:

- For rheumatoid arthritis or osteoarthritis, 50 mg may be taken every 8–12 hours, or 75 mg every 12 hours. The extended-release formula is taken once daily.
- For ankylosing spondylitis, 25 mg is taken four or five times daily, or 50 mg every 12 hours.
- For mild to moderate pain or dysmenorrhea, the initial dose is 100 mg, followed by 50 mg every 8 hours, as needed.
- For migraine headache, one 50 mg packet is dissolved in 30–60 milliliters (mL) of water (1 to 2 ounces) and should be consumed immediately.

Pediatrics

Although diclofenac has been used off label to treat some cases of juvenile arthritis, the drug's safety and efficacy have not been determined in this age group.

Precautions

In the United States, the U.S. Food and Drug Administration (FDA) has given diclofenac a boxed warning stating that NSAIDs may increase the risk of heart attacks and strokes. This risk increases the longer the drugs are used. Patients with heart problems or risk factors for heart problems will be at increased risk.

The FDA also warns that NSAIDs cause an increased risk of adverse reactions affecting the stomach and intestines. These include bleeding, inflammation, ulceration, and perforation of the stomach or intestines, which are possibly fatal.

Long-term use of NSAIDs may cause kidney damage. Patients at the greatest risk include those with kidney or liver problems and the elderly.

Diclofenac, along with other NSAIDs, may cause dizziness, blurred vision, and other central nervous system (brain and spinal cord) damage that can impair both physical and mental function.

Geriatric

Risks of serious adverse effects due to NSAIDs are greatest among the elderly due to natural changes in liver and kidney function, especially among those aged 65 and older. There is also an increased risk of stomach and intestinal damage. A number of methods for protecting the stomach and intestine from NSAID damage have been studied, and patients should discuss these options with their healthcare provider.

Pregnant or breastfeeding

Diclofenac is considered a pregnancy category C drug. The drug can be used if the need outweighs the risk, but if used late in the pregnancy (past 30 weeks), diclofenac may cause improper development of the fetal heart. Diclofenac should not be used 30 or more weeks after gestation. In one large-scale study, use of NSAIDs was documented in 7.5% of cases of spontaneous abortion. Several studies warn that because NSAIDs are often available over the counter, women may take them without realizing the risks.

It is not known whether diclofenac is excreted in human breast milk; however, due to the potential for adverse reactions in a nursing infant, it is recommended that nursing mothers either stop nursing or discontinue use of the drug.

Other conditions and allergies

Diclofenac use may need to be avoided in patients with liver, kidney, or heart problems.

People who are allergic to aspirin may have a cross allergic reaction to NSAIDs. Because NSAIDs can cause very severe skin reactions, they should be discontinued if a rash of any sort develops.

Side effects

For occasional use for mild to moderate pain, diclofenac, like all other NSAIDs, is generally well tolerated. The most common adverse effects are gastrointestinal discomfort, including pain, flatulence, cramps, diarrhea, and constipation. However, these same adverse effects may lead to ulcers, including bleeding ulcers, and gastric and intestinal perforation. These effects can be serious and even fatal. These effects are more common and potentially more serious in patients over the age of 65. The minor gastrointestinal upsets can usually be controlled by taking the medication with a meal.

Other significant adverse effects include liver damage, kidney damage, and fluid retention. Blood pressure increases are possible. Allergic reactions, including dangerous reactions (anaphylaxis), have been reported.

Because diclofenac and other NSAIDs are so widely used, they have been associated with a wide range of adverse effects, including itching, fatigue, headache, dizziness, ringing in the ears, and anemia, as well as other reactions.

Interactions

To avoid drug interactions, individuals should discuss all the drugs they are taking, including over-the-counter drugs and supplements, with their physician and pharmacist.

Drugs

Diclofenac, along with other NSAIDs, increases coagulation (blood clotting) time. If possible, diclofenac should not be used in combination with any other drugs that are known to have anticoagulant properties. If the combination is necessary, clotting time should be monitored and doses adjusted for patient safety. This is a potentially life-threatening interaction.

Diclofenac reduces the elimination of **methotrexate**, leading to possibly toxic blood levels. Methotrexate is used to treat some forms of cancer, skin disease, and arthritis. If possible, the drugs should not be used at the same time. If the two drugs must be used together, blood levels of methotrexate should be carefully monitored.

There is a very extensive list of drugs that interact with NSAIDs. These may not be a problem when taking diclofenac for occasional minor pains, but they may become clinically significant with regular use of the drug. Individuals should discuss all possible interactions with their healthcare provider.

Herbs and supplements

Some herbs and supplements that may interact with diclofenac include:

- dong quai
- feverfew
- ginger
- ginkgo biloba
- panax ginseng
- pau d'arco

Food and other substances

The following foods may interact with diclofenac if used in excessive amounts:

- alfalfa
- cinnamon
- fennel
- garlic
- green tea

Resources

PERIODICALS

- Abebe, W. "Herbal Medication: Potential for Adverse Interactions with Analgesic Drugs." *Journal of Clinical Pharmacy and Therapeutics* 27, no. 6 (2002): 391–401.
- Bhala, N., et al. "Vascular and Upper Gastrointestinal Effects on Non-Steroidal Anti-Inflammatory Drugs: Meta-Analyses of Individual Participant Data from Randomised Trials." *Lancet* 382, no. 9894 (2013): 769–79.
- Bloor, M., and M. Paech. "Nonsteroidal Anti-Inflammatory Drugs during Pregnancy and the Initiation of Lactation." *Anesthesia and Analgesia* 116, no. 5 (2013): 1063–75.
- Cassina, M., et al. "First Trimester Diclofenac Exposure and Pregnancy Outcome." *Reproductive Toxicology* 30, no. 3 (2010): 401–4.
- Fosbøl, E. L., et al. "Risk of Myocardial Infarction and Death Associated with the Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) among Healthy Individuals: A Nationwide Cohort Study." *Clinical Pharmacology and Therapeutics* 85, no. 2 (2009): 190–97.
- McGettigan, Patricia, and David Henry. "Cardiovascular Risk with Non-Steroidal Anti-Inflammatory Drugs: Systematic Review of Population-Based Controlled Observational Studies." *PLOS Medicine* 8, no. 9 (2011). <http://dx.doi.org/10.1371/journal.pmed.1001161>.

org/10.1371/journal.pmed.1001098 (accessed March 5, 2015).

McGettigan, Patricia, and David Henry. "Use of Non-Steroidal Anti-Inflammatory Drugs That Elevate Cardiovascular Risk: An Examination of Sales and Essential Medicine Lists in Low-, Middle-, and High-Income Countries. *PLoS [Public Library of Science] Medicine*, 10, no. 2 (2013). <http://dx.doi.org/10.1371/journal.pmed.1001388> (accessed March 5, 2015).

Van Marter, L. J., et al. "Nonsteroidal Antiinflammatory Drugs in Late Pregnancy and Persistent Pulmonary Hypertension of the Newborn." *Pediatrics* 131, no. 1 (2013): 79–87.

White, W. B. "Cardiovascular Risk, Hypertension, and NSAIDs." *Current Pain and Headache Reports* 11, no. 6 (2007): 428–35.

WEBSITES

A.D.A.M. Medical Encyclopedia. "Interactions with Diclofenac." University of Maryland Medical Center. <http://umm.edu/health/medical/altmed/lookup/interactions-with-diclofenac> (accessed March 5, 2015).

AHFS Consumer Medication Information. "Diclofenac." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a689002.html> (accessed March 5, 2015).

Micromedex. "Diclofenac (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/diclofenac-oral-route/description/DRG-20069748> (accessed March 5, 2015).

Weeks, Carly. "Painkiller Diclofenac Risky, Should Be Removed from Market, Researchers Say." *Globe and Mail*, February 12, 2013. <http://consumer.healthday.com/encyclopedia/holistic-medicine-25/mis-alternative-medicine-news-19/herb-drug-interactions-646428.html> (accessed March 5, 2015).

Woolston, Chris. "Herb-Drug Interactions." HealthDay, March 11, 2014. <http://consumer.healthday.com/encyclopedia/holistic-medicine-25/mis-alternative-medicine-news-19/herb-drug-interactions-646428.html> (accessed March 5, 2015).

Zorvolex.com. <https://www.zorvolex.com/> (accessed March 5, 2015).

ORGANIZATIONS

American Academy of Pain Management, 975 Morning Star Drive, Suite A, Sonoma, CA 95370, (209) 533-9744 info@aapainmanage.org, <http://www.aapainmanage.org/>.

American College of Rheumatology, 2200 Lake Boulevard NE, Atlanta, GA 30319, (404) 633-3777, Fax: (404) 633-1870, acr@rheumatology.org, <http://www.rheumatology.org/>.

National Pain Foundation, 14828 West 6 Avenue, Suite 16-B, Room 1, Golden, CO 80401-5000, (720) 541-6808, Fax: (720) 541-6809, <http://www.thenationalpainfoundation.org/>.

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Diflucan see **Fluconazole**

Digitek see **Digoxin**

Digoxin

Definition

Digoxin is a synthetic drug used to treat heart disease. It falls within the class of drugs known as digitalis glycosides. It is modeled after the foxglove plant, *Digitalis purpurea*.

Purpose

Digoxin increases the strength and speed of heart muscle contractions and is used to treat congestive heart failure, a condition in which the heart is unable to pump all of the blood it receives. It is used to slow the heart rate and improve the efficiency of the ventricles (main pumping chambers) when there is a rapid or irregular heartbeat, like atrial flutter or fibrillation. The drug is also used to strengthen the heart in some cases of shock, like from heart attack or sepsis (overwhelming infection).



Lanoxin (digoxin), 0.25 mg. (© Cengage Learning®)

Description

Digoxin is available in tablet, capsule, liquid, and injectable forms. It is usually prescribed with a diuretic, a drug that increases urine output from the body and lowers blood pressure, and an angiotensin-converting enzyme (ACE) inhibitor, also used to treat high blood pressure.

U.S. brand names

Digoxin is sold in the United States under the brand name Lanoxin.

Recommended dosage

The dose of digoxin is individualized for each patient. Physicians can tailor the dose based on patient response and laboratory measures of blood levels of the drug.

Precautions

This drug should be taken exactly as directed, as there is a narrow therapeutic range between effective and toxic doses of digoxin. Individuals should be alert to the signs and symptoms of digoxin overdose. If any of these signs occur, contact a physician immediately:

- loss of appetite
- nausea
- vomiting
- pain in the lower stomach
- diarrhea
- tiredness or weakness
- extremely slow or irregular heartbeat (or fast heartbeat in children)
- blurred vision or other vision changes
- drowsiness
- confusion, unusual fatigue, or depression
- headache
- fainting

Individuals taking digoxin should regularly check their pulse rate and rhythm; changes can signify side effects and should be reported to treating physicians.

Pediatric

Digitalis drugs are responsible for many accidental poisonings in children. This medicine should be kept out of the reach of children.

Geriatric

Elderly patients are more sensitive to the effects of digoxin.

KEY TERMS

Atrial fibrillation—A condition in which the upper chamber of the heart quivers instead of pumping in an organized way.

Atrial flutter—A rapid pulsation of the upper chamber of the heart that interferes with normal function.

Congestive heart failure—A condition in which the heart cannot pump enough blood to supply the body's tissues with sufficient oxygen and nutrients; backup of blood in vessels and the lungs causes buildup of fluid (congestion) in the tissues.

Pregnant or breastfeeding

Digoxin is classified as pregnancy category C, which means that it may cause adverse effects in a fetus. Women should consult with their healthcare provider about using digoxin during pregnancy. Sometimes drugs must be used when the risks outweigh the benefits.

Other conditions and allergies

Digoxin is used with caution in or not given to patients who have a number of serious heart diseases, such as a recent heart attack, subaortic ventricular stenosis, and second- or third-degree heart block.

Before taking digoxin, individuals with any of the following medical problems should make sure that their physician is aware of their conditions:

- heart disease
- heart rhythm problems
- severe lung disease
- kidney disease
- liver disease
- thyroid disease

Side effects

In therapeutic doses, side effects are rare with digoxin. If skin rash, hives, or any other unusual or troublesome symptoms occur, consult a physician.

Interactions

Many drugs, foods, and herbs can increase or decrease the effectiveness of digoxin. Individuals should consult with a pharmacist or healthcare provider regarding the possible interactions of digoxin with any other medications they are taking.

Drugs

Known interactions with digoxin include:

- Taking digoxin with other heart medicines or stimulant drugs like diet pills, amphetamines, or ephedra can increase the risk of heart rhythm problems.
- Calcium-channel blocking drugs, like **nifedipine** (Procardia) and **amlodipine** (Norvasc), used to treat high blood pressure, may cause higher than usual levels of digoxin.
- Many diuretics, like **hydrochlorothiazide** (Hydro-DIURIL), cause the body to lose potassium and increase the risk of side effects from digoxin.
- Potassium supplements like K-Dur, used to replenish potassium supplies in patients taking diuretics, can increase the risk of digoxin toxicity.
- Cholesterol-lowering drugs like **atorvastatin** (Lipitor) may increase digoxin levels in the blood.
- Cholestyramine (Questran) may reduce the absorption of digoxin. To reduce this possible problem, digoxin should be taken several hours before or after taking this and similar medications.
- Antidiarrheal medicines may decrease the absorption of digoxin.

Herbs and supplements

St. John's wort and natural licorice can decrease the effect of digoxin.

Resources

PERIODICALS

Ouyang, A. J., et al. "Meta-Analysis of Digoxin Use and Risk of Mortality in Patients with Atrial Fibrillation." *American Journal of Cardiology* (January 14, 2015): e-pub ahead of print. <http://dx.doi.org/10.1016/j.amjcard.2015.01.013> (accessed February 22, 2015).

WEBSITES

AHFS Consumer Medication Information. "Digoxin Oral." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682301.html> (accessed February 22, 2015).

American Academy of Family Physicians. "Digoxin: A Medicine for Heart Problems." FamilyDoctor.org. <http://familydoctor.org/familydoctor/en/drugs-procedures-devices/prescription-medicines/digoxin-a-medicine-for-heart-problems.html> (accessed February 22, 2015).

Mayo Clinic staff. "Digoxin (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/digoxin-oral-route/description/drg-20072646> (accessed February 22, 2015).

ORGANIZATIONS

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6000, (800) 274-2237, Fax: (913) 906-6075, contact center@aafp.org, <http://www.aafp.org/>.

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.

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Dilacor see **Diltiazem**

Dilantin see **Phenytoin**

Dilaudid see **Hydromorphone**

Diltiazem

Definition

Diltiazem is one of a group of drugs called calcium channel blockers (CCBs), or sometimes slow channel blockers or calcium antagonists. When the heart contracts, forcing blood into the arteries that carry the blood throughout the body, calcium ions are forced out of the heart muscle. These ions re-enter the muscle through special channels called "slow channels." These drugs limit the ability of the calcium to return to the muscle tissue. This makes the heart beat slightly slower and weaker, which in turn lowers blood pressure and may



Diltiazem, 60 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

help correct problems with heart rhythms. It also reduces the heart's demands for oxygen.

Purpose

Although diltiazem has been prescribed for a variety of uses, it is approved by the U.S. Food and Drug Administration (FDA) only for the treatment of angina (chest pain related to the heart) and hypertension (high blood pressure). Because there are many drugs that can be used to lower blood pressure, the decision of which drug to use can be complex. For patients with elevated blood pressure but no evident related risk factors, a thiazide diuretic (water pill) is the most effective at the lowest price, but other classes of drugs may be added if the diuretic alone does not lower blood pressure to the desired level. In addition, some people respond to CCBs better than to other drugs.

For treatment of angina, **nitroglycerin** remains the first-line drug for a sudden episode. For prevention of attacks, either a beta-blocker or a CCB is the first choice, although there is no clear consensus as to which is preferable.

An injectable form of diltiazem is available to prevent types of cardiac arrhythmia, including atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardias (PSVTs).

Description

CCBs all work essentially the same way, but they have differences based on their chemical structures. Although most CCBs are in a group called dihydropyridines, diltiazem is a benzothiazepine, the only member of this class. Along with verapamil, which is a diphenylalkylamine (and the only drug in its class), diltiazem is referred to as a nondihydropyridine. The two nondihydropyridines have a greater effect on the heart muscle than the dihydropyridines, but a lesser effect on dilating (expanding) the blood vessels. This makes diltiazem and verapamil more suitable for treating patients with kidney disease or kidney damage due to diabetes. However, because the effects of these drugs may be modified by reflex responses, healthcare providers should choose the drug that is best for each individual patient. For example, if a drug starts to lower blood pressure by dilating the blood vessels, there is a normal reflex reaction to constrict the blood vessels. As a result, patient response will help determine the correct course of action.

U.S. brand names

Brand names sold in the United States include:

- Cardizem, available as rapid-acting tablets in 30, 60, 90, and 120 milligram (mg) strengths

- Cardizem CD, available as capsules filled with coated beads for 24-hour release in 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg strengths
- Cardizem LA, available as 24-hour-release tablets in 120 mg, 180 mg, 240 mg, 300 mg, 360 mg, and 420 mg strengths
- Cartia XT, available as capsules filled with coated beads for 24-hour release in 120 mg, 180 mg, 240 mg, and 300 mg strengths
- Dilacor XR, available as capsules filled with coated beads for 24-hour release in a 240 mg strength
- Matzim LA, available as 24-hour-release tablets in 120 mg, 180 mg, 240 mg, 300 mg, 360 mg, and 420 mg strengths
- Taztia XT, available as capsules filled with coated beads for 24-hour release in 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg strengths
- Tiazac, available as capsules filled with coated beads for 24-hour release in 120 mg, 180 mg, 240 mg, 300 mg, 360 mg, and 420 mg strengths

All branded dosage forms are available as generic equivalents. In addition, solutions containing 25 mg per 5 milliliters (mL), 50 mg/10 mL, and 125 mg/25 mL, as well as a 100 mg powder for reconstitution, are available for intravenous injection.

Canadian brand names

Diltiazem is sold under the following brand names in Canada:

- Apo-Diltiaz
- Apo-Diltiaz CD
- Apo-Diltiaz Injectable
- Apo-Diltiaz SR
- Gen-Diltiazem
- Gen-Diltiazem CD
- Novo-Diltiazem
- Novo-Diltiazem CD
- Nu-Diltiaz
- Nu-Diltiaz-CD
- ratio-Diltiazem CD
- Sandoz Diltiazem CD
- Tiazac XC

International brand names

While diltiazem is marketed internationally by a large number of companies, there are no proprietary names available.

KEY TERMS

Angina—A condition marked by severe pain in the chest, often spreading to the shoulders, arms, and neck, caused by an inadequate blood supply to the heart. In stable angina, the pain occurs as a result of exertion. In unstable angina, the pain may occur without exertion.

Atrial fibrillation—A common type of abnormal heartbeat; the heart rhythm is fast and irregular. In atrial fibrillation, the atria (upper chambers of the heart) fibrillate (quiver or twitch quickly) and create an irregular rhythm.

Atrial flutter—A common abnormal heart rhythm, similar to atrial fibrillation. In atrial flutter, the upper chambers (atria) of the heart beat too fast, which results in atrial muscle contractions that are faster than and out of sync with the lower chambers (ventricles).

Diuretic—A drug designed to encourage excretion of urine in people who accumulate excess fluid, such as individuals with high blood pressure or heart conditions.

Hypertension—High blood pressure.

Paroxysmal supraventricular tachycardia—A regular, fast (160 to 220 beats per minute) heart rate that begins and ends suddenly and originates in heart tissue other than in the ventricles. This condition is most common among young people and may occur as a result of vigorous exercise.

Peripheral edema—Swelling of the tissues due to fluid accumulation; occurs most often in the legs.

Recommended dosage

Oral doses

A plain tablet will reach its peak effect in about 2–4 hours after a single dose. Sustained-action dosage forms may take 10–14 hours for a capsule to reach its peak, and 11–18 hours for a sustained-action tablet to peak. The half-life, or the length of time it takes for 50% of a dose to be eliminated from the body, is 3–4 hours for a single-dose tablet and 5–10 hours for a sustained-release capsule.

The recommended dose varies between brands, even with similar products. In all cases, the dosage should be adjusted to the patient's needs with careful monitoring. There is limited general clinical experience with doses above 360 mg, but doses up to 540 mg have been studied

in clinical trials. The incidence of adverse effects increases as the dose increases.

ANGINA. With conventional tablets, the recommended dosage to control angina is 30 mg every 6 hours, increased every one or two days until the angina is controlled (usually 180–360 mg/day), not to exceed 360 mg/day.

Sustained-release tablets have recommended dosages that vary based on the brand:

- Cardizem CD, Cartia XT, Dilt-CD: 120–180 mg/day, adjusted after one or two weeks to reach a maintenance range of 120–320 mg/day; not to exceed 480 mg/day
- Dilacor XR, Dilt-XR: 120 mg/day, adjusted after one or two weeks to a maintenance range of 120–320 mg/day; not to exceed 540 mg/day
- Tiazac, Taztia XT: 120–180 mg/day, adjusted after one or two weeks to a maintenance range of 120–320 mg/day; not to exceed 540 mg/day
- Cardizem LA, Matzim LA: 180 mg/day, adjusted after one or two weeks to a maintenance range of 120–320 mg/day; not to exceed 360 mg/day

HYPERTENSION. With conventional tablets, the recommended dosage to control hypertension is initially 30 mg to 60 mg taken three to four times per day, increased to a maintenance dose of 180–360 mg/day (divided doses).

Sustained-release tablets have recommended dosages that vary based on the brand:

- Cardizem CD, Cartia XT, Dilt-CD: 180–240 mg/day, adjusted after two weeks to a maintenance range of 180–420 mg/day; not to exceed 480 mg/day
- Dilacor XR, Dilt-XR: 180–240 mg/day, adjusted after two weeks to a maintenance range of 180–420 mg/day; not to exceed 540 mg/day
- Tiazac, Taztia XT: 120–240 mg/day, adjusted after two weeks to a maintenance range of 180–420 mg/day; not to exceed 540 mg/day
- Cardizem LA, Matzim LA: 180–240 mg/day, adjusted after two weeks to a maintenance range of 120–540 mg/day
- extended-release twice-daily dosing: 60–120 mg every 12 hours; may be adjusted after two weeks to a maintenance range of 240–360 mg/day

Intravenous use

The diltiazem injection is for use in hospitals only. In addition to the FDA-approved dosage schedule, there are several other dosage schedules recommended by respected authorities. The American Heart Association's guidelines for advanced cardiovascular life support recommend the following dosage schedules.

ATRIAL FIBRILLATION/FLUTTER. For atrial fibrillation/flutter, the recommended dosage is 15–20 mg for an initial bolus dose (a single dose of a drug given all at once) and 20–25 mg for a repeat bolus dose (15 minutes after the initial dose).

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA. For paroxysmal supraventricular tachycardia (an abnormally fast heart rate that begins above the heart's two lower chambers), the recommended dosage is 15–20 mg for an initial bolus dose and 20–25 mg for a repeat bolus dose (15 minutes after the initial dose).

Precautions

There are a large number of warnings regarding the use of diltiazem for a number of possible heart conditions. Diltiazem should be administered only by a physician experienced with its use. Patients should be sure to notify their physician if they have ever experienced the following conditions:

- heart attack
- any condition that would cause food to move through the digestive system more slowly than usual
- low blood pressure (hypotension)
- heart, liver, or kidney disease

Pediatric

Diltiazem has no official pediatric uses and no specified precautions.

Geriatric

Care should be taken in prescribing diltiazem for the elderly because of normal age-related liver and kidney function changes. A lower starting dose and slower dose increases are usually indicated.

Pregnant or breastfeeding

Diltiazem is in the FDA pregnancy category C, which means that although there have been no human studies, adverse events have been observed in animal reproduction studies. However, untreated chronic maternal hypertension has been associated with adverse effects for the fetus, infant, and mother. If treatment for hypertension during pregnancy is needed, other agents are preferred.

Diltiazem may be used to control atrial fibrillation in pregnant women. Women with hypertrophic cardiomyopathy (enlarged heart) who take diltiazem prior to pregnancy may continue therapy, but increased fetal monitoring is recommended.

Diltiazem is found in breast milk in concentrations similar to the mother's blood level of the drug. Breastfeeding is not recommended.

Other conditions and allergies

Diltiazem should not be used in patients with an allergy to the drug or any of its components.

Side effects

The most common side effect of diltiazem is peripheral edema (swelling), which most often occurs within two to three weeks of starting therapy. Headaches have also been reported in a number of patients.

Because diltiazem has been used by many people, the number of reported adverse effects is very high. Many of them are normal effects of the drug and can be resolved by dose adjustments. These include low blood pressure and dizziness. The most commonly reported side effects are:

- body aches or pain
- congestion
- cough
- dry or sore throat
- fever
- hoarseness
- runny nose
- tender or swollen glands in the neck
- trouble swallowing
- voice changes

Interactions

Diltiazem is known to interact with a large variety of drugs, as well as some foods and drinks.

Drugs

It is common for cardiac drugs to be used in combination. This can lead to an increased risk of adverse effects, but these can be dealt with by routine monitoring and dose adjustments.

A large number of drugs interact with diltiazem, including:

- amiodarone
- antibiotics such as **clarithromycin**, **erythromycin**, telithromycin, and dalbapristin/quinupristin
- antifungal medications such as itraconazole, **ketoconazole**, miconazole, and voriconazole
- beta-blockers such as **atenolol**, **carvedilol**, labetalol, metoprolol, nadolol, **propranolol**, and sotalol

- **buspirone**
- **carbamazepine**
- cholesterol medications such as **atorvastatin**, fluvastatin, lovastatin, **pravastatin**, and **simvastatin**
- cimetidine
- **cyclosporine**
- **digoxin**
- HIV/AIDS medications such as atazanavir, delavirdine, fosamprenavir, indinavir, nelfinavir, and ritonavir
- quinidine
- **rifampin**
- sedatives such as midazolam and **triazolam**

Other drugs may interact with diltiazem, so individuals should make sure that their healthcare providers are aware of all other medications they are taking (including over-the-counter drugs and supplements).

Food and other substances

Diltiazem and other CCBs may interact with grapefruit and grapefruit juice. Patients should consult with their doctor about including grapefruit in their diet.

Resources

PERIODICALS

- Christensen, H., et al. "Coadministration of Grapefruit Juice Increases Systemic Exposure of Diltiazem in Healthy Volunteers." *European Journal of Clinical Pharmacology* 58, no. 8 (2002): 515–20.
- Field, J. M., et al. "Part 1: Executive Summary: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care." *Circulation* 18, suppl. 3 (2010): S640–56.
- Frost, C. E., et al. "Effect of Ketoconazole and Ciltiazem on the Pharmacokinetics of Apixaban, an Oral Direct Factor Xa Inhibitor." *British Journal of Clinical Pharmacology* (2014): e-pub ahead of print. <http://dx.doi.org/10.1111/bcp.12541> (accessed February 13, 2015).
- O'Connor R. E., et al. "Part 10: Acute Coronary Syndromes: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care." *Circulation* 18, suppl. 3 (2010): S787–817.
- Ogura T., et al. "Effects of Diltiazem on Sympathetic Activity in Patients with Aneurysmal Subarachnoid Hemorrhage." *Acta Neurochirurgica Supplement* 120 (January 2015): 47–50.

WEBSITES

- American Heart Association. "Types of Blood Pressure Medications." [http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/PreventionTreatmentofHighBloodPressure/Types-of-Blood-Pressure-](http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/PreventionTreatmentofHighBloodPressure/Types-of-Blood-Pressure-Medications_UCM_303247_Article.jsp)

[Medications_UCM_303247_Article.jsp](http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/PreventionTreatmentofHighBloodPressure/Types-of-Blood-Pressure-Medications_UCM_303247_Article.jsp) (accessed February 18, 2015).

Medscape Reference. "Diltiazem (Rx)." <http://reference.medscape.com/drug/cardizem-cd-diltiazem-342374#10> (accessed February 13, 2015).

MedlinePlus. "Diltiazem." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a684027.html> (accessed February 13, 2015).

Merck & Co. "Heart and Blood Vessel Disorders." Merck Manual Home Edition. http://www.merckmanuals.com/home/heart_and_blood_vessel_disorders.html (accessed February 13, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, Texas (800) 242-8721, <http://www.heart.org/>.

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Diovan HCT see **Valsartan/hydrochlorothiazide**

Diphenhydramine

Definition

Diphenhydramine is an antihistamine used in general medicine to treat allergies, allergic reactions, motion sickness, insomnia, cough, and nausea.

Purpose

Diphenhydramine is used to treat allergy symptoms such as runny nose, sneezing, and eye irritation. It is also used to relieve motion sickness, insomnia, cough, nausea, and itching, and it may be used to help limit allergic reactions to transfused blood products. In liquid form, it may relieve minor throat irritation.

In psychiatric medicine, diphenhydramine is sometimes used to control abnormal tremors caused by some psychiatric medications. It may also be used to treat the stiffness and tremor of Parkinson's disease and to induce sleep.

Description

Diphenhydramine is easily absorbed when taken by mouth and is readily distributed throughout the body. Maximal effect occurs approximately one hour after swallowing the drug and continues for four to six hours.



Diphenhydramine, 50 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

U.S. brand names

Diphenhydramine is available both over the counter and as a prescription medication. It is commonly known as Benadryl. It is also available in its generic form and in combination with other medications.

Recommended dosage

Diphenhydramine is available in several formulations, including oral tablets, capsules, and liquids. The dosage of diphenhydramine varies according to the reason for its use. Adults are generally given 25–50 milligrams (mg) orally, three to four times daily. If the drug is injected, the usual dosage is 10–50 mg per injection. The total daily dosage should not exceed 400 mg. People who forget to take a dose of this drug should skip the dose and take the next one at the regularly scheduled time. They should not double up subsequent doses if one is missed.

Precautions

Drowsiness commonly occurs after taking diphenhydramine. This effect may be more pronounced if alcohol or any other central nervous system depressant, such as a tranquilizer or pain medication, is also taken. People taking the drug should not drive, operate machinery, or perform tasks requiring mental alertness until the effects of the medication have worn off.

KEY TERMS

Allergy—Altered body reaction, usually hypersensitivity, as a response to exposure to a specific substance.

Anticholinergic—Related to the ability of a drug to block the nervous system chemical acetylcholine. When acetylcholine is blocked, patients often experience dry mouth and skin, increased heart rate, blurred vision, and difficulty in urinating. In severe cases, blocking acetylcholine may cloud thinking and cause delirium.

Antihistamine—A medication used to alleviate allergy or cold symptoms such as runny nose, itching, hives, watering eyes, or sneezing.

Histamine—Substance released during allergic reactions.

Parkinson's disease—A disease of the nervous system most common in people over 60, characterized by a shuffling gait, trembling of the fingers and hands, and muscle stiffness.

People should not take diphenhydramine if they are taking other preparations that contain antihistamines unless specifically directed to do so by a physician.

Geriatric

Elderly people are more sensitive to the sedating effects of diphenhydramine. The drug may also lower blood pressure, which can cause dizziness and light-headedness when switching from a seated to a standing position. Older patients should move slowly when rising to a standing position to prevent fainting.

Other conditions and allergies

Individuals with peptic ulcer disease, bowel obstructions, an enlarged prostate, angle-closure glaucoma, or difficulty urinating due to a blockage in the bladder should not use diphenhydramine without close physician supervision and monitoring. People with asthma, heart disease, high blood pressure, or an overactive thyroid should use this drug with caution. Before taking diphenhydramine, people with these conditions should discuss the risks and benefits of this drug with their doctor. Individuals should not take diphenhydramine for several days before an allergy test, as it will interfere with the results.

PATIENT PROFILE

A young woman in her 20s sought medical help for allergy symptoms that had appeared when she moved from the city, where she had lived all of her life, to a rural location. She had always been healthy and enjoyed outdoor activities without experiencing any unwanted symptoms. Suddenly, however, she was experiencing symptoms such as a constant runny nose, sneezing, itchy eyes, tearing, and an itchy throat. This came on quickly almost every time she went outdoors and sometimes even when indoors. Her symptoms were relieved somewhat by the over-the-counter multisymptom allergy medication Benadryl Allergy/Cold (acetaminophen/diphenhydramine/phenylephrine), which she took during the day when symptoms were especially uncomfortable. She also took it regularly before bed if her symptoms had not subsided. Because the symptoms never really cleared up entirely, she decided to seek medical help and made an appointment with a family practice physician in her new hometown.

After a thorough medical history and physical examination had determined that the patient was in good general health and was not pregnant, the doctor prescribed diphenhydramine hydrochloride (Benadryl) to control her allergic symptoms, which he diagnosed as allergic rhinitis. Diphenhydramine is an antihistamine with sedative effects that can cause drowsiness; it is intended to provide immediate relief when necessary but is not usually applied for long-term relief. The doctor felt that the young woman was in a process of adjusting to her new environment and her symptoms would eventually abate. She was instructed to take one 25 mg tablet of diphenhydramine HCl as needed to control allergic

symptoms. During a particularly heavy bout of allergic symptoms, the patient could take one 25 mg tablet as needed every 4 to 6 hours. She was advised that this dosage might cause sleepiness or dizziness and therefore should not be exceeded. She should also use caution when driving or using machinery of any kind, making sure that she was able to perform the task.

After three days of taking the medication at least twice a day, the patient reported to her doctor's office that her symptoms were actually worse and she had experienced no relief at all. Her eyes were so irritated that they were swollen, and, besides her itchy throat, her chest also felt irritated and was affecting her breathing. The only benefit so far had been sleeping soundly each night, even when markedly congested. She was instructed to stop the medication immediately. The doctor felt that the patient was undoubtedly allergic to some ingredient in the formulation of diphenhydramine, and it would have to be replaced by another medication. A prescription for 10 mg loratadine (Claritin) tablets was called in to the pharmacy. Loratadine is also an antihistamine, but it controls histamine production somewhat differently than diphenhydramine and without sedation. It also works more slowly than diphenhydramine, so multiple doses are needed before allergy symptoms are controlled, making it suitable for long-term treatment of allergic rhinitis. The patient was advised to wait 24 hours and then begin to take one tablet every 4 to 6 hours. Within a week her symptoms were under control, and she was able to take loratadine long term on an as-needed basis.

Side effects

Diphenhydramine may cause dizziness, difficulties with coordination, confusion, restlessness, nervousness, difficulty sleeping, blurry or double vision, ringing in the ears, headache, or convulsions. Stomach distress is a relatively common side effect of diphenhydramine. Some people may develop poor appetites, nausea, vomiting, diarrhea, or constipation. Individuals also may experience low blood pressure, heart palpitations, rapid or irregular heartbeat, frequent urination, or difficulty urinating. Urine may be retained in the bladder. Other side effects include hives, a rash, sensitivity to the sun, and a dry mouth and nose.

Geriatric

Thickened lung secretions are common among older patients.

Interactions

Individuals should discuss possible drug interactions with their healthcare provider before taking diphenhydramine, even over-the-counter formulations.

Drugs

People should not take diphenhydramine if they are taking other preparations that contain antihistamines unless specifically directed to do so by a physician. Pain medications, sleeping pills, tranquilizers, and antidepressants may make the drowsiness associated with diphenhydramine more severe. Diphenhydramine should not be used by persons taking hay-fever medicines, sedatives, narcotics, anesthetics, barbiturates, or muscle relaxants.

Herbs and supplements

Diphenhydramine should not be used with herbal preparations such as gotu kola, kava kava, or St. John's wort.

Food and other substances

Alcohol may increase the sedative effect of diphenhydramine.

Resources

PERIODICALS

Grillon, Christian, et al. "The Benzodiazepine Alprazolam Dissociates Contextual Fear from Cued Fear in Humans as Assessed by Fear-Potentiated Startle." *Biological Psychiatry* 60, no. 7 (October 1, 2006): 760–66.

WEBSITES

AHFS Consumer Medication Information. "Diphenhydramine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682539.html> (accessed February 27, 2015).

American Academy of Allergy Asthma & Immunology. "Allergies." <http://www.aaaai.org/conditions-and-treatments/allergies.aspx> (accessed February 27, 2015).

Physicians' Desk Reference. "Diphenhydramine HCl Injection." PDR Health. <http://www.pdrhealth.com/drugs/diphenhydramine-hcl-injection> (accessed February 27, 2015).

ORGANIZATIONS

American Academy of Allergy, Asthma & Immunology (AAAAI), 555 East Wells Street, Suite 1100, Milwaukee, WI 53202-3823, (414) 272-6071, <http://www.aaaai.org/>.

American Academy of Family Physicians, 11400 Tomahawk Creek Parkway, Leawood, KS 66211-2672, (913) 906-6000, (800) 274-2237, Fax: (913) 906-6075, contact center@aafp.org, <http://www.aafp.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Dipyridamole see **Aspirin/extended-release dipyridamole**

Ditropan see **Oxybutynin**

Divalproex sodium see **Valproic acid**

Dolophine see **Methadone**

Donepezil

Definition

Donepezil is a drug approved by the U.S. Food and Drug Administration (FDA) to treat symptoms of dementia associated with Alzheimer's disease. It is the only drug in its class that is approved by the FDA to treat all stages of Alzheimer's disease, from mild to severe.

Purpose

Donepezil is used to help treat symptoms in individuals with Alzheimer's disease. The drug may cause small improvements in dementia for a short period of time, but donepezil does not stop the progression of Alzheimer's disease.

Description

Donepezil is in a class of drugs known as cholinesterase inhibitors. Drugs in this class prevent the breakdown of acetylcholine, a neurotransmitter that helps facilitate nerve impulses within the brain. In Alzheimer's disease, cells in specific regions of the brain die, meaning they are no longer able to transmit nerve impulses. By sustaining the concentration of acetylcholine in the brain, donepezil and other cholinesterase inhibitors help maintain the transmission of nerve impulses.

Donepezil is available as tablets in two different strengths.



Donepezil, 23 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

KEY TERMS

Acetylcholine—A naturally occurring chemical in the body that transmits nerve impulses from cell to cell. It causes blood vessels to dilate, lowers blood pressure, and slows the heartbeat. Central nervous system well-being is dependent on a balance among acetylcholine, dopamine, serotonin, and norepinephrine.

Alzheimer's disease—A progressive, neurodegenerative disease characterized by loss of function and death of nerve cells in several areas of the brain, leading to loss of mental functions, including memory and learning. Alzheimer's disease is the most common cause of dementia.

Dementia—A group of symptoms (syndrome) associated with a progressive loss of memory and other intellectual functions that is serious enough to interfere with a person's ability to perform the tasks of daily life. Dementia impairs memory, alters personality, leads to deterioration in personal grooming, impairs reasoning ability, and causes disorientation.

Neurotransmitter—A chemical in the brain that transmits messages between neurons, or nerve cells.

U.S. brand names

In the United States, donepezil is sold under the trade name Aricept.

Recommended dosage

The initial dosage of donepezil is 5 milligrams (mg) taken at bedtime. This dose should be continued for four to six weeks. The dosage may then be increased to 10 mg at bedtime, but there is no clear evidence that the higher dosage is more beneficial. The higher dosage is also likely to cause more side effects.

Precautions

People with certain heart conditions, stomach ulcers, bladder obstruction, asthma, chronic obstructive pulmonary disease (COPD), or a history of seizures should use donepezil with caution under close physician supervision, as the drug may worsen or aggravate these conditions. Patients taking donepezil should be reassessed periodically to determine whether the drug is providing any benefits. When caregivers feel the drug is no longer beneficial, it may be stopped.

Side effects

More than 5% of people taking donepezil experience difficulty sleeping, dizziness, nausea, diarrhea, muscle cramps, headache, or other pains. Diarrhea, nausea, and vomiting occur more often with the 10 mg dose than the 5 mg dosage. These adverse effects are usually mild and short lived and typically subside when the drug is stopped. Other, less common side effects include abnormal dreams, depression, drowsiness, fainting, loss of appetite, weight loss, frequent urination, arthritis, and easy bruising. Donepezil may slow heart rate, increase acid in the stomach, make urination difficult, cause breathing difficulties, and increase the risk of seizures in persons with a history of seizure disorder.

Interactions

Research has found that the effects of donepezil on Alzheimer's disease may be enhanced through combination therapy with memantine (Namenda). Studies have shown that the use of **memantine** in combination therapy with donepezil is frequently more effective than the use of donepezil alone in the treatment of moderate to severe Alzheimer's disease. Using memantine and donepezil in combination therapy does not affect the pharmacokinetics of either drug. Clinical trials have shown such combination therapy to be both safe and effective, although the safety precautions for both drugs must be considered before combination therapy is undertaken.

Drugs

Many drugs may alter the effects of donepezil; likewise, donepezil may alter the action of other drugs. Drugs such as dicyclomine, phenytoin, **carbamazepine**, dexamethasone, **rifampin**, or phenobarbital may lessen the effects of donepezil. Other drugs such as bethanechol, **ketoconazole**, or quinidine may increase some of the side effects associated with donepezil. When donepezil and nonsteroidal anti-inflammatory drugs (NSAIDs) such as **ibuprofen** (Advil) or naproxen (Aleve) are used together, there may be an increased risk of stomach ulcers. Donepezil may increase the side effects associated with use of **fluvoxamine**, an antidepressant. If succinylcholine, a drug commonly used during anesthesia, is used with donepezil, prolonged muscle paralysis may result.

Resources

BOOKS

Labbate, Lawrence A., et al. *Handbook of Psychiatric Drug Therapy*. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2009.

PERIODICALS

- Chen, Xiying, et al. "Donepezil Effects on Cerebral Blood Flow in Older Adults with Mild Cognitive Deficits." *Journal of Neuropsychiatry & Clinical Neurosciences* 18, no. 2 (May 2006): 178–85.
- Cholongitas, Evangelos, Chrysoula Pipili, and Maria Dasenaki. "Recurrence of Upper Gastrointestinal Bleeding after Donepezil Administration." *Alzheimer Disease and Associated Disorders* 20, no. 4 (October–December 2006): 326.
- Cummings, Jeffrey L., Thomas McRae, and Richard Zhang. "Effects of Donepezil on Neuropsychiatric Symptoms in Patients with Dementia and Severe Behavioral Disorders." *American Journal of Geriatric Psychiatry* 14, no. 7 (July 2006): 605–12.
- Hogan, David B. "Donepezil for Severe Alzheimer's Disease." *Lancet* 367, no. 9516 (April 1, 2006): 1031–32.
- Howard, Robert, et al. "Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease." *New England Journal of Medicine* 33 (March 8, 2012): 893–903.
- Lee, J. H., et al. "Donepezil across the Spectrum of Alzheimer's Disease: Dose Optimization and Clinical Relevance." *Acta Neurologica Scandinavica* (February 18, 2015): e-pub ahead of print. <http://dx.doi.org/10.1111/ane.12386> (accessed February 24, 2015).

OTHER

- National Institute for Health and Clinical Excellence. "Donepezil, Galantamine, Rivastigmine and Memantine for Alzheimer's Disease." UK National Health Service. <https://www.nice.org.uk/guidance/ta217/resources/ta217-alzheimers-disease-donepezil-galantamine-rivastigmine-and-memantine-understanding-nice-guidance2> (accessed February 24, 2015).

WEBSITES

- AHFS Consumer Medication Information. "Donepezil." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a697032.html> (accessed February 24, 2015).
- Alzheimer's Association. "Medications for Memory Loss." http://www.alz.org/alzheimers_disease_standard_prescriptions.asp (accessed February 24, 2015).

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Dorzolamide/timolol

Definition

Dorzolamide is a carbonic anhydrase inhibitor that is used to treat elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. Carbonic



Dorzolamide/timolol ophthalmic solution. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

anhydrase is an enzyme found in many body tissues, including the eye. When carbonic anhydrase is inhibited, the eye produces less aqueous humor, which is the thin, watery liquid that fills the anterior chamber of the eye (the space between the cornea and the iris). The aqueous humor provides nutrients to the lens and the cornea, but excessive amounts raise the level of pressure within the eye (intraocular pressure).

Timolol is a beta-adrenergic blocking agent that is also used to reduce intraocular pressure.

Purpose

Dorzolamide/timolol is used to treat glaucoma, a condition in which increased intraocular pressure damages the optic nerve (the nerve that transmits images to the brain). If left untreated, glaucoma can cause blindness. Open-angle glaucoma, also called wide-angle glaucoma, is the most common form of glaucoma and occurs when the intraocular fluid does not flow properly through the drain of the eye (trabecular meshwork). The aqueous humor drains from the eye and goes into the aqueous veins and the bloodstream. This by itself does not cause glaucoma, but patients with elevated intraocular pressure (IOP) are at risk of glaucoma.

Description

There are a number of classes of drugs that are used to treat glaucoma, as well as surgical methods. Drug

KEY TERMS

Aqueous humor—A transparent liquid, contained within the eye, that is composed of water, sugars, vitamins, proteins, and other nutrients.

Beta-blocker—A class of drugs that is widely used to treat high blood pressure and congestive heart failure. Beta-blockers work by blocking the effects of epinephrine (adrenaline) and slowing the heart's rate, thereby decreasing the heart's demand for oxygen.

Carbonic anhydrase inhibitors—A group of drugs that inhibits the production of fluid inside the eye, lowering the pressure on the optic nerve.

Glaucoma—A condition in which increased fluid pressure inside the eye damages the optic nerve (the nerve that goes from the eye to the brain). If left untreated, glaucoma can lead to blindness.

Hyperthyroidism—A condition in which the thyroid gland in the throat is overactive and produces too much thyroid hormone.

Intraocular—Within the eye.

Trabecular meshwork—A sponge-like tissue located near the cornea and iris that functions to drain the aqueous humor from the eye into the blood.

therapy may increase the outflow of fluid in the eye, reduce production of aqueous humor, or both. In some patients, combinations of drugs are most effective, but others require surgical intervention.

Dorzolamide/timolol solutions contain 22.3 milligrams (mg) of dorzolamide and 6.8 mg of timolol maleate per milliliter (mL). One drop is approximately 1/20 of a mL.

U.S. brand names

Dorzolamide/timolol eyedrops are available as generics or under the brand name Cosopt.

International brand names

The brand name Cosopt appears to be in use almost worldwide, although other local brand names may be in use. The combination drug has been widely distributed as a generic formulation.

Recommended dosage

One drop of dorzolamide/timolol is instilled into the affected eye(s) two times a day, every 12 hours. This dose applies to all patients over the age of two.

Pediatric

The safety and efficacy of dorzolamide/timolol have not been established for patients under the age of two.

Precautions

Even though dorzolamide/timolol is applied to the eye, the drugs can be absorbed into the body and carry the same risks as oral forms.

Pregnant or breastfeeding

Dorzolamide/timolol is classified as a pregnancy category C drug. Animal reproductive studies have shown no harm to a fetus, but there have been no human studies.

The National Library of Medicine's LactMed database reviews dorzolamide and timolol individually and concludes that each should pose little risk to breastfeeding infants. In order to reduce the amount of drug reaching breast milk after using eyedrops, the mother should place pressure over the tear duct by the corner of the eye for one minute, then remove the excess fluid with a tissue.

Other conditions and allergies

Individuals who are allergic to sulfonamide drugs may also experience a reaction to dorzolamide.

Timolol particularly causes risks in patients with asthma, chronic obstructive pulmonary disease, and heart disease. In patients with diabetes, beta-blocking agents like timolol may mask the symptoms of low blood sugar (hypoglycemia). In a similar manner, beta-blockers may mask the rapid heartbeat seen in patients with hyperthyroidism. Abrupt withdrawal of timolol in patients with hyperthyroidism may precipitate a thyroid storm (a rare but dangerous condition caused by excessive thyroid hormone).

Timolol may exacerbate existing muscle weakness in patients with certain conditions, such as myasthenia gravis.

Side effects

Side effects of dorzolamide are common. Most apply to irritation of the eye following administration. One-third of patients complain of stinging or burning sensations. Other complaints include dryness, eye redness, and increased light sensitivity. Blurred vision is also common. Additional reported adverse effects include a bitter taste, fatigue, nausea, and vomiting.

Interactions

Generally, drugs that are applied topically, including eyedrops, do not get distributed through the body and therefore have no significant interactions. In contrast, both dorzolamide and timolol do have general distribution, and so patients should be aware of potential drug interactions.

Drugs

The effects of dorzolamide/timolol may be additive with other drugs that lower blood pressure, such as other beta-blockers and diuretics (water pills).

Insulin may also interact with dorzolamide/timolol, causing hypotension (low blood pressure). Patients using dorzolamide/timolol may also have adverse effects if taking high-dose **aspirin**. This combination may affect the acid-base balance and cause electrolyte disturbances. Selective serotonin reuptake inhibitors (SSRIs), used to treat depression, may increase the effects of timolol, leading to slower heart rates. These interactions call for close monitoring of the dose of all medications, so individuals should make sure to tell their healthcare provider all drugs they are currently taking, including over-the-counter drugs and supplements.

Resources

PERIODICALS

Takeda, S., T. Mimura, and M. Matsubara. "Effect of 3 Years of Treatment with a Dorzolamide/Timolol (1%/0.5%) Combination on Intraocular Pressure." *Clinical Ophthalmology* 8 (September 9, 2014): 1773–82. <http://dx.doi.org/10.2147/OPTH.S69359> (accessed March 5, 2015).

Takeda, S., T. Mimura, and M. Matsubara. "Effect of Dorzolamide/Timolol Combination on the Visual Field in Glaucoma." *Clinical Ophthalmology* 8 (August 25, 2014): 1579–90. <http://dx.doi.org/10.2147/OPTH.S71162> (accessed March 5, 2015).

OTHER

American Optometric Association. "Care of the Patient with Open Angle Glaucoma." <http://www.aoa.org/documents/optometrists/CPG-9.pdf> (accessed March 5, 2015).

Merck & Co. "Cosopt." http://www.merck.com/product/usa/pi_circulars/c/cosopt/cosopt_pi.pdf (accessed March 5, 2015).

WEBSITES

AHFS Consumer Medication Information. "Dorzolamide and Timolol Ophthalmic." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a602022.html> (accessed March 5, 2015).

Micromedex. "Dorzolamide and Timolol (Ophthalmic Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/dorzolamide-and-timolol-ophthalmic-route/description/drg-20061826> (accessed March 5, 2015).

U.S. National Library of Medicine. "LactMed: Dorzolamide." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?db+LactMed:@term+@DOCNO+98> (accessed March 5, 2015).

U.S. National Library of Medicine. "LactMed: Timolol." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?db+LactMed:@term+@DOCNO+305> (accessed March 5, 2015).

ORGANIZATIONS

American Academy of Ophthalmology, PO Box 7424, San Francisco, CA 94120-7424, (415) 561-8500, Fax: (415) 561-8533, <http://www.aao.org/>.

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Doxepin

Definition

Doxepin is an antidepressant drug. It is considered to be within the class of drugs known as tricyclic antidepressants.

Purpose

Doxepin is used primarily to treat depression and to treat the combination of symptoms of anxiety and depression. It is also approved by the U.S. Food and Drug Administration to treat insomnia.

Off-label use

Like most antidepressants, doxepin has also been used to treat panic disorder, obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), enuresis (bed-wetting), eating disorders such as bulimia nervosa, cocaine addiction, and the depressive phase of bipolar (manic-depressive) disorder. It has also been used to support smoking cessation programs.

Description

Doxepin acts to change the balance of naturally occurring chemicals in the brain that regulate the transmission of nerve impulses among cells. Its action primarily increases the concentration of norepinephrine and serotonin (both chemicals that stimulate nerve cells) and, to a lesser extent, blocks the action of another brain chemical, acetylcholine. Studies comparing doxepin with other tricyclic antidepressants—including **amitriptyline**, clomipramine, desipramine, **imipramine**, **nortriptyline**, protriptyline, and trimipramine—have shown that doxepin is no more or less effective than other antidepressants of its



Doxepin, 150 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

type. Its choice for treatment is as much a function of physician preference as any other factor.

The therapeutic effects of doxepin, like other antidepressants, appear slowly. Maximum benefit is often not evident for at least two weeks after starting the drug. People taking doxepin should be aware of this and continue taking the drug as directed even if they do not see immediate improvement.

Doxepin is available as 10, 25, 50, 75, 100, and 150 milligram (mg) oral capsules as well as an oral concentrate solution containing 10 mg of drug in each milliliter (mL) of solution.

U.S. brand names

Doxepin is sold in the United States under the brand names Sinequan (for depression) and Silenor (for insomnia), and it is also available under its generic name.

Recommended dosage

As with any antidepressant, doxepin must be carefully adjusted by the physician to produce the desired therapeutic effect. Therapy is usually started at 30–150 mg per day and gradually increased to 300 mg daily if needed. There is little evidence that doses above 300 mg daily provide any additional benefits. Amounts up to 150 mg may be taken as a single dose at bedtime to decrease daytime sleepiness. Doses of more than 150 mg per day should be divided into two or three doses and taken throughout the day.

If the oral concentrate of doxepin is used, each dose should be diluted in at least 4 oz. (120 mL) of milk or orange, prune, tomato, pineapple, or grapefruit juice just before administration. Doxepin is not compatible with many carbonated beverages and should not be diluted in them.

Geriatric

In patients over age 60, therapy should be maintained at the low end of the dosing range and increased cautiously and with physician supervision. Patients with organic brain syndrome (psychiatric symptoms of dementia often seen in elderly patients) generally require daily doses of only 25–50 mg.

Precautions

As with other tricyclic antidepressants, doxepin should be used cautiously and with close physician supervision, particularly in the elderly and individuals who have benign prostatic hypertrophy (enlarged prostate), urinary retention, or glaucoma, especially angle-closure glaucoma (the most severe form). Before starting treatment, people with these conditions should discuss the relative risks and benefits of treatment with their doctors to help determine if doxepin is the right antidepressant for them.

Several antidepressants, including doxepin, have been found to potentially increase the risk of suicidal thoughts and actions in patients younger than 25. All persons taking doxepin, regardless of age, should be monitored for signs of worsening depression or self-harm.

A common effect of antidepressants is sedation (drowsiness, lack of physical and mental alertness). This side effect is especially noticeable early in therapy. In most patients, sedation decreases or disappears entirely with time, but until then patients taking doxepin should not perform activities requiring mental alertness, such as driving or operating machinery.

Use of Silenor for insomnia has been associated with sleepwalking and similar events. If individuals suspect that they are engaging in activities during sleep, including walking, eating, talking on the phone, or driving, they should contact their healthcare provider.

Pregnant or breastfeeding

Doxepin should not be taken by nursing mothers because it is secreted into breast milk and may cause side effects in the nursing infant.

Other conditions and allergies

Doxepin may increase heart rate and stress on the heart. It may be dangerous for people with cardiovascular

KEY TERMS

Acetylcholine—A naturally occurring chemical in the body that transmits nerve impulses from cell to cell. Generally, it has opposite effects from dopamine and norepinephrine; it causes blood vessels to dilate, lowers blood pressure, and slows the heartbeat. Central nervous system well-being is dependent on a balance among acetylcholine, dopamine, serotonin, and norepinephrine.

Anticholinergic—Related to the ability of a drug to block the nervous system chemical acetylcholine. When acetylcholine is blocked, patients often experience dry mouth and skin, increased heart rate, blurred vision, and difficulty urinating. In severe cases, blocking acetylcholine may cloud thinking and cause delirium.

Depression—A mental state characterized by excessive sadness and loss of interest in life; other symptoms may include altered sleep or eating patterns, loss of concentration, agitation, lack of energy, and, in severe cases, attempts at self-harm or suicide.

Insomnia—A chronic inability to sleep or to remain asleep throughout the night.

Norepinephrine—A neurotransmitter in the brain that acts to constrict blood vessels and raise blood pressure. It works in combination with serotonin.

Organic brain syndrome—A class of disorders characterized by progressive deterioration of mental processes caused by temporary brain dysfunction or permanent brain damage. Symptoms include delusions, dementia, amnesia, and delirium that are not caused by drugs, alcohol, or medications.

Serotonin—A widely distributed neurotransmitter that is found in blood platelets, the lining of the digestive tract, and the brain and that works in combination with norepinephrine. It causes very powerful contractions of smooth muscle and is associated with mood, attention, emotions, and sleep. Low levels of serotonin are associated with depression.

disease, especially those who have recently had a heart attack, to take this drug or other antidepressants in the same pharmacological class. In rare cases where patients with cardiovascular disease must receive doxepin, they should be monitored closely for cardiac rhythm disturbances and signs of cardiac stress or damage. Doxepin may also increase the possibility of having seizures. Patients should tell their physician if they have a history

of seizures, including seizures brought on by the abuse of drugs or alcohol. These people should use doxepin only with caution and be closely monitored by their physician.

Men with prostate enlargement who take doxepin may be especially likely to have problems with urinary retention. Symptoms include having difficulty starting a urine flow and more difficulty than usual passing urine. In most cases, urinary retention is managed with dose reduction or by switching to another type of antidepressant. In extreme cases, patients may require treatment with bethanechol, a drug that reverses this particular side effect.

Side effects

Doxepin shares the side effects of tricyclic antidepressants. The most frequent of these are dry mouth, constipation, urinary retention, increased heart rate, sedation, irritability, dizziness, and decreased coordination. As with most side effects associated with tricyclic antidepressants, the intensity is highest at the beginning of therapy and tends to decrease with continued use.

Dry mouth, if severe to the point of causing difficulty speaking or swallowing, may be managed by dosage reduction or temporary discontinuation of the drug. Patients may also chew sugarless gum or suck on sugarless candy in order to increase the flow of saliva. Some artificial saliva products may give temporary relief.

Interactions

To avoid drug interactions, individuals should alert their healthcare provider to all medications they are currently taking, including over-the-counter drugs and supplements.

Drugs

Dangerously high blood pressure has resulted from the combination of antidepressants such as doxepin and members of another class of antidepressants known as monoamine oxidase inhibitors (MAOIs). Because of this, doxepin should never be taken in combination with MAOIs. Patient's taking any MAOIs—for example, Nardil (phenelzine sulfate) or Parnate (tranylcypromine sulfate)—should stop the MAOI and wait at least 14 days before starting doxepin or any tricyclic antidepressant. The same holds true when discontinuing doxepin and starting an MAOI.

Doxepin may decrease the blood pressure—lowering effects of clonidine. Patients who take both drugs should be monitored for loss of blood pressure control, and the dose of **clonidine** may need to be increased.

The sedative effects of doxepin are increased by other central nervous system depressants, such as sedatives and sleeping medications, antihistamines, or medications used for other mental disorders such as schizophrenia. The

anticholinergic effects of doxepin are additive with other anticholinergic drugs such as **benztropine**, biperiden, trihexyphenidyl, and antihistamines.

Food and other substances

Alcohol enhances the sedative effects of doxepin and increases the risk of sleepwalking when taking Silenor.

Resources

BOOKS

American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda, MD: American Society of Health-System Pharmacists, 2015.

PERIODICALS

Yeung, W. F., et al. "Doxepin for Insomnia: A Systematic Review of Randomized Placebo-Controlled Trials." *Sleep Medicine Reviews* 19 (February 2015): 75–83.

OTHER

U.S. Food and Drug Administration. "Medication Guide (Silenor)." <http://www.fda.gov/downloads/drugs/drugsafety/ucm206668.pdf> (accessed February 24, 2015).

U.S. Food and Drug Administration. "Medication Guide: Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions." <http://www.fda.gov/downloads/Drugs/DrugSafety/ucm089129.pdf> (accessed February 24, 2015).

WEBSITES

Micromedex. "Doxepin (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/doxepin-oral-route/description/drg-20072083> (accessed February 24, 2015).

Physicians' Desk Reference. "Silenor." PDR Health. <http://www.pdrhealth.com/drugs/silenor> (accessed February 24, 2015).

U.S. Food and Drug Administration. "Antidepressant Use in Children, Adolescents, and Adults." <http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm096273.htm> (accessed February 24, 2015).

ORGANIZATIONS

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Doxycycline

Definition

Doxycycline is an antibiotic and is a member of the tetracycline family. The tetracyclines are broad-spectrum,



Doxycycline, 100 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

bacteriostatic drugs. They are effective against many different types of bacteria but do not actually kill the bacteria. Rather, they act by preventing bacterial growth so that the body's immune system can destroy the bacteria. Although the members of the **tetracycline** group have similar actions and side effects, there are minor differences in the species of bacteria that the drug works against, the drugs' side effects, distribution throughout the body, and other considerations that make a difference in choosing one or another for specific needs. Doxycycline is also useful in prophylaxis (prevention) of several diseases.

Purpose

Doxycycline is one of the most versatile antibiotics known. It is used to treat many different bacterial infections, such as acne, urinary tract infections (UTIs), intestinal infections, eye infections, gonorrhea, chlamydia, syphilis, rosacea, and periodontitis (gum disease). It is also used to prevent Lyme disease and malaria. While antibiotics, for the most part, are effective only against bacteria, doxycycline, along with related tetracyclines, has shown activity against some other pathogens, including some virus species. Tetracyclines may also be used as second-line drugs in patients who are allergic to penicillin.

Off-label uses

Doxycycline has been used for a large number of off-label indications, including some difficult-to-treat

gonococcal infections (infections caused by *Neisseria gonorrhoeae*). It was formerly used in treatment of traveler's diarrhea and the prevention of sexually transmitted diseases (STDs) in assault cases, but this is no longer recommended due to bacterial resistance.

Besides its value in treatment of infectious diseases, doxycycline has some anti-inflammatory properties, and recent studies have been exploring the value of doxycycline for nonantibiotic uses, including diabetic retinopathy.

Description

Doxycycline is commercially available in a variety of dosage forms:

- doxycycline hyclate tablets: 20, 75, 150 milligrams (mg)
- doxycycline hyclate delayed-release tablets: 75 mg, 100 mg, 150 mg, 200 mg
- doxycycline hyclate intravenous (IV) solution: 100 mg
- doxycycline monohydrate tablets: 75 mg, 100 mg, 150 mg
- doxycycline monohydrate capsules: 50 mg, 75 mg, 100 mg, 150 mg
- doxycycline monohydrate oral suspension: 25 mg per 5 milliliters (mL, or one teaspoon)
- doxycycline eyelid cleanser kit: 20 mg, 50 mg
- doxycycline intravenous (IV) solution (powder or premixed): 100 mg
- doxycycline delayed-release capsules: 40 mg
- doxycycline calcium oral syrup: 50 mg/5 mL

Additional dosage forms may be available.

U.S. brand names

Doxycycline is widely available in generic form. Brand names sold in the United States include:

- Acticlate
- Adoxa
- Alodox
- Doryx
- Doxy
- Monodox
- Ocudox
- Vibramycin

Canadian brand names

The brand names sold in the United States are also available in Canada.

International brand names

International brand names for doxycycline include:

- Doxycyclinum
- Doxin
- Dumoxin
- Medomycin
- Unidox

Origins

The tetracyclines have been available since the 1940s and were once among the most valuable and widely used classes of antibiotics. Inevitably, bacterial resistance developed, and generally, resistance to one of the tetracyclines leads to all members of the drug class. Among the diseases that have shown resistance patterns are gonorrhea, cholera, and infections with *Salmonella* or *Pseudomonas* species. Tetracycline resistance has also been reported against rare strains of methicillin-resistant *Staphylococcus aureus* (MRSA). Still, tetracyclines remain the treatment of choice for infections caused by *Chlamydia* (trachoma, psittacosis, salpingitis, urethritis, and *L. venereum* infection), *Rickettsia* (typhus, Rocky Mountain spotted fever), brucellosis, and spirochetal infections (borreliosis, syphilis, and Lyme disease).

Recommended dosage

The most common dosing regimen is 100 mg taken twice a day. This dosage may be continued or dropped to 100–200 mg taken per day, divided into two doses. Specific conditions may have different dosage schedules.

To treat rosacea, 40 mg is taken daily.

For prevention of malaria, 100 mg is taken every day, starting one to two days before travel and stopping four weeks after leaving the infected area.

Pediatrics

Doxycycline should not normally be given to children under the age of eight because of the high risk of tooth discoloration and possible problems with tooth enamel formation. For children older than eight years, dose recommendations are based on patient weight. Children over 90 pounds (45 kilograms [kg]) may be given 100 mg every 12 hours. Below that weight, a dose of 4.4 mg/kg (2.2 lb.) is usually recommended as either a single dose or two divided doses.

Precautions

Because doxycycline has such a wide spectrum of action, there is a high risk of superinfection. This may occur with any antibiotic, and it is seen when the

KEY TERMS

Antibiotic resistance—The ability of infectious agents to change their biochemistry in such a way as to make an antibiotic no longer effective.

Diabetic retinopathy—A condition in which the tiny blood vessels to the retina, the tissues that sense light at the back of the eye, are damaged, leading to blurred vision, sudden blindness, or black spots, lines, or flashing lights in the field of vision.

Diplopia—Double vision (seeing two images).

Papilledema—Swelling of the optic disc due to increased intracranial pressure.

Pathogen—Disease-causing organism.

Prophylaxis—Prevention.

Rosacea—A chronic skin disease characterized by persistent redness of the skin and periodic outbreaks of pustules, usually affecting the middle third of the face.

Sexually transmitted disease (STD)—A disease that is passed from one person to another through sexual intercourse or other intimate sexual contact; also referred to as a sexually transmitted infection (STI). STDs include gonorrhea, chlamydia, and syphilis.

Superinfection—Infection by a second virus after a previous infection with a different virus has become well established.

antibiotic eliminates the primary infection, leaving other resistant bacteria and fungus to grow. It is most likely when doxycycline is used for relatively long periods of time, such as with malaria prophylaxis and acne treatment. This may cause fungal growth in the mouth (black tongue) or *Clostridium difficile*-associated diarrhea (CDAD), which may range in severity from mild diarrhea to fatal colitis.

Intracranial hypertension (pseudotumor cerebri) has been associated with the use of doxycycline. Symptoms of intracranial hypertension include headache, blurred vision, diplopia (double vision), vision loss, and papilledema (swelling of the optic nerve). While the condition usually resolves itself after the drug is discontinued, permanent vision loss is possible.

Doxycycline may cause kidney damage.

In common with other members of the tetracycline group, doxycycline may cause sensitization to sunlight

with increased risk of serious sunburn. Although doxycycline is less photosensitizing than some other members of the group, persons using doxycycline should avoid prolonged exposure to direct sunlight and use sunscreen.

Pediatric

No tetracycline drug should be given to children under the age of eight except in the treatment of anthrax or conditions where other drugs cannot be used or are unlikely to be effective.

Pregnant or breastfeeding

Doxycycline is in pregnancy category D. There is evidence of human fetal risk, so it should be used during pregnancy only in life-threatening emergencies when no safer drug is available.

Doxycycline enters breast milk and should not be used while breastfeeding.

Other conditions and allergies

Doxycycline preparations should not be administered to patients who are allergic to the drug or any component of its formulation (such as dyes or preservatives).

Women of childbearing age who are overweight or have a history of intracranial hypertension are at greater risk for developing tetracycline-associated intracranial hypertension.

Allergic reactions to tetracyclines are rare, but as with all other drugs, they may be serious.

Side effects

Doxycycline is usually well tolerated compared to other tetracyclines. Because doxycycline is almost completely absorbed from the stomach, very little of it reaches the lower bowel, and so antibiotic-associated diarrhea is less common than with some other tetracyclines. Similarly, doxycycline is somewhat less likely to cause photosensitization (sensitivity to sunlight) than other members of this drug class.

Because doxycycline has been so widely used, the list of reported adverse effects is extremely long, and many of the reports may be coincidental and not a result of the drug. Stomach upset, diarrhea, loss of appetite, and headache have been reported. Severe skin reactions have also been reported. Doxycycline should be discontinued if a rash develops. Other side effects have included low blood sugar (hypoglycemia) and some types of anemia.

Interactions

Individuals should inform their healthcare providers of all drugs they are currently taking, including over-the-counter drugs and supplements, before using doxycycline.

Drugs

Doxycycline has a large number of interactions. The most serious are acitretin (used to treat psoriasis) and tretinoin (used to treat severe acne), since these drugs all may cause increased intracranial pressure. The most evident symptom is headache and blurred vision, but if the drugs are not promptly discontinued, this may lead to permanent vision loss. Lomitapide, which is used to treat some types of elevated cholesterol, should not be used with doxycycline, since doxycycline may reduce the elimination of lomitapide and increase levels of the drug in the blood.

There are a large number of other drugs that should not be administered with doxycycline. Many of them contain calcium, including calcium-containing antacids; iron; or other metals. Most of these interactions can be avoided by separating the doses by at least one hour. It has been commonly recommended that tetracyclines not be used at the same time as penicillins, but recent studies indicate that in many cases the combination is more effective than larger doses of either drug alone.

Doxycycline and other tetracyclines have been reported to reduce the effectiveness of **oral contraceptives**. A literature review published in 2001 reported that while there does not appear to be a general interaction between antibiotics and contraceptives, in some women the blood levels of the contraceptive drops by as much as 20% when taken with tetracyclines or penicillins. Alternate means of birth control are recommended while taking antibiotics.

Herbs and supplements

Calcium, iron, and other metals may bind to doxycycline and impair absorption. Supplements containing these substances should be taken two hours before or after taking doxycycline, or avoided if not necessary.

Food and other substances

Dairy products and other high-calcium foods should not be consumed for two hours before and after taking doxycycline. For best results, the drug should be taken on an empty stomach.

Resources

PERIODICALS

- Dickinson, B. D., et al. "Drug Interactions between Oral Contraceptives and Antibiotics." *Obstetrics & Gynecology* 98, no. 5 (2001): 853–60.
- Scott, I. U., et al. "Effect of Doxycycline vs. Placebo on Retinal Function and Diabetic Retinopathy Progression in Mild to Moderate Nonproliferative Diabetic Retinopathy." *JAMA Ophthalmology* 132, no. 9 (2014): 1137–42.
- Speer, B. S., et al. "Bacterial Resistance to Tetracycline: Mechanisms, Transfer, and Clinical Significance." *Clinical Microbiology Reviews* 5, no. 4 (1992): 387–99.
- Teh, B., et al. "Doxycycline vs. Macrolides in Combination Therapy for Treatment of Community-Acquired Pneumonia." *Clinical Microbiology and Infection* 18, no. 4 (2012): E71–73.

WEBSITES

- U.S. Food and Drug Administration. "Vibramycin [prescribing information]." http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/050006s082,050007s023,050480s047,050533s0381bl.pdf (accessed March 5, 2015).

WEBSITES

- AHFS Consumer Medication Information. "Doxycycline." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682063.html> (accessed March 5, 2015).
- Centers for Disease Control and Prevention. "Malaria and Travelers." <http://www.cdc.gov/malaria/travelers/index.html> (accessed March 5, 2015).
- Physicians' Desk Reference. "Vibramycin." PDR Health. <http://www.pdrhealth.com/drugs/vibramycin> (accessed March 5, 2015).

ORGANIZATIONS

- Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30329-4027, (800) CDC-INFO (232-4636), <http://www.cdc.gov/>.
- National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, MSC 9806, Bethesda, MD 20852, (301) 496-5717, (866) 284-4107, Fax: (301) 402-3573, TTY: (800) 877-8339, postoffice@niaid.nih.gov, <http://www.niaid.nih.gov/>.

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Duloxetine

Definition

Duloxetine is a medication used to treat a variety of nervous system-oriented illnesses, including depression



Cymbalta (duloxetine), 60 mg. (© Cengage Learning®)

and neuropathic pain. Neuropathic pain is pain generated by the nervous system and is also known as neurogenic pain. Duloxetine belongs to a class of drugs known as serotonin and norepinephrine reuptake inhibitors (SNRIs), which specifically acts on two chemicals called serotonin and norepinephrine. These chemicals are types of neurotransmitters involved in normal brain function. These neurotransmitters can affect the physiological state of clinical depression as well as neuropathic pain.

Purpose

Duloxetine can be used to treat a broad range of mood and stress-related psychiatric illnesses as well as illnesses involving neuropathic pain. It is mainly used to treat clinical depression, generalized anxiety disorder (GAD), and pain associated with diabetic peripheral neuropathy or fibromyalgia. Choice of using duloxetine alone or in combination with other drugs depends on the medical disorder and individual health parameters.

Description

Duloxetine acts upon the natural body chemicals serotonin and norepinephrine. Serotonin and norepinephrine are neurotransmitters in the nervous system. Neurotransmitters like serotonin and norepinephrine bind to chemical

receptors on the surface of neurons (brain cells). Once bound to a receptor, they affect physiological processes.

The receptors activate a sequence of cellular events known as a chemical cascade or signaling pathway. Neurotransmitter signaling pathways are responsible for many regulatory processes in the body, including mood and pain. During the signaling process, neurotransmitters such as serotonin travel from one neuron to the next. Any extra serotonin or norepinephrine is taken back up by neuron one in a process known as reuptake. It is believed that a decrease in serotonin and norepinephrine signaling contributes to illness such as depression and anxiety disorders. SNRIs like duloxetine decrease the reuptake of these neurotransmitters by neuron one, allowing for more neurotransmitter signaling. An increase in serotonin and norepinephrine in the spinal cord is believed to inhibit the signaling of neurogenic pain pathways, hence their use in controlling pain associated with diabetic neuropathy or fibromyalgia.

Whether a patient is going to benefit from any SNRI medication may have a genetic component. Individual response to each SNRI varies greatly, and these drugs tend to require several weeks to take effect. The particular SNRI that works best for one patient may have no effect on another patient. Also, having no response to one SNRI does not mean that a patient will not have a good therapeutic response to another SNRI. Finding which SNRI is going to work for a patient may require a trial of multiple drugs until an effective agent is found. Generally, an agent is attempted for four to six weeks before concluding it will not have an effect and switching to another agent. If there is an effect but the healthcare provider judges that it could be improved, the dose is often increased, if the patient is able to tolerate the effects. Duloxetine is often the SNRI of initial choice, because it is effective and generally well tolerated by many patients.

U.S. brand names

Duloxetine is sold under the brand name Cymbalta.

Recommended dosage

Duloxetine is taken as an oral medication. The dosage used varies depending on the medical condition being treated, individual patient response to the medication regarding its effectiveness, and individual patient response to the medication regarding side effects. Some people naturally require a higher dose of duloxetine in order to achieve the desired effect. Other patients require a lower dose either for effect or because they quickly develop side effects that are not tolerable.

Duloxetine used for major depressive disorder and generalized anxiety disorder is usually dosed at 60 milligrams (mg) daily. Duloxetine used for neuropathic pain in diabetic neuropathy or fibromyalgia is dosed similarly. The dose can be taken in one pill or in increments of 30 mg twice daily. Patients may start at the lower 30 mg daily dose for the first week of treatment and gradually work their way up to the dose needed in 10 mg weekly increments, or they may go directly to 60 mg after one week at 30 mg per day. The maximum dose that may be used is 120 mg per day, but doses higher than 60 mg per day have rarely been shown to improve symptoms further and may not be tolerable to the patient.

Patients are dosed at the lowest possible effective dose to avoid the development of adverse side effects. Slowly increasing the dose over time helps with minimizing side effects, and some side effects become lessened with continued use. Patients are periodically reassessed to determine whether there is need for continued treatment with duloxetine. All SNRIs, including duloxetine, need to be slowly tapered off if discontinued to avoid withdrawal symptoms.

Geriatric

Elderly patients are usually started at a lower dose due to their increased sensitivity to these medications and their side effects.

Precautions

SNRIs have many side effects. It usually takes several weeks of medication for the treatment effect to occur, while the undesirable side effects may occur at the onset of treatment. When an SNRI is prescribed to a patient with a disease like major depression or severe pain, this time lapse in beneficial versus adverse effects may be difficult for patient compliance with treatment. The classic description is that patients who are already feeling depressed or in pain take an SNRI, experience side effects, and feel worse, all while being told that they will eventually get better. This situation can be frustrating for patients with depression or severe pain. Fortunately, SNRIs do help many people and have fewer overall side effects than some older medications used for the same purpose. Great benefit may be gained if a patient is able to get past the first couple of weeks of treatment.

When a patient discontinues the use of duloxetine, the dose needs to be tapered down slowly. SNRIs have little to no abuse potential, but if an SNRI is abruptly discontinued without tapering, there may be symptoms of withdrawal known as SNRI discontinuation syndrome. Withdrawal

symptoms of this syndrome may include flulike symptoms, anxiety, agitation, vivid or bizarre dreams, insomnia, nausea, vomiting, diarrhea, sense of imbalance, chills, fatigue, dizziness, headache, numbness and tingling of the extremities, and other sensory disturbances. Discontinuation syndrome may be avoided completely if the dose of duloxetine is properly tapered down over time.

SNRI overdose may result in a condition known as serotonin syndrome, which is also called serotonin toxicity, serotonin poisoning, and serotonin storm. Serotonin overdose may be caused by taking multiple drugs that increase the amount of serotonin signaling in the body. These drugs can cause serotonin overdose if used at the same time or in time periods too close together. Symptoms of serotonin overdose may range from mild to life threatening, depending on the individual situation. Symptoms may include high blood pressure, high fever, nausea, diarrhea, headache, sweating, increased heart rate, tremor, muscle twitching, delirium, shock, coma, and death.

Use of certain antidepressants, including duloxetine, has been associated with an increased risk of suicidal thoughts and actions in a small number of individuals aged 24 and younger. All patients taking duloxetine should be monitored for signs of worsening depression and suicidal behaviors.

Pregnant or breastfeeding

Duloxetine is classified as category C for pregnancy, which means either that there are no adequate human or animal studies, or that adverse fetal effects were found in animal studies, but there is no available human data. The decision whether or not to use category C drugs in pregnancy is generally based on weighing the critical needs of the mother against the risk to the fetus. Other, lower-category agents are used whenever possible. The safety of duloxetine use during breastfeeding is unknown, so its use is not recommended.

Other conditions and allergies

Duloxetine may be contraindicated or may require caution in use in patients with uncontrolled hypertension, liver function impairment or liver disease, kidney function impairment, seizure disorder, bleeding disorders, glaucoma, dehydration, or a history of alcohol abuse. Kidney and liver function, as well as blood pressure and behavioral changes, may be monitored while taking duloxetine. SNRIs such as duloxetine are discouraged from use in patients with bipolar disorder, as they can induce a state of mania in these individuals. There are selective conditions under which a doctor may prescribe an SNRI such as duloxetine to a bipolar patient for a short period of time under careful monitoring.

KEY TERMS

Bipolar disorder—Psychiatric mood disorder characterized by periods of manic behavior that may alternate with periods of depression; also known as manic depressive disorder.

Diabetic peripheral neuropathy—Complication of long-term diabetes involving damage to nerves in the periphery (outside of the brain and spinal cord) that may include symptoms such as numbness and burning pain.

Fibromyalgia—Chronic condition in which patients experience widespread musculoskeletal pain and fatigue; an amplified neuropathic pain pathway may be involved.

Generalized anxiety disorder (GAD)—An anxiety disorder characterized by daily irrational worry that is often excessive and uncontrolled.

Major depressive disorder—A clinical psychiatric diagnosis of chronic depressed mood that interferes with normal life activities.

Mania—Physiological state of hyperactivity experienced by patients with certain psychiatric illnesses and involving inappropriate elevated mood, pressured speech, poor judgment, and sometimes psychotic episodes superimposed on the state of mania.

Monoamine oxidase inhibitors (MAOIs)—Class of antidepressant medication that affects various kinds of neurotransmitters, including serotonin.

Neuropathic pain—State of pain also known as neurogenic pain that is caused by neurotransmitter signaling in nervous system pain pathways between either the peripheral nervous system or the spinal cord and the brain.

Neurotransmitter—A chemical messenger that travels through the body and acts in the nervous

system. Neurotransmitter signaling is responsible for a wide range of bodily processes and is often the target of medications involving the brain and cardiovascular system.

Neurotransmitter receptor—A physical recipient for chemicals called neurotransmitters. Receptors sit on the surface of cells that make up body tissues; once bound to the neurotransmitter, they initiate the chemical signaling pathway associated with neurotransmitters.

Selective serotonin norepinephrine reuptake inhibitors (SNRI)—Drug class that acts to specifically inhibit the reuptake of serotonin and norepinephrine in the neuronal synapse with little effect on other types of neurotransmitters, thereby decreasing side effects associated with broader-acting drugs.

Selective serotonin reuptake inhibitors (SSRI)—Drug class that acts to specifically inhibit the reuptake of serotonin only in the neuronal synapse with little effect on other types of neurotransmitters, thereby decreasing side effects associated with broader-acting drugs.

Serotonin—A type of neurotransmitter involved in regulation of the blood vessels, brain processes, and disease states such as depression.

Serotonin syndrome—A potentially life-threatening drug reaction involving an excess of the neurotransmitter serotonin, usually occurring when too many medications that increase serotonin are taken together, such as antimigraine triptans and certain antidepressants.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

Side effects

SNRIs are known for having fewer side effects than other types of older antidepressant medications, which is one reason why they tend to be the drug of choice in treatment of depression. However, as with all medications, SNRIs such as duloxetine do have side effects. Sensitivity to duloxetine varies among patients, and some patients may find lower doses are more than their body systems can tolerate. Common side effects of duloxetine include nausea, headache, dizziness, constipation, sexual dysfunction, diarrhea, sweating, dry mouth, shakiness, tremor, loss of appetite, weight changes, hot flashes,

elevated blood pressure, yawning, anxiety, and insomnia. Rare but serious potential side effects include mania, worsened depression and suicidality, seizures, serotonin syndrome, discontinuation syndrome, electrolyte imbalances, urinary retention, skin reactions, abnormal bleeding, liver damage, and glaucoma.

Interactions

Patients should make their doctor aware of all medications and supplements they are taking before using duloxetine.

Drugs

SNRIs such as duloxetine should not be used at the same time as other medications that increase levels of serotonin. Antidepressants called selective serotonin reuptake inhibitors (SRIs) function similarly to duloxetine and should not be used concurrently due to additive effects. Antidepressants called monoamine oxidase inhibitors (MAOIs) also increase levels of serotonin and cannot be used concurrently with duloxetine. Switching drug treatment for an individual patient from an MAOI to duloxetine may require a waiting period of up to two weeks between drugs. Switching from duloxetine to an MAOI may require a waiting period of up to five weeks' duration.

Another example of a medication that has additive serotonin effects with duloxetine is **sumatriptan** (Imitrex). The combination of an SNRI and sumatriptan may produce undesirable additive effects or overdose. Other drugs that cannot be combined with duloxetine due to risk of serotonin syndrome are the antipsychotics chlorpromazine and fluphenazine.

Duloxetine may inhibit the metabolism of heart drugs known as beta-blockers (e.g., **propranolol**), causing increased toxic levels in the blood. Other drugs may cause toxicity when used with duloxetine, either through additive effects or through inhibition of duloxetine metabolism, causing toxic levels of duloxetine in the blood. Drugs that may cause toxicity with duloxetine include:

- diuretics (water pills), such as **hydrochlorothiazide**
- diet pills, such as sibutramine (Meridia)
- the heart drug amiodarone
- certain antibiotics, such as **ciprofloxacin** and **linezolid**
- mood stabilizers, such as lithium
- antipsychotics, such as **haloperidol** and **clozapine**
- certain antiseizure drugs, such as **phenytoin**

There is increased risk of internal bleeding when duloxetine is used with anticoagulant drugs such as **aspirin** or **warfarin**. Duloxetine cannot be combined with the antipsychotic medications pimozide (Orap) or thioridazine (Mellaril) due to dangerous cardiac complications.

Herbs and supplements

The herbal supplements yohimbe and St. John's wort may increase the risk of serotonin syndrome.

The risk of bleeding is increased with large doses of the herbal supplements red clover, pimozide, feverfew, and concentrated green tea.

Food and other substances

Using alcohol while taking duloxetine may create toxic reactions in the body and should be avoided.

Caffeine may impact the metabolism of duloxetine and cause a toxic buildup.

Resources

BOOKS

Brunton, Laurence L., et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill Medical, 2011.

Stargrove, Mitchell Bebel, et al. *Herb, Nutrient, and Drug Interactions: Clinical Implications and Therapeutic Strategies*. St. Louis: Mosby, 2007.

PERIODICALS

Mahmoudi-Gharaei, J., et al. "Duloxetine in the Treatment of Adolescents with Attention Deficit/Hyperactivity Disorder: An Open-Label Study." *Human Psychopharmacology* 26, no. 2 (2011): 155–60.

OTHER

U.S. Food and Drug Administration. "Highlights of Prescribing Information (Cymbalta)." http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021427s037s0421bl.pdf (accessed February 24, 2015).

U.S. Food and Drug Administration. "Medication Guide: Cymbalta." <http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088579.pdf> (accessed February 24, 2015).

WEBSITES

AHFS Consumer Medication Information. "Duloxetine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a604030.html> (accessed February 24, 2015).

Micromedex. "Duloxetine." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/duloxetine-oral-route/description/drg-20067247> (accessed February 24, 2015).

U.S. Food and Drug Administration. "Antidepressant Use in Children, Adolescents, and Adults." <http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm096273.htm> (accessed February 24, 2015).

U.S. Food and Drug Administration. "Information for Healthcare Professionals: Duloxetine (Marketed as Cymbalta)—Selective Serotonin Reuptake Inhibitors (SSRIs) or Selective Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) and 5-Hydroxytryptamine Receptor Agonists (Tryptans)." <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124915.htm> (accessed February 24, 2015).

ORGANIZATIONS

American College of Neuropsychopharmacology, 5034-A Thoroughbred Lane, Brentwood, TN 37027, (615) 324-2360, Fax: (615) 523-1715, acnp@acnp.org, <http://www.acnp.org/default.aspx>.

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Fax: (703) 684-5968, <http://www1.nmha.org/>.
National Institute of Mental Health (NIMH), 6001 Executive
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Maria Eve Basile, PhD

REVIEWED BY JAMES E. WAUN, MD, RPh

DuoNeb see **Albuterol/ipratropium**

Duragesic see **Fentanyl**

Dutasteride

Definition

Dutasteride is a drug used to treat men with enlarged prostate glands. The drug inhibits the conversion of testosterone to dihydrotestosterone (DHT), the androgen hormone that is primarily responsible for development and growth of the prostate gland. Dutasteride acts by binding with an enzyme called 5-alpha-reductase, which is responsible for the conversion to DHT. In long-term use, dutasteride can reduce DHT levels by more than 90%, thus slowing prostate growth.

Purpose

Dutasteride is used to slow or cease prostate enlargement in men. According to the U.S. Agency for Healthcare Research and Quality, more than half of men over age 60 and about 80% of men at age 80 have enlarged but noncancerous prostates, called benign prostate hyperplasia (BPH). There are a number of treatments for BPH, ranging from lifestyle changes such as reducing fluid intake and avoiding caffeinated and alcoholic beverages, both of which have diuretic properties, to surgery. Dutasteride inhibits prostate growth but only rarely causes prostate shrinkage, so it is primarily useful for the treatment of only moderately enlarged prostates.

Off-label use

Dutasteride has been studied for treatment of androgenetic baldness (male pattern) in both men and women. Although some reports indicate that the drug is



Avodart (dutasteride), 0.5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved)

effective, the nature of potential adverse effects (the increased rate of prostate cancer in males and fetal abnormalities in females) raises questions about the use of this drug for a nonmedical purpose.

Description

The prostate gland is located directly below the bladder in males. It has been described as the size of a small kiwi fruit or a large walnut. During the male orgasm, the prostate releases fluid into the urethra, where it acts as a carrier for sperm. As men age, it is common for the prostate to enlarge, but sometimes this enlargement results in troublesome symptoms. The enlargement of the prostate constricts the urethra, which reduces the flow of urine. Symptoms of BPH include frequent urination, straining to urinate, a weak urine stream, and a sensation that the bladder has not completely emptied. If left untreated, BPH can block the flow of urine so that the urine backs up to the point of causing bladder and kidney damage.

Dutasteride is sold as a yellow, soft-gelatin capsule containing 0.5 milligrams (mg) of the drug.

U.S. brand names

Dutasteride is marketed by GlaxoSmithKline LLC under the brand name Avodart. The capsules have the imprint GX CE2. The drug is not available as a generic.

KEY TERMS

Androgens—Male sex hormones.

Benign—Noncancerous. A benign tumor is a growth that does not invade surrounding tissue or spread to other parts of the body.

Benign prostate hyperplasia (BPH)—A noncancerous swelling of the prostate.

Diuretic—A medication or substance that increases urine excretion and removes water and salt from the body.

Enzyme—A substance produced by a living organism that speeds up a specific chemical reaction.

Hyperplasia—The enlargement of an organ or tissue due to an increase in its cellular growth rate.

Prostate-specific antigen (PSA)—A protein made by the cells of the prostate that is increased by both BPH and prostate cancer.

Testosterone—A steroid hormone, one of the androgens. Testosterone is produced primarily in the testes but also in the adrenal gland and ovaries.

Urethra—The tube that carries urine from the bladder to outside the body.

Canadian brand names

Dutasteride is sold in Canada as Avodart.

International brand names

The name Avodart appears to be in use over most of the world.

Recommended dosage

The normal dose is one capsule daily. Dutasteride is routinely used in combination with **tamsulosin**, a muscle relaxant that relaxes the muscles in the prostate and bladder neck, making it easier to urinate.

Precautions

Before starting treatment with dutasteride, a complete examination should be made to determine the cause of the prostate enlargement and rule out prostate cancer. After three months of treatment, a prostate-specific antigen (PSA) level should be taken and used as the baseline for future monitoring. PSA is a protein that is elevated in people with BPH and prostate cancer. Any increase in PSA from this baseline may be a sign of

prostate cancer. It is possible to have both prostate cancer and BPH at the same time.

Men being treated with dutasteride should not donate blood until at least six months after taking their last dose. The purpose of this delay is to prevent administration of dutasteride to a pregnant female recipient by transfusion.

Pediatric

Dutasteride should not be used in pediatric patients.

Pregnant or breastfeeding

Dutasteride should never be used by pregnant or breastfeeding women. The capsules should not even be handled by a woman who is pregnant or who could become pregnant. Dutasteride is absorbed through the skin and could result in unintended fetal exposure. If a woman who is pregnant or who could become pregnant comes in contact with leaking dutasteride capsules, the contact area should be washed immediately with soap and water.

Side effects

In general, dutasteride is well tolerated, but it does cause impairment of sexual function in some patients. The most common adverse reactions seen in studies are impotence, decreased libido, breast disorders (including breast enlargement and tenderness), and ejaculation disorders. The rate of adverse effects is lower in men taking dutasteride alone than in men taking both dutasteride and tamsulosin. According to one 2014 review of studies, these side effects go away with continued use of the drug.

There have been some instances of allergic reactions, ranging from a mild rash and itching to serious skin reactions. Male breast cancer has been reported, and some patients have complained of emotional depression. There have also been complaints of pain and testicular swelling.

Interactions

Dutasteride does not have any clinically significant interactions with drugs or foods.

Resources

PERIODICALS

Bird, S. T., et al. "Male Breast Cancer and 5 α -reductase Inhibitors Finasteride and Dutasteride." *Journal of Urology* 190, no. 5 (2013): 1811–14.

Klotz, L., et al. "Effect of Dutasteride in Men Receiving Intermittent Androgen Ablation Therapy: The AVIAS

Trial.” *Canadian Urological Association Journal* 8, nos. 11–12 (2014): E789–94.

Levy, L. L., and J. J. Emer. “Female Pattern Alopecia: Current Perspectives.” *International Journal of Women’s Health* 5 (August 2013): 541–56.

Loke, Y. K., et al. “Systematic Review Evaluating Cardiovascular Events of the 5-Alpha Reductase Inhibitor Dutasteride.” *Journal of Clinical Pharmacy and Therapeutics* 38, no. 5 (2013): 405–15.

Traish, A. M., A. Mulgaonkar, and N. Giordano. “The Dark Side of 5 α -reductase Inhibitors’ Therapy: Sexual Dysfunction, High Gleason Grade Prostate Cancer and Depression.” *Korean Journal of Urology* 55, no. 6 (2014): 367–79.

von Wahlde, M. K., et al. “The Anti-Androgen Drug Dutasteride Renders Triple Negative Breast Cancer Cells More Sensitive to Chemotherapy via Inhibition of HIF-1 α -/VEGF-Signaling.” *Gynecological Endocrinology* 31, no. 2 (2015): 160–64.

Yim, E., K. L. Nole, and A. Tosti. “5 α -Reductase Inhibitors in Androgenetic Alopecia.” *Current Opinion in Endocrinology, Diabetes, and Obesity* 21, no. 6 (2014): 493–98.

OTHER

GlaxoSmithKline. “Highlights of Prescribing Information—Avodart.” <https://www.gsksource.com/gskprm/htdocs/documents/AVODART-PI-PIL.PDF> (accessed February 28, 2015).

WEBSITES

DailyMed. “Avodart—Dutasteride Capsule, Liquid Filled.” U.S. National Library of Medicine, National Institutes of Health. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=dc330e70-a1d3-400b-3aaf-46067e3fd090> (accessed February 28, 2015).

“Dutasteride.” Drugs.com. <http://www.drugs.com/international/dutasteride.html> (accessed February 28, 2015).

Mayo Clinic staff. “Dutasteride (Oral Route).” MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/dutasteride-oral-route/description/drg-20063575> (accessed February 28, 2015).

McCullough, Marie. “Avodart May Promote Some Tumor Growth.” *Inquirer*, April 1, 2010. http://www.philly.com/philly/health/20100401_Avodart_may_promote_some_tumor_growth.html (accessed February 28, 2015).

U.S. Food and Drug Administration. “Avodart (Dutasteride) Soft Gelatin Capsules.” <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm218858.htm> (accessed February 28, 2015).

ORGANIZATIONS

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E

Efavirenz/emtricitabine/tenofovir

Definition

Efavirenz/emtricitabine/tenofovir is a fixed combination antiretroviral that may be used alone as a complete regimen for human immunodeficiency virus (HIV), the virus that causes acquired immune deficiency syndrome (AIDS). There is no current treatment that can cure AIDS and no single drug that is effective against the virus for a prolonged period. Although single agents may stop the progression of the disease for some time, the virus is known to mutate rapidly and develop drug resistance. Combinations of three or more drugs have been shown to have prolonged benefit.

Purpose

Efavirenz/emtricitabine/tenofovir tablets are indicated for the treatment of HIV disease. They may be used alone or in combination with other antiretroviral agents.

Description

Efavirenz/emtricitabine/tenofovir is a combination of three drugs. Emtricitabine (Emtriva) and tenofovir (Viread) are classified as nucleoside reverse transcriptase inhibitors (NRTIs); efavirenz (Sustiva) is a non-nucleoside reverse transcriptase inhibitor (NNRTI). Each tablet contains 600 milligrams (mg) of efavirenz, 200 mg of emtricitabine, and 300 mg of tenofovir.

The three drugs included in Atripla all act against reverse transcriptase, an enzyme that is essential for the reproduction of the virus. If reverse transcriptase can be inactivated, the virus cannot reproduce, and while this is far from a cure, it has resulted in longer survival times for people living with HIV infection.

Although all three drugs act on the same part of the viral reproduction cycle, they do so in different ways,

making it more difficult for the virus to mutate and develop resistance. If viral reproduction can be stopped, this may be sufficient to reduce the severity of the infection and perhaps increase the number of T cells, which are white blood cells that support the immune system and that are affected by HIV infection. This in turn may reduce the risk or frequency of developing other opportunistic infections.

U.S. brand names

Efavirenz/emtricitabine/tenofovir is marketed as Atripla.

Recommended dosage

For adults and adolescents aged 12 and older and with a body weight of at least 40 kilograms (88 pounds), the dose of efavirenz/emtricitabine/tenofovir is one tablet once daily taken orally on an empty stomach. Dosing at bedtime may improve the tolerability of nervous system symptoms. The combination may be used alone or in conjunction with other antiretroviral agents as appropriate.

The issue of when to initiate treatment for HIV disease is uncertain, and HIV specialists may recommend waiting until a specific T-cell count is reached or some other marker before starting drug therapy. Even so, it is generally recommended that drug treatment not be started if any of the following circumstances are present:

- severe symptoms of HIV disease
- development of an opportunistic infection (such as AIDS)
- T-cell count of 350 cells/mm³ or less
- pregnancy
- development of HIV-related kidney disease

Because this is a fixed combination product, it is unsuited for patients who require special dose adjustments.



Atripla (efavirenz/emtricitabine/tenofovir, 600 mg/200 mg/300 mg). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Precautions

The package carries a boxed warning declaring the risk of lactic acid buildup (lactic acidosis) and severe liver enlargement (hepatomegaly) with fatty accumulations in the liver (steatosis), along with post-treatment exacerbation of hepatitis B. These severe reactions have been reported with tenofovir, which is a component of Atripla. At the same time, severe worsening of hepatitis B infections has been reported after patients discontinued the use of emtricitabine and tenofovir. Liver function should be routinely monitored in patients taking this drug, and treatment for hepatitis B should be considered if the infection is present.

Kidney function tests should be conducted before and during treatment with this drug since kidney impairment, including severe kidney damage, has been reported with tenofovir.

Serious psychiatric adverse experiences have been reported in some patients treated with efavirenz. These include depression, suicidal thoughts, aggressive behavior, paranoid reactions, and manic reactions.

Pregnant or breastfeeding

Efavirenz/emtricitabine/tenofovir is in pregnancy category D. Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. There are no adequate and well-controlled studies of the combination drug in pregnant women, so

it should be used only when the potential benefit justifies the potential risk to the fetus. In animal studies, efavirenz was seen to cause failure of development of the fetal brain. Women should be tested for pregnancy prior to starting this drug and are advised to use barrier contraception in addition to other forms of birth control.

The U.S. Centers for Disease Control and Prevention (CDC) recommend that women infected with HIV-1 not breastfeed their infants in order to avoid risking postnatal transmission of HIV-1.

Other conditions and allergies

Efavirenz/emtricitabine/tenofovir should not be given to patients who are allergic to any of the components, either the drugs or inactive ingredients.

Side effects

Because efavirenz/emtricitabine/tenofovir is a fixed combination of three drugs, the list of reported adverse effects is exceptionally large. It is difficult to determine whether all of the reported adverse effects are directly related to the drugs or are caused by other factors.

Nervous system symptoms include insomnia, impaired concentration, drowsiness, strange dreams, and hallucinations. Other, less frequent reports have included amnesia and depersonalization. In controlled studies, these adverse effects began shortly after starting treatment but resolved themselves after two to four weeks.

Rash, including severe skin reactions, has been reported. Mild rashes commonly appear after 10–14 days of treatment but often spontaneously resolve after a month.

Convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures.

Pediatric

Rash seems to be more common in younger patients and appears earlier. Administration of antihistamines before starting this product should be considered, particularly in pediatric patients.

Interactions

Because of the risk of drug interactions, individuals should be sure that their healthcare provider is aware of all other drugs they are currently taking, including over-the-counter drugs and supplements.

Drugs

The list of drug interactions with efavirenz/emtricitabine/tenofovir is unusually long and includes many

KEY TERMS

Acquired immune deficiency syndrome (AIDS)—HIV infection that has led to certain opportunistic infections, cancers, or a T blood cell count lower than 200/mL.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Depersonalization—A dissociative symptom in which a patient feels that his or her body is unreal, is changing, or is dissolving.

Hepatomegaly—Enlargement of the liver beyond normal size. This is a symptom of a large number of conditions including cancer and several types of infections.

Human immunodeficiency virus—The virus that causes acquired immune deficiency syndrome (AIDS).

Lactic acidosis—Buildup of lactic acid in the blood faster than it can be removed. While this condition may be caused by intense exercise, it is also seen in HIV disease, cancer, kidney failure, respiratory failure, and infections. Common symptoms are nausea and weakness.

Manic—The condition of showing wild and apparently deranged excitement and energy.

Non-nucleoside reverse transcriptase inhibitors—A class of antiretroviral drugs that work by inhibiting reverse transcriptase.

Opportunistic infection—An infection that is normally mild in a healthy individual, but that takes advantage of an ill person's weakened immune system to move into the body, grow, spread, and cause serious illness.

Resistance—The ability of infectious agents such as viruses to change their biochemistry in such a way that renders drug treatments no longer effective.

Reverse transcriptase—An enzyme that is essential to the reproduction of HIV cells.

Steatosis—Fatty accumulations in the liver.

T cells—White blood cells that originate in the thymus gland. T cells regulate the immune system's response to infections, including HIV. CD4 lymphocytes are a subset of T lymphocytes.

drugs, including other antiretroviral and anti-infective agents that may be needed for treatment. In these cases, dose adjustments may be possible. More than 300 drugs have been identified as having significant or serious interactions. Individuals should consult with their healthcare provider regarding possible interactions.

Herbs and supplements

A number of herbs and supplements have been identified as interacting with efavirenz/emtricitabine/tenofovir, including black cohosh and dehydroepiandrosterone (DHEA).

Food and other substances

Grapefruit and grapefruit juice may interact with efavirenz/emtricitabine/tenofovir. Marijuana may also adversely interact with the drug.

Resources

PERIODICALS

- Gianotti, N., et al. "Number of Daily Pills, Dosing Schedule, Self-Reported Adherence and Health Status in 2010: A Large Cross-Sectional Study of HIV-Infected Patients on Antiretroviral Therapy." *HIV Medicine* 14, no. 3 (2013): 153–60.
- Jackson, A., et al. "Tenofovir, Emtricitabine Intracellular and Plasma, and Efavirenz Plasma Concentration Decay Following Drug Intake Cessation: Implications for HIV Treatment and Prevention." *Journal of Acquired Immune Deficiency Syndromes* 62, no. 3 (2013): 275–81.
- Juday, T, et al. "Cost-Effectiveness of the Once-Daily Efavirenz/Emtricitabine/Tenofovir Tablet Compared with the Once-Daily Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Tablet as First-Line Antiretroviral Therapy in HIV-Infected Adults in the U.S." *ClinicoEconomics Outcomes Research* 5 (September 2, 2013): 437–45. <http://dx.doi.org/10.2147/CEOR.S47486> (accessed March 3, 2015).
- Langebeek, N., et al. "Predictors and Correlates of Adherence to Combination Antiretroviral Therapy (ART) for Chronic HIV Infection: A Meta-Analysis." *BMC Medicine* 12 (August 21, 2014): 142. <http://dx.doi.org/10.1186/s12916-014-0142-1> (accessed March 3, 2015).
- Mocroft, A., et al. "A Survey of ATRIPLA Use in Clinical Practice as First-Line Therapy in HIV-Positive Persons in Europe." *Infection* 42, no. 4 (2014): 757–62.
- Permpalung, N., et al. "Treatment of HIV Infection with Once-Daily Regimens." *Expert Opinion Pharmacotherapy* 13, no. 16 (2012): 2301–17.
- Pistone, G., et al. "Cutaneous Adverse Reactions to Highly Antiretroviral Therapy in HIV-Positive Patients." *Case Reports in Dermatology* 6, no. 2 (2014): 145–49.
- Qayyum, S., et al. "Combination Therapy Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate Associated with Hepatic Failure." *Current Drug Safety* 7, no. 5 (2012): 391–93.

Trottier, B., et al. "Tolerability Is More Important than Simplicity for Treatment Durability." *Journal of the International AIDS Society* 17, suppl. 3 (2014): 19765.

WEBSITES

- Bristol-Myers Squibb Company. "Atripla." <http://www.atrila.com/index.aspx> (accessed January 25, 2015).
- U.S. Department of Health and Human Services. "Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate." AIDSinfo.gov. <http://aidsinfo.nih.gov/drugs/424/atrila/0/professional> (accessed March 3, 2015).
- U.S. Department of Health and Human Services. "Reasons to Start Treatment." AIDS.gov. <http://www.aids.gov/hiv-aids-basics/just-diagnosed-with-hiv-aids/treatment-options/reasons-to-start-treatment/index.html> (accessed January 25, 2015).
- U.S. National Library of Medicine. "Label: ATRIPLA—Efavirenz, Emtricitabine and Tenofovir Disoproxil Fumarate Tablet, Film Coated." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2e97aa6d-09f7-46df-9499-63db7e9bac35> (accessed January 25, 2015).
- U.S. National Library of Medicine. "Retroviruses." National Center for Biotechnology Information. <http://www.ncbi.nlm.nih.gov/books/NBK19424> (accessed January 25, 2015).

ORGANIZATIONS

- American Academy of HIV Medicine, 1705 DeSales Street NW, Suite 700, Washington, DC 20036, (202) 659-0699, Fax: (202) 659-0976, <http://www.aahivm.org/>.
- amfAR (Foundation for AIDS Research), 120 Wall Street, 13th Floor, New York, NY 10005-3908, (212) 806-1600, Fax: (212) 806-1601, <http://www.amfar.org/>.
- San Francisco AIDS Foundation, 1035 Market Street, Suite 400, San Francisco, CA 94103, (415) 581-7077, (866) 245-3424, info@aidslifecycle.org, <http://sfaf.org/>.

Samuel D. Uretsky, PharmD

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Effexor see **Venlafaxine**

Effient see **Prasugrel**

Efudex see **Fluorouracil**

Elavil see **Amitriptyline**

Elidel see **Pimecrolimus**

Emtricitabine/efavirenz/tenofovir see
Efavirenz/emtricitabine/tenofovir

Purpose

The basic role of ACE inhibitors such as enalapril is to lower blood pressure, but they are used as part of the routine treatment of a number of conditions where lowering blood pressure or the work of the heart may keep the condition from getting worse. These conditions include coronary artery disease, heart failure, diabetes, chronic kidney diseases, heart attacks, scleroderma, and migraine headaches.

The 2014 guidelines for the management of high blood pressure (hypertension) in adults, as advised by the Eighth Joint National Committee (JNC), recommends starting drug treatment to lower blood pressure for the following patients:

- patients 60 years and older with systolic blood pressure 150 mm Hg or higher or diastolic blood pressure 90 mm Hg or higher
- patients younger than 60 years with systolic blood pressure 140 mm Hg or higher or diastolic blood pressure 90 mm Hg or higher
- patients 18 years and older with diabetes and systolic blood pressure 140 mm Hg or higher or diastolic blood pressure 90 mm Hg or higher
- patients 18 years and older with chronic kidney disease and systolic blood pressure 140 mm Hg or higher or diastolic blood pressure 90 mm Hg or higher



Enalapril maleate, 10 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Enalapril

Definition

Enalapril is a drug that lowers blood pressure. It is an angiotensin-converting enzyme (ACE) inhibitor.

In patients with chronic kidney diseases, ACE inhibitors should be part of the initial treatment, since they have shown to delay the progression of kidney diseases. However, there is a type of hypertension called low-renin hypertension that is seen more often in the elderly and patients of African descent. These patients should be started on a thiazide-type diuretic or a calcium channel blocking agent rather than an ACE inhibitor.

Description

Enalapril lowers blood pressure due to its action on the renin-angiotensin-aldosterone system (RAAS). RAAS is a complex of enzymes and hormones that raise blood pressure by different mechanisms. Low blood pressure causes the kidneys to release the enzyme renin, which splits the protein angiotensinogen to form angiotensin I. Angiotensin I is a mild vasoconstrictor (a substance that causes the blood vessels to tighten or constrict). When the blood vessels tighten, the heart has to work harder to supply blood to the rest of the body. When angiotensin I comes into contact with angiotensin-converting enzyme, angiotensin I is converted to angiotensin II, a far more potent vasoconstrictor. Enalapril and other ACE inhibitors block this conversion to angiotensin II to help keep the blood pressure down.

In addition to this action, angiotensin II stimulates the release of aldosterone from the adrenal gland. The role of aldosterone is to regulate the ratio of water and electrolytes (such as sodium and potassium); this sometimes causes water retention. Since aldosterone has the effect of increasing total blood volume, it is also a potential cause of high blood pressure. Enalapril is often combined with a diuretic, a drug that increases urine output, to counteract this effect. Angiotensin II also stimulates the secretion of the water-retaining hormone vasopressin (also called AVP) in the pituitary gland as well as the release of adrenaline and noradrenaline, both of which cause additional vasoconstriction and increase the heart rate. This results in more blood pumped through constricted arteries, increasing the blood pressure. An ACE inhibitor such as enalapril is administered to help break this cycle.

U.S. brand names

Enalapril is available either as a generic or under the following brand names:

- Vasotec, sold in tablets containing 2.5, 5, 10, and 20 milligrams (mg).
- Epaned, sold as a powder for oral solution.

A generic intravenous (IV) injection of enalaprilat, the active form of the drug, is available at 1.25 mg per milliliter (mL).

Enalapril is also combined with the diuretic **hydrochlorothiazide** either generically or under the brand name Vaseretic in the following combinations: 5 mg/12.5 mg or 10 mg/25 mg (enalapril/hydrochlorothiazide)

The Vasotec tablets vary in shape but are typically imprinted with VASO followed by the strength.

Canadian brand names

Vasotec is sold in Canada.

International brand names

Enalapril is available both by itself and in combination with hydrochlorothiazide as a generic in most of the world. Merck Sharp & Dohme (MSD) uses the brand name Renitec internationally, with some variation—Renitec Compound or Renitec Plus to indicate an enalapril/hydrochlorothiazide compound. Other brand names are used by regional manufacturers.

Recommended dosage

Enalapril requires several weeks to achieve its full effect. Patients should start with a low dose and adjust upward at intervals of one to two weeks, following their healthcare provider's instructions. After a single oral dose of enalapril, the drug reaches a peak level in the bloodstream in about an hour. However, it may take an additional 2 hours before enalapril is converted to its active form. The half-life of a dose (the length of time it takes for half of the dose to be removed from the body) is about 11 hours. A single dose may remain active for over 24 hours.

Adults

HYPERTENSION (ORAL). The starting dose is 2.5 to 5 mg daily, increased as needed to 10–40 mg daily, taken either once a day or in two divided doses.

HYPERTENSION (IV). The IV is started at 1.25 mg/dose over five minutes every six hours. Doses up to 5 mg/dose have been administered.

LEFT VENTRICULAR DYSFUNCTION. Doses are started at 2.5 mg every 12 hours. The dose may be gradually increased up to 20 mg/day.

CONGESTIVE HEART FAILURE (ORAL). The starting dose is 2.5 mg once or twice daily. The dose may be increased at two-week intervals to 5–40 mg/day.

KEY TERMS

Aldosterone—A hormone produced in the cortex of the adrenal gland that increases the reabsorption of sodium and water and the release of potassium in the kidneys.

Blood pressure—The pressure of circulating blood on the walls of blood vessels. If blood pressure is too high, it can lead to heart attacks, strokes, and damage to vital organs such as the kidneys. Low blood pressure can lead to dizziness and fainting.

Diastolic blood pressure—Pressure when the heart relaxes.

Diuretic—A drug designed to encourage excretion of urine in people who accumulate excess fluid such as individuals with high blood pressure or heart conditions.

Hypertension—High blood pressure.

Metabolize—The change of a chemical from one form to another, most often in the liver. Drugs that are taken in an inactive form but are metabolized to an active form, such as enalapril, are known as prodrugs.

mm HG—Millimeters of mercury; based on the old-fashioned method of measuring blood pressure by seeing how much pressure would raise a column of mercury, the liquid metal also found in thermometers, in a tube. Although the mercury has mostly been replaced by electronic measurements, the unit of millimeters of mercury remains in use.

Scleroderma—One of the autoimmune diseases, a progressive hardening of body tissues, most commonly the skin.

Systolic blood pressure—Pressure when the heart contracts.

Vasoconstriction—Constriction of a blood vessel.

CONGESTIVE HEART FAILURE (IV). Approximately 1.25 to 5 mg is administered every six hours. Intravenous dosing should not be used in cases of unstable heart failure or acute heart attack.

KIDNEY DISEASE. Dosing in patients with kidney disease is based on creatinine clearance (CrCl) levels, which indicate the degree of kidney impairment by measuring how much creatinine is present in the blood.

Creatinine is a waste product that is typically cleared by the kidneys through the urine, so high blood levels indicate reduced kidney function.

Oral:

- CrCl levels of less than 30 mL/min: Doses start at 2.5 mg and should not exceed 40 mg.
- CrCl levels greater than or equal to 30 mL/min: Doses start at 5 mg/day. Dosing may be adjusted but should not exceed 40 mg/day.
- For patients on dialysis: 2.5 mg is administered on the day of dialysis. The dose is adjusted on non-dialysis days according to blood pressure levels.

Intravenous dosing:

- CrCl levels of less than 30 mL/min: The IV is started at 0.625 mg every six hours and is adjusted based on patient response.
- CrCl greater than or equal to 30 mL/min: The IV is started at 1.25 mg every six hours and is adjusted based on response.

Pediatric

The following dosage recommendations are used in children 1 month to 16 years:

- Oral doses are started at 0.08 mg per kilogram (kg, or 2.2 lb.) of body weight each day, either as a single dose or divided into two doses given every 12 hours. The total dose should not exceed 5 mg/day. The dose may then be increased as needed at two-week intervals per the healthcare provider's instructions, with the maximum dose not to exceed 0.58 mg/kg/day (or 40 mg/day).
- Intravenous doses are started at 0.01 to 0.02 mg/kg/day, divided into two doses set 12 hours apart.
- In a hypertensive crisis, 0.05 to 0.1 mg/kg may be administered intravenously with a syringe.

Precautions

Enalapril may cause angioedema, a type of allergic reaction marked by facial swelling. Because angioedema can affect the ability to breathe, it is a potentially serious condition.

Pediatric

The injection contains benzyl alcohol as a preservative. This substance has been linked to gasping syndrome, characterized by trouble breathing and central nervous system depression. The condition is potentially fatal in premature infants but is rarely seen since physicians are aware of the risk.

Geriatric

Elderly patients with elevated blood pressure levels may have low-renin hypertension, which is less responsive to ACE inhibitors than to diuretics.

Pregnant or breastfeeding

The manufacturer's package insert contains a boxed warning that enalapril should be discontinued if pregnancy is detected. Use of the drug during pregnancy may cause oligohydramnios, a condition in which there is not enough amniotic fluid surrounding the fetus, causing fetal injury or death. The risk is especially high if the drug is used after the first trimester.

Other conditions and allergies

Persons of African descent may be more likely than people of other races to have low-renin hypertension. Although patients with this type of hypertension will respond to ACE inhibitors, the response will be limited. Thiazide diuretics are the first choice for treating low-renin hypertension.

Side effects

Enalapril is relatively free of adverse effects compared to most drugs. It can cause hypotension (low blood pressure), particularly when used in combination with a diuretic. This can usually be prevented by starting with a low dose and increasing the dose slowly, usually at one- to two-week intervals.

Other adverse effects include hyperkalemia (elevated potassium in the blood). This risk is increased in patients with kidney problems or diabetes, or patients who are taking other drugs that might elevate potassium levels.

Less severe and less frequent side effects include the development of a dry cough, headache, chest pain, or a rash.

Interactions

Individuals should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs or supplements, before starting treatment with enalapril.

Drugs

The main interactions of enalapril are with other drugs that act in a similar manner. It is specifically contraindicated in combination with aliskiren (Tekturna), which is a renin inhibitor, and with AT-1 inhibitors. The AT-1 inhibitors can generally be recognized because

their names end in "sartan": "azilsartan," "candesartan," "eprosartan," "losartan" and others.

Use of **allopurinol** should be avoided. Although the mechanism of this interaction is unknown, concurrent use appears to increase the risk of allergic reactions to enalapril. There are a large number of other interacting drugs that may require dose adjustments of one or the other drug.

People with hypertension who are already taking diuretics should discontinue the diuretic for two days before starting treatment with enalapril.

Food and other substances

Enalapril should be taken on an empty stomach, because the presence of food in the stomach may reduce its absorption by 30%–40%.

Resources

PERIODICALS

- Bahm, M., et al. "Effect of Comorbidities on Outcomes and Angiotensin Converting Enzyme Inhibitor Effects in Patients with Predominantly Left Ventricular Dysfunction and Heart Failure." *European Journal of Heart Failure* 16, no. 3 (2014): 325–33.
- De Ciuceis, C, et al. "Effect of Antihypertensive Treatment on Microvascular Structure, Central Blood Pressure and Oxidative Stress in Patients with Mild Essential Hypertension." *Journal of Hypertension* 32, no. 3 (2014): 565–74.
- James, P. A., et al. "2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)." *JAMA* 311, no. 5 (2014): 507–20.
- Lindle, K. A., et al. "Angiotensin-Converting Enzyme Inhibitor Nephrotoxicity in Neonates with Cardiac Disease." *Pediatric Cardiology* 35, no. 4 (2014): 499–506.
- Nedogoda, S. V., et al. "Randomized Trial of Perindopril, Enalapril, Losartan and Telmisartan in Overweight or Obese Patients with Hypertension." *Clinical Drug Investigation* 33, no. 8 (2013): 553–61.
- Robiner, W. N., et al. "Adherence and Renal Biopsy Feasibility in the Renin Angiotensin-System Study (RASS) Primary Prevention Diabetes Trial." *Diabetes Research and Clinical Practice* 102, no. 1 (2013): 25–34.
- Russo, A., et al. "Enalapril-Induced Acute Kidney Injury in Neonates." *Journal of Neonatal-Perinatal Medicine* 6, no. 2 (2013): 179–81.

OTHER

- Merck & Co. "Center for Drug Evaluation and Research Approval Package: Vaseretic." http://www.drugbank.ca/system/fda_labels/DB00584.pdf?1265922813 (accessed December 23, 2014).
- U.S. Food and Drug Administration. "Vasotec Proposed Labeling." http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/018998s0761bl.pdf (accessed December 23, 2014).

WEBSITES

A.D.A.M. Medical Encyclopedia. "Creatinine Clearance Test." Available from: <http://www.nlm.nih.gov/medlineplus/ency/article/003611.htm> (accessed December 22, 2014).

AHFS Consumer Medication Information. "Enalapril." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a686022.html> (accessed December 22, 2014).

"Enalapril (International)." Drugs.com. <http://www.drugs.com/international/enalapril.html> (accessed December 23, 2014).

ORGANIZATIONS

National Heart, Lung, and Blood Institute (NHLBI), PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbinfo@nhlbi.org, <http://www.nhlbi.nih.gov/>.

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Enbrel see **Etanercept**

Endocet see **Oxycodone/acetaminophen**

Enoxaparin

Definition

Enoxaparin is an anticoagulant used to prevent or break up blood clots in the circulatory system. It is classified as a low molecular weight heparin (LMWH).

Purpose

Enoxaparin is used to treat and prevent deep vein thrombosis (DVT). This is a condition in which blood clots form inside blood vessels, usually those of the legs. The clots have the potential for breaking loose and causing a pulmonary embolism. It is also used to treat clots forming in other areas and to prevent the formation of clots following some types of surgery or during prolonged bed rest. It is commonly prescribed to patients recovering from hip or knee replacement surgery or abdominal surgery.

Anticoagulants are also used to reduce the risk of clotting in people who have had conditions caused by clots, such as heart attacks, or who have conditions that may predispose them to clots, such as some types of heart arrhythmias. Enoxaparin is routinely used in treatment of a severe type of heart attack known as ST segment elevation myocardial infarction (STEMI). In a STEMI, the coronary artery is completely blocked off, preventing blood from reaching the heart. In these cases,



Enoxaparin (injection). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

LMWHs are used for a few days followed by an oral anticoagulant, but sometimes, enoxaparin or other LMWHs may be used for a longer period. Enoxaparin may also be given in combination with other anticoagulants such as **aspirin**.

Description

Low molecular weight heparins are derived from unfractionated heparin (UHF), a natural anticoagulant. LMWHs have largely replaced unfractionated heparin for most uses, and there are a large number of low molecular weight heparins available worldwide. They are all similar in use but may vary in onset and duration of action, so they cannot be substituted for each other.

Enoxaparin is routinely given either by intravenous (IV, into a vein) or subcutaneous (SC, under the skin) administration. When given subcutaneously, the absorption varies with the size of the dose, and so the onset, peak, and duration of action vary. The onset of action generally occurs 3 to 5 hours after a subcutaneous injection and lasts for 12 hours, although the duration increases when the drug is given in repeated doses. The half-life of a single dose, or the time it takes for the body to eliminate half the dose, is about 4.5 hours, but this increases to around 7 hours with repeated doses.

The solution for subcutaneous injection is available in the following concentrations:

- 30 milligrams (mg) per 0.3 milliliters (mL)

- 40 mg per 0.4 mL
- 60 mg per 0.6 mL
- 80 mg per 0.8 mL
- 100 mg per mL
- 120 mg per 0.8 mL
- 150 mg per mL
- 300 mg/3 mL (single-use vial)

U.S. brand names

Enoxaparin is available as a generic or under the brand name Lovenox.

Canadian brand names

Enoxaparin is also sold as Lovenox in Canada.

International brand names

Enoxaparin is available as a generic in most nations. Sanofi-Winthrop markets the drug as Clexane but also uses the names Lovenox. A number of other brand names are also in use.

Recommended dosage

Dosages of enoxaparin vary depending on the condition being treated:

- DVT prophylaxis (prevention) in abdominal surgery: 40 mg once daily
- DVT prophylaxis in knee replacement surgery: 30 mg every 12 hours
- DVT prophylaxis in hip replacement surgery: 30 mg every 12 hours or 40 mg once daily
- DVT prophylaxis in hospital patients: 40 mg once daily
- inpatient treatment of acute DVT with or without pulmonary embolism: 1 mg per kilogram (kg, or 2.2 lb.) of body weight every 12 hours, or 1.5 mg/kg once daily
- outpatient treatment of acute DVT without pulmonary embolism: 1 mg/kg every 12 hours
- unstable angina and non-Q-wave myocardial infarction (heart attack): 1 mg/kg every 12 hours (with aspirin)
- acute STEMI in patients under 75 years of age: 1 mg/kg every 12 hours

Pediatric

For infants younger than two months, the following dosages are used:

- prophylaxis: 0.75 mg/kg every 12 hours
- treatment: 1.5 mg/kg every 12 hours

For infants and children from 2 months to 18 years, the following dosages are used:

KEY TERMS

Anticoagulant—A drug that keeps blood from clotting.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Coagulation—Blood clotting. This is achieved by the coagulation cascade, a complex series of steps that result in formation of a clot.

Coronary artery—The vessels that carry blood to the heart.

Deep vein thrombosis (DVT)—A clot forming in one of the deeper blood vessels, usually in the legs.

Hematoma—A localized pooling of blood outside the blood vessels; a bruise.

Heparin—An injectable drug that is used to prevent blood clotting. Heparin does not break down clots that have already formed. The term “heparin” normally refers to unfractionated heparin, which has largely been replaced in use by low molecular weight heparin, which is formed by fragmentation of the heparin molecule.

Myocardial infarction—Heart attack.

Prophylaxis—Preventive.

- prophylaxis: 0.5 mg/kg every 12 hours
- treatment: 1 mg/kg every 12 hours

Geriatric

To treat acute STEMI in patients 75 years or older, 0.75 mg/kg is given every 12 hours (with aspirin).

Precautions

Enoxaparin carries a U.S. Food and Drug Administration (FDA) boxed warning that epidural or spinal hematomas may occur in patients taking low molecular weight heparins who receive anesthesia via the central nervous system (such as through a spinal epidural). The risk is increased by the use of indwelling catheters or simultaneous use of other drugs that affect blood clotting. A history of spinal surgery or spinal deformity also increases this risk. These hematomas may cause long-term or even permanent paralysis. In contrast to this warning, however, an extensive review of cases at U.S.

military hospitals reported no increase in frequency of blood clots in patients receiving low molecular weight heparins and epidural anesthesia.

Enoxaparin should be used with great care in the presence of conditions that promote bleeding, such as bacterial endocarditis or gastric ulcers, or shortly after brain, eye, or spinal surgery.

Thrombocytopenia, a deficiency in the number of blood platelets, may occur with enoxaparin use. This has been reported in 1.3% of patients. If a patient's platelet count falls below 100,000/mm³, enoxaparin use should be discontinued.

Pediatric

Enoxaparin multidose vials contain benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal gasping syndrome, though this risk is rare.

Geriatric

The risk of enoxaparin-associated bleeding increases with age. The likeliness of serious adverse reactions increases with age for patients receiving enoxaparin. Dose levels may require modifications due to age-related declines in kidney function.

Pregnant or breastfeeding

Enoxaparin is considered a pregnancy category B drug, which means that although there are no well-controlled studies in pregnant women, animal reproduction studies have failed to demonstrate risk to a fetus.

The manufacturer's package insert states that excretion of enoxaparin into milk is unknown, so use while breastfeeding is not recommended. However, the U.S. National Library of Medicine's LactMed database states that available information, although limited, indicates that doses of enoxaparin up to 40 mg/day do not have adverse effects on breastfed infants.

Side effects

The most important adverse effect associated with enoxaparin is excessive bleeding. This can be corrected with protamine, which is an antidote for heparin overdoses. However, protamine is less effective in neutralizing low molecular weight heparins than it is at neutralizing unfractionated heparin.

Anemia and ecchymosis (bruising caused by escape of blood from the vessels and into the skin) are common. Confusion and nausea occur rarely. Very rarely, disturbances of heart rhythms, heart failure, and

pneumonia have been reported. Other adverse reactions include fever, nausea, and swelling of the limbs (edema).

Interactions

Individuals should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs and supplements, before starting treatment with enoxaparin.

Drugs

Enoxaparin should not be used at the same time as anticoagulants and other drugs that may increase coagulation time unless they are prescribed by a physician, as may be done when transitioning a patient from an injected anticoagulant to one that can be taken by mouth. These include aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), both prescription and over the counter, such as **ibuprofen** and naproxen.

Resources

PERIODICALS

- Caruso, J. D., E. A. Elster, and C. J. Rodriguez. "Epidural Placement Does Not Result in an Increased Incidence of Venous Thromboembolism in Combat-Wounded Patients." *Journal of Trauma and Acute Care Surgery* 77, no. 1 (2014): 61–66.
- Changolkar, A., et al. "Comparison of Injectable Anticoagulants for Thromboprophylaxis after Cancer-Related Surgery." *American Journal of Health-System Pharmacy* 71, no. 7 (2014): 562–69.
- Gritsiouk, Y., et al. "A Retrospective Analysis of the Effectiveness of Low Molecular Weight Heparin for Venous Thromboembolism Prophylaxis in Trauma Patients." *American Journal of Surgery* 207, no. 5 (2014): 648–52.
- Hawes, E. M., and A. J. Viera. "Anticoagulation: Choosing the Optimal Anticoagulant." *FP Essentials* 422 (July 2014): 18–23.
- Levitani, B., et al. "Benefit-Risk Assessment of Rivaroxaban versus Enoxaparin for the Prevention of Venous Thromboembolism after Total Hip or Knee Arthroplasty." *Vascular Health and Risk Management* 10 (March 26, 2014): 157–67.
- Lewis, C. G., et al. "Evaluation of the First-Generation AAOS Clinical Guidelines on the Prophylaxis of Venous Thromboembolic Events in Patients Undergoing Total Joint Arthroplasty: Experience with 3289 Patients from a Single Institution." *Journal of Bone and Joint Surgery (American)* 96, no. 16 (2014): 1327–32.
- Louis, S. G., et al. "Correlation of Missed Doses of Enoxaparin with Increased Incidence of Deep Vein Thrombosis in Trauma and General Surgery Patients." *JAMA Surgery* 149, no. 4 (2014): 365–70.

WEBSITES

AHFS Consumer Medication Information. "Enoxaparin Injection." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601210.html> (accessed March 5, 2015).

"Lovenox Prescribing Information." <http://products.sanofi.us/lovenox/lovenox.html> (accessed March 6, 2015).

Mayo Clinic staff. "Deep Vein Thrombosis (DVT)." Mayo Clinic.org. <http://www.mayoclinic.org/diseases-conditions/deep-vein-thrombosis/basics/definition/con-20031922> (accessed March 6, 2015).

U.S. Food and Drug Administration. "Low Molecular Weight Heparins: Drug Safety Communication - Recommendations to Decrease Risk of Spinal Column Bleeding and Paralysis." <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm373918.htm> (accessed March 6, 2015).

U.S. National Library of Medicine. "Enoxaparin Sodium—Enoxaparin Sodium Injection." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3e6bf2b3-9339-4104-bda3-ad86a1949703> (accessed March 6, 2015).

U.S. National Library of Medicine. "LactMed: Enoxaparin." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+104> (accessed March 6, 2015).

ORGANIZATIONS

American Society of Hematology, 2021 L Street NW, Suite 900, Washington, DC 20036, (202) 776-0544, Fax: (202) 776-0545, <http://www.hematology.org/>.

National Heart, Lung, and Blood Institute (NHLBI), PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbinfo@nhlbi.org, <http://www.nhlbi.nih.gov/>.

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away. Examples of the actions caused by "fight or flight" are:

- constriction of blood vessels in some parts of the body while the blood vessels in muscles expand
- increase in heartbeat and breathing rate
- dilation of the pupils of the eye
- release of glycogen for increased energy
- slowed digestion
- relaxation of the bronchial smooth muscle

Purpose

The most important use of epinephrine is the emergency treatment of allergic reactions. These may be mild irritations but can also be severe and even fatal reactions such as anaphylactic shock. Treatment normally calls for a combination of epinephrine, antihistamines, and corticosteroids. The most serious reactions are allergic asthma, anaphylaxis, and angioedema. The role of epinephrine in anaphylaxis is to reduce the leakage of fluids from blood vessels. Patients who are at risk of these conditions may be advised to carry an epinephrine injector for emergency use. A 2014 review of treatment of anaphylaxis noted that while antihistamines are valuable in the treatment of anaphylaxis, they do not act as quickly as epinephrine, and because of the potentially life-threatening nature of anaphylaxis, epinephrine should be more widely used. Parents and/or caregivers should be carefully trained to use injector devices in case of emergency.

Entocort see **Budesonide**

Epinephrine

Definition

Epinephrine is an endocrine hormone and a neurotransmitter. It is commonly referred to as adrenaline. Epinephrine and norepinephrine are two separate but closely related hormones secreted by the adrenal glands. The adrenal glands are located on top of the kidneys. Epinephrine and norepinephrine are also secreted by the fibers of the sympathetic nervous system, where they help produce the body's "fight or flight" response. This is the reaction of the body to threats that prepares the body to either confront the danger or run



EpiPen (epinephrine). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

In asthmatic attacks, epinephrine is used as a bronchodilator, making it easier to breathe. According to the American Heart Association, epinephrine is a second-line drug to be used only if drugs such as **albuterol** or **levalbuterol** are ineffective or unavailable.

The American Heart Association also lists epinephrine as a second-line choice for other conditions where the initial treatment has failed. In the case of heart attacks with no pulse, the preferred treatment is use of a defibrillator, but if the shocks fail, epinephrine may be administered. Similarly, epinephrine may be given in hypovolemic shock (shock caused by excessive bleeding) if fluid replacement does not restore blood pressure.

Epinephrine may also be administered as a nasal decongestant when used in the form of drops or applied with a cotton swab, but its use for this purpose has been largely replaced by other drugs with similar activity.

Description

Epinephrine is available in natural and synthetic forms. The natural form is much more powerful at constricting blood vessels, but its effects do not last as long as the synthetic form. For this reason, a combination of the two forms may be most useful for indications where a longer duration of action is needed.

Epinephrine may be administered in several different ways:

- Auto-injectors are devices for the self-administration of epinephrine either by patients or by caregivers in case of emergency. They are specially designed syringes that deliver a measured dose of epinephrine into a muscle, usually the thigh. They typically contain 0.15 milligrams (mg) of epinephrine in 0.15 milliliters (mL) of liquid, or 0.3 mg of epinephrine in 0.3 mL.
- Inhalers for asthma are sold without a prescription and are designed to be used with a nebulizer, which is a device that turns liquid forms of medicine into a vapor that can be inhaled.
- A nasal solution is available that contains 0.1% epinephrine and may be used as a nose drop or applied with a cotton swab.
- The solution for intravenous injection contains 1 mg/mL.

U.S. brand names

Epinephrine is sold under various brand names, depending on its format:

- Adrenaclick (injector)
- Adrenalin (injector)
- Auvi-Q (injector)
- EpiPen (injector)

- Twinject (injector)
- Asthmanefrin (nebulizer)
- Micronefrin (nebulizer)
- Primatene Mist (inhalation aerosol)

Generic injectors are also available.

Canadian brand names

All U.S. brand names are also available in Canada.

International brand names

Although Adrenalin is a registered trademark in the United States, it is used as a generic name in most countries. The brand name EpiPen is also widely used, and a similar product is sold as Anapen in Germany. Fastjekt, another auto-injector, is marketed in Germany and Poland.

Origins

Epinephrine was isolated in 1901 and was first synthesized in 1904.

Recommended dosage

Auto-injectors are standardized but come in age-appropriate doses. They should be injected into the outer thigh only and held in place for five to ten seconds, depending on the manufacturer's instructions. The injection may be given through clothing. Any remaining solution should be discarded. A second dose may be administered if needed.

When administered by qualified medical personnel, the dose for anaphylaxis is 0.3 to 0.5 mg (0.3 to 0.5 mL), administered intramuscularly (IM) or subcutaneously (into the skin) and repeated every five to ten minutes as necessary, with a maximum dose of 0.5 mg in each dose.

Intravenous use is normally restricted to emergency rooms and operating rooms. Dosage schedules vary, and individual institutions may have their own protocols. Maximum doses have not been established.

Rapid intravenous administration (IV) push may cause death as a result of cerebrovascular hemorrhage (stroke) or cardiac arrhythmias (irregular heartbeat), but sometimes it must be used in the event of pulseless cardiac arrest.

Precautions

When administered intravenously, the 1:1000 (1 mg/mL) solution must be diluted to 1:10,000 (0.1 mg/mL). Failure to do so can cause serious overdose and has resulted in death.

KEY TERMS

Adrenal gland—An endocrine gland located above each kidney. The inner part of each gland secretes epinephrine (adrenaline) and the outer part secretes steroid hormones.

Agonist—A substance that acts like another substance and therefore stimulates an action. Agonist is the opposite of antagonist.

Allergy—A damaging immune response by the body to a substance (such as peanuts, pollen, insect bites, bee stings, or cat dander) to which it has become hypersensitive.

Anaphylaxis—An intense and sudden allergic reaction. The effects may include sudden drops in blood pressure, narrowing of airways, and a weak pulse. Failure to get prompt treatment may lead to loss of consciousness and death.

Angioedema—An allergic skin disease characterized by patches of confined swelling involving the skin, the layers beneath the skin, the mucous membranes, and sometimes the viscera; also called angioneurotic edema, giant urticaria, Quincke's disease, or Quincke's edema.

Endocrine—A gland that releases a hormone directly into the blood stream.

Hypovolemic shock—Low blood pressure caused by blood loss as in injury.

Pregnancy category C—No adequate human or animal studies exist, or adverse fetal effects have been found in animal studies, but there is no available human data.

Sympathetic nervous system—A division of the autonomic nervous system, the portion of the nervous system that controls involuntary bodily functions such as heart rate.

Care must be used to assure proper needle placement when administering epinephrine solution intravenously. The solution should not be injected into surrounding tissues.

Pregnant or breastfeeding

Epinephrine is classified as a pregnancy category C drug. There have been no studies of epinephrine safety during pregnancy, but the actions of epinephrine indicate that it might reduce blood supply to the uterus. Studies in

small animals have shown that epinephrine may cause problems in fetal development when administered at doses 10 to 25 times the normal human dose. If used during labor and delivery, epinephrine may increase the fetal heart rate.

The U.S. National Library of Medicine's LactMed database reports that there have been no studies of epinephrine during breastfeeding, but because of its short half-life, epinephrine is not expected to be harmful to an infant. However, the database warns that epinephrine could reduce milk production. This risk is greatest in the first day or two after delivery. Mothers who have been breastfeeding for several days with established milk production would not likely experience issues.

Other conditions and allergies

There are no absolute contraindications to the use of epinephrine injection; however, there are a number of conditions for which the manufacturer advises that the drug be used with caution, because it may worsen the underlying condition for at least a short period. These include high blood pressure, cerebrovascular disease, diabetes, Parkinson's disease, and thyroid disorders. For patients with a history of angina or coronary artery disease, epinephrine injection may cause an excessive rise in blood pressure with a risk of cerebral hemorrhage.

Although some epinephrine products contain sulfites as preservatives, the injection should still be administered as treatment for severe allergic reactions, even if the patient is sensitive to sulfites.

Side effects

Epinephrine has a relatively short list of adverse effects, most of which are related to the drug's action. For example, epinephrine increases blood pressure by constricting blood vessels, and its side effects include high blood pressure (hypertension), blood vessel constriction (vasoconstriction), headache, and pale skin (pallor). Epinephrine speeds up the heart, and so tachycardia, or rapid heart rate, is also to be expected. Some of these effects may be extremely serious, leading to heart attack or stroke due to increased blood pressure, but because epinephrine is often used in instances where other treatments have failed, the drug is considered appropriate.

Repeated injections at the same site may cause severe tissue damage and tissue death (necrosis) as a result of repeated vasoconstriction at the same location.

Short-lived effects may include nausea and vomiting as well as nervousness, anxiety, and fear. Other reported adverse effects include weakness and sweating.

Interactions

Individuals should make sure that their healthcare providers are aware of all other drugs they are currently taking, including over-the-counter drugs and supplements.

Drugs

Because epinephrine has such generalized effects, it interacts with any drugs that may have either similar effects or opposite effects. The severity and significance of these interactions will vary with the use and route of administration. Intranasal epinephrine, administered as nose drops or nasal spray, has a very localized effect and poses little risk of interactions.

Epinephrine may interact with antihistamine drugs, including those available over the counter or included in fixed-combination cold remedies, such as chlorphenhydramine and **diphenhydramine** (Benadryl). The combination may cause increased blood pressure. The same increase in blood pressure may occur when epinephrine is used in combination with thyroid hormones and some types of antidepressant drugs.

Resources

PERIODICALS

- Breuer, C., et al. "Pharmacokinetics and Pharmacodynamics of Moist Inhalation Epinephrine Using a Mobile Inhaler." *European Journal of Clinical Pharmacology* 69, no. 6 (2013): 1303–10.
- Camargo, C. A. Jr., et al. "Auvi-Q versus EpiPen: Preferences of Adults, Caregivers, and Children." *Journal of Allergy and Clinical Immunology in Practice* 1, no. 3 (2013): 266–72.
- Chad, L., et al. "A Majority of Parents of Children with Peanut Allergy Fear Using the Epinephrine Auto-Injector." *Allergy* 68, no. 12 (2013): 1605–9.
- Fineman, S. M. "Optimal Treatment of Anaphylaxis: Antihistamines versus Epinephrine." *Postgraduate Medicine* 126, no. 4 (2014): 73–81.
- Frew, A. J. "What are the 'Ideal' Features of an Adrenaline (Epinephrine) Auto-Injector in the Treatment of Anaphylaxis?" *Allergy* 66, no. 1 (2011): 15–24.
- Sheikh, A., et al. "Adrenaline Auto-Injectors for the Treatment of Anaphylaxis with and without Cardiovascular Collapse in the Community." *Cochrane Database of Systematic Reviews* 8, art. no. CD008935 (2012). <http://dx.doi.org/10.1002/14651858.CD008935.pub2> (accessed March 6, 2015).

WEBSITES

- EpiPen.com. <https://www.epipen.com/en/> (accessed March 6, 2015).
- Micromedex. "Epinephrine (Injection Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/>

epinephrine-injection-route/description/drg-20072429 (accessed March 6, 2015).

U.S. Food and Drug Administration. "Epinephrine (Injection Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/epinephrine-injection-route/description/drg-20072429> (accessed March 6, 2015).

U.S. National Library of Medicine. "LactMed: Epinephrine." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+742> (accessed March 6, 2015).

ORGANIZATIONS

- American Academy of Allergy, Asthma & Immunology (AAAAI), 555 East Wells Street, Suite 1100, Milwaukee, WI 53202-3823, (414) 272-6071, <http://www.aaaai.org/>.
- National Institute of Allergy and Infectious Diseases, NIAID Office of Communications and Government Relations, 5601 Fishers Lane, MSC 9806, Bethesda, MD 20892-9806, (301) 496-5717, (866) 284-4107, Fax: (301) 402-3573, TTY: (800) 877-8339, ocpostoffice@niaid.nih.gov, <http://www.niaid.nih.gov/>.

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Epoetin alfa

Definition

Epoetin alfa is a man-made (synthetic) version of a substance normally produced by the kidneys. It is an erythropoiesis-stimulating agent (ESA). Epoetin increases the rate of production and the release of red blood cells (RBC), the oxygen-carrying cells of the blood stream. Red blood cells are produced in the bone marrow, but they require epoetin—also known as erythropoietin (EPO)—for the newly formed cells to develop adequate amounts of hemoglobin, the colored, oxygen-carrying component of these cells, and to be released into the blood stream.

Purpose

The primary use of EPO is treatment of anemia caused by chronic kidney disease. It may be administered to patients both on and off dialysis. Normally these patients still require red blood cell transfusions, but EPO may reduce the frequency of need for transfusions.

EPO is also indicated for use in cancer patients with tumors that do not affect the blood-forming organs and in whom the anemia is caused by chemotherapy. EPO should not be used unless the treatment plan calls for at least two more months of chemotherapy. There are limitations to the use of EPO in cancer treatment. It



Procrit (epoetin alfa). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

should not be used in patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless they are receiving myelosuppressive chemotherapy at the same time. It is also unsuited for cancer patients receiving chemotherapy who are expected to be cured.

EPO may be used to treat the anemia caused by zidovudine (AZT, Retrovir) in some patients infected with human immunodeficiency virus (HIV).

Erythropoietin injections are used to reduce the need for allogeneic RBC transfusion in patients undergoing elective, noncardiac, nonvascular surgery when there is a risk of a blood loss caused by the surgery. Whenever possible, patients should bank their own blood prior to a surgical procedure. Since patients undergoing surgery are at risk for deep vein thrombosis (blood clots in the legs), steps to prevent deep vein thrombosis should also be taken.

EPO is not appropriate for patients who need an immediate increase in red blood cells.

Description

EPO is marketed in 1 milliliter (mL) vials for injection. The commercially available strengths are 2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL, 20,000 units/mL, and 40,000 units/mL.

U.S. brand names

Epoetin is manufactured by Amgen and is marketed as Epogen. It is also produced by Johnson & Johnson's

subsidiary, Janssen, as Procrit. The 40,000 unit/mL concentration is only available from Janssen.

Canadian brand names

Both Epogen and Procrit are available in Canada.

International brand names

Janssen markets epoetin alfa internationally under the brand name Eprex. Sandoz Laboratories markets EPO as Binocrit in most of Western Europe.

Recommended dosage

For patients with chronic kidney disease who are not on dialysis, initial treatment should be 50–100 units per kilogram (kg, or 2.2 lb.) of body weight, given either intravenously (into a vein) or subcutaneously (into the skin) three times a week. Patients who are receiving dialysis should receive the drug only by intravenous injection. Treatment with epoetin should be interrupted or the dose reduced when the hemoglobin level reaches 11 grams per deciliter (g/dL). If dose levels must be increased, the dose should not be adjusted more often than once every four weeks.

For patients with zidovudine-related anemia, the initial dose should be 100 units/kg three times a week given either subcutaneously or intravenously. If the response is inadequate after eight weeks, the dose may be increased by 50–100 units/kg at four- to eight-week intervals.

Patients scheduled for surgical procedures that do not involve the heart or cardiovascular system, which involves the risk of significant blood loss, and who cannot bank their own blood to be returned during the procedure may be given 300 units/kg/day subcutaneously for the ten days preceding surgery and for four days afterward.

Precautions

The package insert of epoetin alfa, along with those of other erythropoiesis stimulating agents (ESAs), carries a boxed warning—the highest level warning the U.S. Food and Drug Administration (FDA) can issue. Chronic kidney disease patients who were receiving ESAs in controlled clinical trials had an increased risk of serious adverse events, including stroke and death. No safe level or dosing strategy has been found that does not increase these risks, and so physicians are advised to use the lowest dose that reduces the need for red blood cell transfusions.

In cancer patients, some studies showed that patients with a variety of cancers—including breast, head, and neck cancers; lymphomas; non-small cell lung cancers;

KEY TERMS

Allogenic—Being genetically different but from individuals of the same species—in this case, a blood transfusion using blood donated by another person.

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values.

Autologous—Cells from the same individual—for example, when a patient banks their blood in advance of surgery so that their own blood can be returned to them in case of need.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Dialysis—A blood filtration therapy that replaces the function of the kidneys, filtering fluids and waste products out of the bloodstream. There are two types of dialysis treatment: hemodialysis, which uses an artificial kidney, or dialyzer, as a blood filter; and peritoneal dialysis, which uses the patient's abdominal cavity (peritoneum) as a blood filter.

Erythropoiesis—Production of red blood cells.

Erythropoietin—A hormone produced by the kidneys that stimulates the production of red blood cells by bone marrow.

Hemoglobin—A protein-iron compound in red blood cells that functions primarily in carrying oxygen from the lungs to the tissues of the body.

Intravenous—Into a vein; a needle is inserted into a vein in the back of the hand, inside the elbow, or some other location on the body so that fluids, nutrients, and drugs can be injected.

Myelosuppression—Bone marrow suppression, reducing the ability of bone marrow to produce blood cells.

Zidovudine—A widely used drug for treatment of HIV+ disease (AIDS), also known as AZT or Retrovir®.

and cervical cancers—had lower overall survival rates or an increased risk of tumor growth and resistance than patients who did not receive ESAs. To prescribe or dispense ESAs to cancer patients, prescribers and

hospitals must enroll in and comply with an Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs (ESA APPRISE) Oncology Program. The ESA APPRISE is part of a Risk Evaluation and Mitigation Strategy (REMS) designed for healthcare providers treating patients with an ESA for their cancer.

Under the terms of the ESA APPRISE program, healthcare providers must enroll in a training program. After training, providers must counsel each patient on the risks of ESA treatment. Each patient will sign the acknowledgment form and will be given a copy of the form. If the healthcare provider or hospital is not in full compliance with the program, then their ability to obtain and administer ESAs will be suspended.

Pediatric

Epogen multidose formulations contain benzyl alcohol, which is associated with potentially fatal “gasping syndrome” in premature neonates, although this is rare.

Pregnant or breastfeeding

Epoetin is considered a pregnancy category C drug, which means it may cause adverse effects in a developing fetus. Polyhydramnios, the accumulation of excess amniotic fluid, and growth retardation have been observed when ESAs were used during pregnancy; in other cases, the drug was administered without event. Erythropoietin should be given during pregnancy only when the benefits exceed the risks.

Women who become pregnant during treatment with epoetin are encouraged to enroll in Amgen's Pregnancy Surveillance Program (1-800-772-6436).

The National Institutes of Health LactMed database reports that erythropoietin is a normal component of human milk. There have been no formal studies of the effect of EPO treatment of the mother on breast milk, and some experts have suggested that the erythropoietin in breast milk might have some small advantages to both mother and infant, such as increasing the infant's red blood cell production and, when the mother is HIV infected, reducing the risk of mother-to-child virus transmission, although there is no formal confirmation of these ideas. No special precautions are required during breastfeeding.

Side effects

Epoetin has a large number of adverse effects. Fever is the most common, followed by nausea. Other adverse effects reported include high blood pressure, cough, vomiting, itch, rash, headaches, and joint pain.

Less frequent but more severe effects include blood clots, including pulmonary embolism (clots in the lungs) and clots affecting artificial kidney function. Seizures have also been observed along with edema and chest pain. Injection-site irritation and respiratory tract congestion have been observed, as well as serious allergic reactions such as anaphylaxis. A large number of other adverse reactions have been reported, but some may be due to the condition being treated rather than the drug itself.

In studies of epoetin alfa in cancer patients, the frequency of adverse reactions was lower overall than when the drug was used to treat anemia caused by chronic kidney disease.

Interactions

Epoetin alfa has no known interactions.

Resources

PERIODICALS

Aapro, M., et al. "Safety and Efficacy Outcomes with Erythropoiesis-Stimulating Agents in Patients with Breast Cancer: A Meta-Analysis." *Annals of Oncology* (December 26, 2014): e-pub ahead of print. <http://dx.doi.org/10.1093/annonc/mdl579> (accessed March 6, 2015).

Bellinghieri, G., et al. "Erythropoiesis-Stimulating Agents: Dose and Mortality Risk." *Journal of Renal Nutrition* 25, no. 2 (2014): 164–68.

Debus, J., et al. "Prospective, Randomized, Controlled, and Open Study in Primarily Inoperable, Stage III Non-Small Cell Lung Cancer (NSCLC) Patients Given Sequential Radiochemotherapy with or without Epoetin Alfa." *Radiotherapy and Oncology*. 112, no. 1 (2014): 23–29.

Kuwahara, M., et al. "Responsiveness to Erythropoiesis-Stimulating Agents and Renal Survival in Patients with Chronic Kidney Disease." *Clinical and Experimental Nephrology* (September 3, 2014): e-pub ahead of print. <http://dx.doi.org/10.1007/s10157-014-1023-9> (accessed March 6, 2015).

Palmer, S. C., et al. "Erythropoiesis-Stimulating Agents for Anaemia in Adults with Chronic Kidney Disease: A Network Meta-Analysis." *The Cochrane Database of Systematic Reviews* 12, art. no. CD 010590 (2014). <http://dx.doi.org/10.1002/14651858.CD010590.pub2> (accessed March 6, 2015).

Voravud, N., and V. Sriuranpong. "Clinical Benefits of Epoetin Alfa (Eprex) 10,000 Units Subcutaneously Thrice Weekly in Thai Cancer Patients with Anemia Receiving Chemotherapy." *Journal of the Medical Association of Thailand* 88, no. 5 (2005): 607–12.

OTHER

Amgen. "Epogen Safety Data Sheet." http://msds.amgen.com/datasheets/Epogen_Safety_Data_Sheet_20130213_rev_4.pdf (accessed March 6, 2015).

WEBSITES

Amgen. "Pregnancy and Lactation Surveillance Program." <http://www.amgenpregnancy.com/en-us/hcp/pregnancy-surveillance-program.aspx> (accessed March 6, 2015).

Epogen.com. <http://www.epogen.com/> (accessed February 28, 2015).

ESA APPRISE Oncology Program. <https://www.esa-apprise.com/ESAAppriseUI/ESAAppriseUI/default.jsp> (accessed February 28, 2015).

Micromedex. "Epoetin Alfa (Injection Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/epoetin-alfa-injection-route/proper-use/drg-20068065> (accessed February 28, 2015).

MedlinePlus. "Epoetin Alfa Injection." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginform/meds/a692034.html> (accessed February 28, 2015).

Procrit.com. <http://www.procrit.com/> (accessed February 28, 2015).

U.S. National Library of Medicine. "Highlights of Prescribing Information: Epogen." <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=129199> (accessed March 6, 2015).

U.S. National Library of Medicine "LactMed: Epoetin Alfa." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+496> (accessed March 6, 2015).

ORGANIZATIONS

American Society of Hematology, 2021 L Street NW, Suite 900, Washington, DC 20036, (202) 776-0544, Fax: (202) 776-0545, <http://www.hematology.org/>.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 9000 Rockville Pike, Bethesda, MD 20892-2560, (301) 496-3583, <http://www.niddk.nih.gov/>.

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REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Epogen see **Epoetin alfa**

Erbitux see **Cetuximab**

Erythromycin

Definition

Erythromycin is an antibiotic drug in the family of macrolide drugs.

Purpose

Erythromycin is administered for treatment of a variety of infections, including those in the respiratory tract, skin, intestine, and female genitourinary tract. Erythromycin is



Ery-Tab (erythromycin), 250 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

used to treat diphtheria, intestinal amoebiasis, pelvic inflammatory disease (PID), acne vulgaris, Legionnaires' disease, pertussis (whooping cough), gastroenteritis, erythrasma, endocarditis, syphilis, and nongonococcal urethritis. Susceptible bacterial infections that can be treated with erythromycin include those caused by *Streptococcus pyogenes*, some *Streptococcus pneumoniae*, some *Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Entamoeba histolytica*, and *Campylobacter*.

Description

Erythromycin is available in oral tablet, capsule, and liquid suspension forms, as well as ophthalmic ointment, injectable (intravenous), and topical gel forms. The medication must be prescribed by a physician. Erythromycin is used internationally and is also frequently used in veterinary medicine.

Erythromycin is available in the following forms and strengths:

- Tablets, various colors: 200-, 250-, 333-, 400-, 500-, 600-milligram (mg) strengths are available. The printing on the tablet varies with the manufacturer. Some are chewable; others are delayed-release and should not be chewed, crushed, or split.
- Delayed-release capsules, various colors: 250 mg strength is available. The printing on the capsule varies with the manufacturer.

- Liquid suspension: When mixed with water, the suspension reconstitutes to a pink, cherry-flavored suspension. Dosage strength per 5 milliliters (mL) includes 200 mg or 400 mg of active drug.
- Eye ointment: 0.5% tube is available.
- Intravenous: 500 mg vials are available.
- Topical gel: 2% strength is available.

U.S. brand names

In the United States, erythromycin is sold under the brand names EES 200, EES 400, Eryc, EryPed, Ery-Tab, Erythrocin, Ilosone, PCE, and PCE Dipertab.

International brand names

Erythromycin is sold under a number of different brand names internationally, including:

- Bonac (Peru)
- Calthrox (India)
- Deripil (Spain)
- Edry (Bangladesh)
- Erybenz (Greece)
- Narlecin (Indonesia)
- Sanasepton (Germany)
- Tiloryth (United Kingdom)

In some countries, erythromycin is only one component of the medication, and there are other medications included in the formulation. In some locations, it is only available for veterinary, not human, use.

Recommended dosage

Recommended dosages are based on the amount of erythromycin needed to treat the infection.

- Recommendations for mild to moderate infections: 30–50 mg per kilogram (kg, or 2.2 lb.) of body weight per day, divided into four doses given every six hours (about 400 mg four times a day for 10 days, or 800 mg twice a day for 10 days).
- Usual adult dose for mild to moderate cases of *Campylobacter* gastroenteritis, chancroid, lymphogranuloma venereum, mycoplasma pneumonia, nongonococcal urethritis, otitis media (ear infection), pharyngitis (sore throat), pneumonia, skin or soft tissue infection, syphilis, upper respiratory tract infection, bronchitis, chlamydia, or Lyme disease: 250 to 500 mg (base, estolate, stearate) or 400 to 800 mg (ethylsuccinate) orally every six hours.
- Severe cases of above infections: 60–100 mg/kg/day, divided into four doses given every six hours.

KEY TERMS

Anaphylaxis—A severe, systemic allergic reaction that can be potentially life-threatening.

Antibiotic—A drug used to treat infections caused by bacteria and other microorganisms.

Clostridium-difficile associated diarrhea (CDAD)—Diarrhea caused by *Clostridium difficile*, a type of bacteria that can develop with antibiotic use.

Endocarditis—A dangerous infection of the heart valves caused by certain bacteria.

Gastroenteritis—An inflammation of the lining of the stomach and intestines, usually caused by a viral or bacterial infection.

Hepatitis—An inflammation of the liver that can be due to infection or damage from chemical agents, including medications.

Nongonococcal urethritis—Inflammation of the urethra that is not caused by gonorrhea.

Pelvic inflammatory disease (PID)—Inflammation of the female genital tract, especially of the fallopian tubes, caused by any of several microorganisms, chiefly chlamydia and gonococci.

Pertussis—Whooping cough.

A daily dose may be divided in half and given every 12 hours, or may be divided into three doses and administering every 8 hours.

The length of treatment with erythromycin is dictated by the type and the severity of the infection:

- upper respiratory infections: 7–10 days
- tonsillitis or pharyngitis: minimum of 10 days
- ear infections: 10–14 days
- pertussis: 14 days
- pneumonia: between 10 days and 3 weeks
- skin/soft tissue infections: 7–10 days
- urinary tract infections: 7–14 days
- PID: 10–14 days
- syphilis: 14 days
- Lyme disease: 14–21 days
- gastroenteritis: 3–5 days

Other dosing formats may be followed for specific infections or circumstances.

Pediatric

The usual pediatric dosage is 50 mg/kg/day, taken orally in divided doses every six hours for at least two weeks.

Adolescents usually follow adult dosing.

Geriatric

Older patients should be more closely monitored when receiving erythromycin, as they are more susceptible to some of its side effects, including cardiac arrhythmia (irregular heartbeat), hearing loss, and increased risk of bleeding if undergoing anticoagulant therapy.

Precautions

The following precautions apply to all individuals:

- This drug should be taken for the entire length of the prescription. Failure to take a complete course of the medication can result in the return of symptoms.
- Erythromycin can be taken with or without food, although the best therapeutic levels are reached if taken at least 30 minutes to 2 hours before or after eating. Individuals who notice stomach sensitivity from the drug may need to take it with food, however.
- Use over a long period of time can increase the risk of developing another fungal or bacterial infection.
- *C. difficile*-associated diarrhea and pseudomembranous colitis have both been associated with long-term use of erythromycin (and other antibiotics), even months after the drug has been discontinued.
- Erythromycin-induced hepatitis necessitates discontinuation of the drug and may manifest with yellowing of the skin and whites of the eyes, abdominal pain, and chalky-white stools.
- Erythromycin may make the skin more sensitive to sun exposure and tanning lights, resulting in more easily (and potentially severely) burned skin.

Pregnant or breastfeeding

Erythromycin carries the FDA pregnancy category B, which means that it is not believed to cause harm to a human fetus but has not been well studied in pregnant women. Women who are pregnant should consult with their doctor before taking erythromycin.

This drug does not pass into breast milk in large amounts and is considered safe for breastfeeding mothers. Infants should be monitored for yeasty diaper rash or thrush in the mouth, as well as loose stools and diarrhea, both due to changes in the intestinal flora (microorganisms) secondary to antibiotic exposure.

Other conditions and allergies

Individuals who are allergic to erythromycin or any other macrolide drug should not take erythromycin. Individuals with a history of severe allergies, asthma, and prior drug reactions involving anaphylaxis, hives, or severe swelling (angioedema) are at higher risk for serious reactions to erythromycin.

Special care and monitoring should be taken in patients with a history of liver problems, kidney disease, heart dysrhythmias, myasthenia gravis, and electrolyte imbalance.

Side effects

Serious and sometimes fatal reactions can occur in individuals who are allergic to erythromycin drugs. Anyone who has had a severe reaction to any drug should alert their physician before taking this drug.

The most common adverse side effects of erythromycin for all age groups tend to be mild. They include:

- upset stomach
- loose stools or diarrhea
- nausea and vomiting
- decreased appetite
- weight loss

These side effects should be brought to the doctor's attention if they do not go away within a few days.

Whitish vaginal discharge or white coating of the tongue and inside of the mouth should also be reported to the doctor.

A doctor should be notified immediately if any of these less common, but more serious, side effects occur:

- wheezing or difficulty breathing or swallowing; may indicate a severe allergic reaction and require immediate medical attention
- severe skin rash, itching, blister, peeling, or hives
- swelling
- yellowing of the skin or the whites of the eyes
- hearing loss
- abdominal pain or bloating
- seizures
- dizziness, fainting
- severe, watery, and/or bloody diarrhea, even if it occurs two months after ending erythromycin treatment
- easy bruising or bleeding
- very dark urine
- white or light-colored stools
- numbness, tingling

- confusion, hallucinations
- severe fatigue, weakness

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients should tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Erythromycin is known to interact with a large number of pharmaceutical drugs. These interactions can result in an increase or decrease in the effectiveness of either erythromycin, the other medication, or both drugs. In particular, erythromycin is problematic when administered along with other drugs that are metabolized by the liver. Other interactions are possible. An individual who develops any unusual or unexpected symptoms should contact a physician.

Severely ill patients using the cholesterol-lowering drug lovastatin along with erythromycin have experienced muscle breakdown (rhabdomyolysis) leading to kidney failure, so this combination is discouraged.

Women using hormonal birth control should consult with their physician about alternative forms of contraception while using erythromycin, as this drug can interfere with the effectiveness of **oral contraceptives**.

Other drugs with which erythromycin is known to have interactions include alfentanil, benzodiazepines, blood-thinning drugs, bromocriptine, **carbamazepine**, cilostazol, **cyclosporine**, **digoxin**, dihydroergotamine, disopyramide, ergotamine, hexobarbital, **lovastatin**, methylprednisolone, quinidine, rifabutin, anticonvulsant drugs, **sildenafil**, simvastatin, **tacrolimus**, theophylline, and vinblastine. However, it is important that patients check with the prescribing doctor before combining erythromycin with any other medications.

Resources

BOOKS

- Bennett, John E., Raphael Dolin, and Martin J. Blaser. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia: Saunders, 2014.
- Cherry, James, et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Saunders, 2014.
- Lexicomp. *Drug Information Handbook*. 23rd ed. Hudson, OH: Lexicomp Inc., 2014.

Magill, Alan, et al. *Hunter's Tropical Medicine and Emerging Infectious Diseases*. Philadelphia: Saunders, 2013.

Rang, Humphrey, et al. *Rang and Dale's Pharmacology*. 7th ed. London: Churchill Livingstone, 2012.

WEBSITES

"Erythromycin." Drugs.com. <http://www.drugs.com/erythromycin.html> (accessed February 7, 2015).

MedlinePlus. "Erythromycin." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682381.html> (accessed February 7, 2015).

U.S. Food and Drug Administration. "Erythromycin." <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=ERYTHROMYCIN> (accessed February 7, 2015).

U.S. National Library of Medicine. "LactMed: Erythromycin." <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+351> (accessed February 7, 2015).

ORGANIZATIONS

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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REVIEWED BY KEVIN GLAZA, RPh

Erythropoietin see **Epoetin alfa**

Escitalopram

Definition

Escitalopram (Lexapro) is a medication that belongs to the drug class called selective serotonin reuptake inhibitors (SSRIs). Selective serotonin reuptake inhibitors are a group of medications used to treat clinical depression, anxiety, and other psychiatric disorders. They specifically act on a chemical called serotonin, a type of brain neurotransmitter that is involved in normal brain function and can affect the physiological state of clinical depression.

Purpose

SSRIs such as escitalopram can be used to treat a broad range of mood- and stress-related psychiatric illnesses. They are mainly used to treat clinical depression and anxiety disorders, including generalized anxiety disorder (GAD), panic disorder, post-traumatic stress syndrome (PTSD), premenstrual syndrome disorders



Lexapro (escitalopram), 10 mg. (© Cengage Learning®.)

(PMS), stress-related irritable bowel syndrome, social phobia, and the eating disorder bulimia nervosa. Choice of agent and whether they are used alone or in combination with other drugs depends on the medical disorder and individual health parameters. Escitalopram specifically is most often used for major depression and generalized anxiety disorder.

Description

Selective serotonin reuptake inhibitors like escitalopram have a therapeutic mechanism of action that is focused on the modulation of the natural body chemical serotonin. Serotonin is a type of neurotransmitter in the brain. Neurotransmitters like serotonin bind to chemical receptors on the surface of neurons (brain cells). Once bound to a receptor, they affect physiological processes. The receptors activate a sequence of cellular events known as a chemical cascade or signaling pathway. Neurotransmitter signaling pathways are responsible for many normal brain functions. During the signaling process, serotonin is released from the end of neuron one and crosses to a specific receptor for serotonin on the surface of the next neuron (neuron two). Any leftover serotonin is taken back up by neuron one in a process known as reuptake. SSRIs such as escitalopram decrease this reuptake, allowing for more serotonin signaling. It is believed that a decrease in serotonin signaling contributes

to illness such as depression and anxiety disorders. SSRIs help by increasing serotonin signaling, with little effect on the levels of other neurotransmitters.

Whether a patient is going to benefit from an SSRI such as escitalopram may have a genetic component. Individual response to each SSRI varies greatly, and these drugs tend to require several weeks to take effect. Generally, escitalopram is attempted for four to six weeks before concluding it will not have an effect and switching to another agent. Having one SSRI fail in treatment for an individual patient does not mean that another SSRI will not work for that person. Sometimes multiple drugs need to be attempted under physician care before the proper treatment is found for a patient.

Recommended dosage

SSRIs such as escitalopram are taken as oral medications. The dosage varies depending on the individual patient response to the medication regarding its effectiveness, and the individual patient response to the medication regarding side effects. Some people naturally require a higher dose of escitalopram in order to achieve the desired effect. Other patients require a lower dose either for therapeutic effect or to lessen adverse effects.

Escitalopram used for major depressive disorder or generalized anxiety disorder is dosed at 10–20 milligrams (mg) daily. Patients generally start at the 10 mg dose and gradually work their way up to the dose needed for effect after a week at the 10 mg dose. Slowly increasing the dose helps with minimizing side effects, and some side effects become lessened with continued use. The maximum dose that may be used is 20 mg per day. All SSRIs, including escitalopram, need to be slowly tapered off if discontinued to avoid withdrawal symptoms.

Pediatric

Children ages 12 to 17 may be given a trial of 10 mg per day of escitalopram under select circumstances with careful medical supervision. The dose may be increased to 20 mg after three weeks at a lower dose in some circumstances.

Geriatric

Elderly patients are usually kept at a lower dose of 10 mg, due to their increased sensitivity to these medications and their side effects.

Precautions

SSRIs such as escitalopram are associated with many adverse effects. It usually takes several weeks of medication for the treatment effects to occur, while the

undesirable side effects may occur at the onset of treatment. When an SSRI such as escitalopram is prescribed for a patient with a disease like major depression, this time lapse in beneficial versus adverse effects may be difficult for patient compliance with treatment. A patient who is already feeling depressed may feel frustrated after taking an SSRI and feeling no relief, despite being told the condition will improve. Fortunately, SSRIs like escitalopram do help many people and have fewer overall side effects than some older medications used for the same purpose. Great benefit may be gained if a patient is able to get past the first couple weeks of treatment.

When a patient discontinues escitalopram, the dose needs to be tapered down slowly. SSRIs have little to no abuse potential, but if SSRI is abruptly discontinued without tapering, there may be symptoms of withdrawal known as SSRI discontinuation syndrome. Withdrawal symptoms of this syndrome may include flu-like symptoms, anxiety, agitation, vivid or bizarre dreams, insomnia, nausea, vomiting, diarrhea, sense of imbalance, chills, fatigue, dizziness, headache, and other sensory disturbances. Discontinuation syndrome may be avoided completely if the dose of escitalopram is properly tapered over time.

Children and adults up to age 24 are at risk for developing suicidal thoughts and aggressive behavior when taking antidepressants, including escitalopram. Persons of any age should be monitored for worsening depression or suicidal behavior when taking antidepressant drugs. If a patient goes from depressed and unmotivated to depressed and highly motivated in the first few weeks of treatment, it may increase the risk of harmful behavior.

Escitalopram overdose may result in a condition known as serotonin syndrome, which is also called serotonin toxicity, serotonin poisoning, and serotonin storm. Serotonin overdose may be caused by taking multiple drugs that increase the amount of serotonin signaling in the body. Symptoms of serotonin overdose may range from mild to life-threatening, depending on the individual situation. Symptoms may include high blood pressure, high fever, nausea, diarrhea, headache, sweating, increased heart rate, tremor, muscle twitching, delirium, shock, coma, and death.

Pediatric

Escitalopram is not approved for use in children younger than 12 years of age.

Pregnant or breastfeeding

If used during pregnancy, SSRIs such as escitalopram cross the placenta and may affect the fetus. SSRI use

KEY TERMS

Anxiety—A psychological state characterized by strong feelings of worry, nervousness, apprehension, or agitation; may also be accompanied by physical symptoms, including sweating, tension, and increased pulse.

Bipolar disorder—Psychiatric mood disorder characterized by periods of manic behavior that may alternate with periods of depression; also known as manic depressive disorder.

Depression—A mental state characterized by excessive sadness and loss of interest in life; other symptoms may include altered sleep or eating patterns, loss of concentration, agitation, lack of energy, and, in severe cases, attempts at self-harm or suicide.

Monoamine oxidase inhibitors (MAOIs)—Type of antidepressant medication that affects various kinds of neurotransmitters, including serotonin.

Neurotransmitter—A chemical messenger that travels through the body and acts in the nervous system. Neurotransmitter signaling is responsible for a wide range of bodily processes and is often the target of medications involving the brain and cardiovascular system.

Neurotransmitter receptor—A physical recipient for chemicals called neurotransmitters. Receptors sit on the surface of cells that make up body tissues,

and once bound to the neurotransmitter, they initiate the chemical signaling pathway associated with neurotransmitters.

Post-traumatic stress syndrome (PTSD)—Psychiatric disorder in which the patient experiences persistent disturbing anxiety-based symptoms after experiencing a traumatic event.

Selective serotonin reuptake inhibitors (SSRIs)—A class of antidepressants that works by blocking the reabsorption of serotonin in brain cells, raising the level of the chemical in the brain.

Serotonin—A type of neurotransmitter involved in regulation of the blood vessels, brain processes, and disease states such as depression.

Serotonin syndrome—A potentially life-threatening drug reaction involving an excess of the neurotransmitter serotonin, usually occurring when too many medications that increase serotonin are taken together, such as antimigraine triptans and certain antidepressants.

Social phobia—Psychiatric disorder involving excessive fear and anxiety due to social situations with other people.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

during the third trimester of pregnancy is associated with some newborn medical problems. Potential effects on the newborn include respiratory problems, gastrointestinal problems, seizures, and feeding problems. SSRIs such as escitalopram may also cause a withdrawal syndrome in newborn babies known as neonatal abstinence syndrome. Symptoms of neonatal abstinence syndrome in a newborn include irritability, physical agitation and restlessness, tremors, increased breathing rate, nasal congestion, nausea, vomiting, and diarrhea. Symptoms usually end by two weeks of age and are most commonly caused by maternal use of **fluoxetine** and **paroxetine** SSRIs; they are less common with escitalopram.

Other conditions and allergies

Escitalopram and other SSRIs are discouraged from use in patients with bipolar disorder, as they can induce a state of mania in these individuals. There are selective conditions under which a doctor may prescribe SSRIs to

a bipolar patient for a short period of time under careful monitoring.

Escitalopram may not be appropriate for use or may require careful monitoring in patients with liver or kidney impairment, electrolyte imbalances, or seizure disorders.

Side effects

SSRIs such as escitalopram are known for having fewer side effects than other types of antidepressant medications, which is one reason why they tend to be the drug of choice in treatment of depression. However, as with all medication, escitalopram does have side effects. Common side effects of escitalopram include nausea, headache, dizziness, constipation, sexual dysfunction, diarrhea, sweating, dry mouth, shakiness, loss of appetite, weight loss, rash, and insomnia. Rare but serious potential side effects include mania, worsened depression and suicidality (especially in the pediatric population), pediatric growth suppression in younger age groups,

seizures, serotonin syndrome, discontinuation syndrome, electrolyte imbalances, hypoglycemia, abnormal bleeding, priapism, and glaucoma.

Interactions

Patients should make their doctor aware of all medications and supplements they are taking before using SSRIs like escitalopram.

Drugs

Switching drug treatment for an individual patient from a monoamine oxidase inhibitor (MAOI) to an SSRI may require a waiting period of up to two weeks between drugs. Switching from an SSRI to an MAOI may require a waiting period of up to five weeks duration.

An example of a medication that has additive serotonin effects with escitalopram or other SSRIs is **sumatriptan** (Imitrex). Sumatriptan is a drug used to treat migraine headaches. The combination of an SSRI and sumatriptan may produce undesirable side effects or overdose. Other drugs that cannot be combined with escitalopram due to risk of serotonin syndrome are the antibiotic **linezolid** and the drug methylene blue, used in some blood-related illnesses.

Escitalopram may increase the potency and side effects of:

- warfarin
- digoxin
- beta blocker cardiac drugs such as metoprolol
- benzodiazepines such as diazepam (Valium)
- antipsychotics such as haloperidol and clozapine
- certain antiseizure drugs such as phenytoin

Drugs that may cause toxicity with escitalopram include:

- diuretics (water pills)
- sleep aids like zolpidem (Ambien)
- diet pills such as sibutramine (Meridia)
- mood stabilizers such as lithium

Escitalopram cannot be combined with the antipsychotic medications pimozide (Orap) or thioridazine (Mellaril) due to dangerous cardiac complications. The risk of gastrointestinal bleeding may be increased when escitalopram is combined with nonsteroidal anti-inflammatory drugs (NSAIDs) such as **ibuprofen** (Motrin), **aspirin** (Bayer, Excedrin), and naproxen sodium (Aleve).

Herbs and supplements

The use of the herbs St. John's wort or yohimbe while taking escitalopram may also cause toxicity.

Food and other substances

Using alcohol while taking escitalopram can create toxic reactions in the body, and alcohol should be avoided while taking this drug.

Resources

BOOKS

Brunton, Laurence L., et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill Medical, 2011.

Stargrove, Mitchell Bebel, et al. *Herb, Nutrient, and Drug Interactions: Clinical Implications and Therapeutic Strategies*. St. Louis: Mosby, 2007.

PERIODICALS

Souery, D., et al. "What to Expect from a Third Step in Treatment Resistant Depression: A Prospective Open Study on Escitalopram." *World Journal of Biological Psychiatry* (December 23, 2014): e-pub ahead of print. <http://dx.doi.org/10.3109/15622975.2014.987814> (accessed February 24, 2015).

OTHER

U.S. Food and Drug Administration. "Medication Guide: Lexapro." <http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088620.pdf> (accessed February 24, 2015).

WEBSITES

AHFS Consumer Medication Information. "Escitalopram." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a603005.html> (accessed February 24, 2015).

American Pregnancy Association. "Escitalopram during Pregnancy." <http://americanpregnancy.org/medication/escitalopram-during-pregnancy/> (accessed February 24, 2015).

National Alliance on Mental Illness. "Lexapro® (Escitalopram)." <http://www2.nami.org/Template.cfm?Section=Helpline1&template=/ContentManagement/ContentDisplay.cfm&ContentID=168467> (accessed February 24, 2015).

U.S. Food and Drug Administration. "Antidepressant Use in Children, Adolescents, and Adults." <http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm096273.htm> (accessed February 24, 2015).

U.S. Food and Drug Administration. "Escitalopram (Marketed as Lexapro) Information." <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm053342.htm> (accessed February 24, 2015).

ORGANIZATIONS

American College of Neuropsychopharmacology, 5034-A Thoroughbred Lane, Brentwood, TN 37027, (615) 324-2360, Fax: (615) 523-1715, acnp@acnp.org, <http://www.acnp.org/default.aspx>.

American Psychiatric Association, 1000 Wilson Boulevard,
Suite 1825, Arlington, VA 22209-3901, (703) 907-7300,
apa@psych.org, <http://www.psych.org/>.

Mental Health America, 2000 N. Beauregard Street, 6th Floor,
Alexandria, VA 22311, (703) 684-7722, (800) 969-6642,
Fax: (703) 684-5968, <http://www1.nmha.org/>.

National Alliance on Mental Illness, 3803 N. Fairfax Drive,
Suite 100, Arlington, VA 22203, (703) 524-7600, (800)
950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.

National Institute of Mental Health (NIMH), 6001 Executive
Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-
9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-
4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

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Eskalith see **Lithium**

Esomeprazole

Definition

Esomeprazole is a medication taken by mouth to ease the symptoms of gastroesophageal reflux disease (GERD), a condition that allows some acid from the stomach to go back up into the esophagus, the tube that leads from the throat to the stomach. A hallmark symptom of GERD is heartburn. It is in a class of drugs known as proton pump inhibitors.

Purpose

People who have GERD have symptoms such as pain near the breast bone that burns, especially when they lie down or bend over. Although GERD may seem harmless, the constant reflux of stomach acid can eventually harm the thin lining of the esophagus. Esomeprazole and other proton pump inhibitors reduce the amount of stomach acid, which helps to control the symptoms of GERD. Esomeprazole also gives the esophagus a chance to heal from the damage caused by the acid reflux.

Description

Esomeprazole comes in a delayed-release capsule and is available by prescription only in brand and generic formulas. The capsule is usually taken whole by mouth, but its contents can be mixed with water or administered by caregivers through a feeding tube if needed. The medication should be taken at least one hour before eating.



Nexium (esomeprazole), 20 mg. (© Cengage Learning®)

U.S. brand names

In the United States, esomeprazole is sold under the brand name Nexium. A combination formula containing esomeprazole and the nonsteroidal anti-inflammatory drug (NSAID) naproxen is available under the brand name Vimovo.

Recommended dosage

For most adults with GERD, the esomeprazole dosage is one 20-milligram (mg) capsule once a day, taken at least an hour before any meal. This dosage is used for those taking the medication to relieve GERD symptoms and to maintain healing of any damage to the esophagus from past reflux. The drug is typically taken for a period of four weeks to relieve symptoms, but it may be taken longer if symptoms are not relieved and the doctor recommends another course, or for up to six months to maintain healing of the esophagus.

When taking esomeprazole to begin healing of the esophagus, the doctor may recommend an adult dosage of 20 mg or 40 mg once a day for four to eight weeks. Some patients do not heal within this time and take the medication for an additional four to eight weeks.

KEY TERMS

Gastroesophageal reflux disease (GERD)—A condition in which gastric juice from the stomach backs up into the bottom of the esophagus and causes irritation, inflammation, or erosion of the cells lining the esophagus.

Neuroendocrine—The endocrine system involves cells that make hormones in the body. Neuroendocrine refers to cells that are found in organs that make hormones but also have nerve cells. They may be found in organs throughout the body.

Osteoporosis—A chronic and progressive disease that leads to bone weakening and brittleness.

Proton pump inhibitor—These medicines reduce how much acid is made by glands that are located in the stomach's lining. When less acid is made, less makes its way back into the esophagus, and the symptoms of gastroesophageal reflux disease are eased.

Pediatric

Children ages 1–11 can take 10–20 mg of esomeprazole once a day for up to eight weeks. Those 12–17 years old can take 20 mg or 40 mg once a day for up to eight weeks. Infants from one month to less than one year old can have between 2.5 mg and 10 mg of esomeprazole once a day, based on their weight, for up to six weeks.

Precautions

Doctors and patients should be aware that some stomach cancers can cause similar symptoms to GERD, and the fact that esomeprazole relieves symptoms does not completely rule out the possibility of cancer as the cause of symptoms; the doctor should make a thorough diagnosis as part of the management plan. Long-term use of esomeprazole can increase risk of osteoporosis-related bone fractures.

Pediatric

Esomeprazole should only be given to children younger than one year if they have erosion or damage to the esophagus.

Geriatric

Overall, research has shown no difference in safety or how well esomeprazole works in older adults compared with all adults. It is possible that seniors are more sensitive to the drug's effects, so anyone older than 65 may need dose adjustment or more careful monitoring. For instance, side effects such as diarrhea can cause more serious problems in older adults.

Pregnant or breastfeeding

Esomeprazole is a pregnancy category C drug, meaning that women who are pregnant should only take the medication if the potential benefits outweigh possible risks. It is not known whether the medicine is excreted in breast milk, so nursing mothers should decide whether to stop using esomeprazole while nursing or continue using the drug and choose not to breastfeed their infants.

Other conditions and allergies

People who have neuroendocrine tumors, which are growths that develop in hormone-producing cells of certain organs, may need to stop taking esomeprazole before having laboratory tests for the tumors because the medication can interfere with test results. People who have a history of liver disease or low magnesium levels in their blood should discuss these conditions with their doctor when considering taking esomeprazole.

Side effects

Some of the common side effects of esomeprazole include:

- dry mouth
- constipation
- gas or nausea
- headache

Some side effects from taking esomeprazole can be severe and if they occur, the patient should contact a doctor immediately. These include:

- diarrhea that persists
- hives, rash, and itching
- problems with breathing or swallowing
- swelling of the face, throat, lips, tongue, hands, or lower limbs
- blisters or skin that peels
- rapid or irregular heartbeat
- extreme fatigue

Interactions

Esomeprazole can interact with some drugs and herbal remedies. It is important to tell the doctor about any medications, herbal therapies, or vitamins being used before taking esomeprazole.

Drugs

Some drugs can significantly decrease the amount of esomeprazole in the body. Among these are **rifampin**, a drug used to treat tuberculosis and some forms of meningitis. People who take **clopidogrel** (Plavix) to

prevent problems with the heart and blood vessels need to discuss the drug with their doctor because esomeprazole can affect how well the clopidogrel works. Esomeprazole may increase levels of **methotrexate** (Rheumatrex), which is used to treat severe psoriasis.

Herbs and supplements

Esomeprazole should not be taken at the same time as St. John's wort because the herb can reduce the effectiveness of esomeprazole.

Resources

PERIODICALS

Bezabeh, Shewit, et al. "Accumulating Evidence for a Drug-Drug Interaction between Methotrexate and Proton Pump Inhibitors." *The Oncologist* 17, no. 4 (2012): 550–54.

Regenbogen, Elliot. "Esophageal Reflux Disease Proton Pump Inhibitor Therapy Impact on Sleep Disturbance: A Systematic Review." *Otolaryngology-Head and Neck Surgery* 146, no. 4 (2012): 524–32.

WEBSITES

AHFS Consumer Medication Information. "Esomeprazole." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699054.html> (accessed March 6, 2015).

MedlinePlus. "GERD." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/gerd.html> (accessed March 6, 2015).

Physicians' Desk Reference. "Nexium." PDR Health. <http://www.pdrhealth.com/drugs/nexium> (accessed March 6, 2015).

ORGANIZATIONS

American Gastroenterological Association, 4930 Del Ray Avenue, Bethesda, MD 20814, (301) 654-2055, Fax: (301) 654-5920, <http://www.gastro.org/>.

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, 1501 Bethlehem Pike, Flourtown, PA 19031, (215) 233-0808
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Estrace see **Estradiol, micronized**

Estradiol, micronized

Definition

Estradiol is a form of oral estrogen, a steroid hormone used to treat symptoms of estrogen deficiency



Estradiol, 2 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

that occur during the perimenopausal (premenopausal) and menopausal phases in women.

Purpose

Estradiol is prescribed primarily to relieve menopause-related symptoms, such as hot flashes, mood swings, tender breasts, vaginal dryness, lower sex drive, and sometimes migraine headaches. Nearly two-thirds of perimenopausal and menopausal women take oral estrogen at some point to relieve such symptoms. Women who have had a hysterectomy, which is considered surgical menopause, may also be advised to take estradiol.

The use of estradiol to help correct estrogen hormone deficiency and to reduce related symptoms is called estrogen replacement therapy. Aside from relieving short-term symptoms, the benefits of hormone replacement therapy are also reported to include reduced incidence of osteoporosis-related fractures, especially hip fractures, and reduced incidence of diabetes among postmenopausal women. In addition, estrogen may be prescribed to treat endocrine disorders and reproductive problems in younger women.

Local conditions such as atrophic vaginitis and atrophic urethritis may also be treated with the topical application of estradiol preparations, such as gels and creams containing the estrogen hormone.

Oral estrogens such as estradiol are sometimes prescribed for treating conditions in which estrogen

deficiency plays a role, including hypothyroidism and diabetes. Estradiol is also prescribed for the palliative treatment of breast cancer and prostate cancer.

Description

Estradiol is the main form of the steroid hormone estrogen and the most abundant sex hormone in women of childbearing age. It is produced in the follicles of the ovaries, in the adrenal glands, and in fat tissue, and it is then released into the bloodstream. Estrogen circulating in the bloodstream attaches to estrogen receptors in the cells of certain tissues, including the breasts, uterus, brain, bones, liver, heart, and other body tissues.

Estrogen is responsible for the development of female sexual characteristics and reproductive functioning. Estrogen production declines prior to menopause and gradually throughout the menopausal years. This natural transition of estrogen levels typically begins between the ages of 40 and 55 and may continue for several years, even up to 10 years in some women.

Certain other conditions may cause estrogen deficiency, including failed ovary function (female hypogonadism), polycystic ovarian syndrome, pituitary gland dysfunction (hypopituitarism), abnormal kidney and liver function, extreme weight loss from illness or eating disorders, and certain drugs (e.g., clomiphene, **phenytoin**, phenobarbital and other barbiturates, and **rifampin**). The decline of estrogen production causes symptoms such as hot flashes, night sweats, and mood swings and is associated with various symptomatic conditions such as osteoporosis, cardiovascular diseases, diabetes, and age-related dementia.

When estrogen levels decline during and after menopause, after hysterectomy, or due to premature ovarian failure (female hypogonadism), estrogen replacement therapy with estradiol may be recommended. Sometimes estrogen replacement is also given to prevent osteoporosis and to improve women's overall health. However, because studies have shown the influence of synthetic estrogens on the development of certain breast cancers (estrogen receptor positive cancer) and other gynecologic cancers, the U.S. Food and Drug Administration (FDA) and certain healthcare organizations (e.g., North American Menopause Society, International Menopause Society) advise healthcare professionals to prescribe the lowest possible doses for the shortest possible time period to achieve individual treatment goals. Treatment is most often targeted to managing menopause symptoms rather than preventing disease.

U.S. brand names

Estradiol is sold in the United States under the brand name Estrace.

International brand names

Internationally, estradiol is sold under the brand names Alora, Climara, Delestrogen, Depo-Estradiol, Divigel, Elestrin, Estrasorb, Estrogel, Menostar, Minivelle, and Vivelle.

Recommended dosage

Estradiol can be administered in several forms depending on the reason for taking the hormone and the patient's preference. Estradiol is prepared in tablets as a micronized powder. The standard adult dose for postmenopausal symptoms is 0.45–2 milligrams (mg) orally once a day. Estradiol prepared as estradiol cypionate can also be given by intramuscular injection, 1–5 mg every three to four weeks. Insertion of a vaginal ring releases 0.05–0.1 mg/day directly into the vaginal tissue; the ring typically stays in place for three months and is then replaced if therapy is continued.

Topical preparations of estradiol are also available, not only for treating symptoms of vulvar and vaginal atrophy but also for treatment of the symptoms of menopause. Estradiol transdermal film is a topical form, with dosage ranging from 0.025 mg to 0.1 mg applied twice or three times weekly either on the lower thigh, upper abdomen, buttocks, or upper arm. It should not be applied to breast tissue. Other types of gels and sprays may be prescribed with dosages ranging from 0.05 to 0.25 mg per day, or, for sprays, 0.87–1.25 grams (g) per single spray. The spray should be applied to the arms once daily and always at the same time.

Women who have been taking oral estradiol or other oral estrogen therapy and are changing to transdermal (topical) estradiol are advised to wait one week after discontinuing the oral estradiol before beginning the transdermal application.

Precautions

Estradiol should not be used to prevent diseases caused by estrogen deficiency. The use of estradiol may actually increase the risk of developing heart disease, stroke, or age-related dementia, and the drug should not be used to prevent these diseases. Estradiol may also increase the risk of breast cancer or of developing blood clots that can lead to heart attack or stroke. These risks are especially high in women with diabetes, high blood pressure, or high cholesterol or triglycerides, and in women who smoke or who are overweight or obese.

KEY TERMS

Atrophic urethritis—Inflammation of the outer urinary tract due to thinning and shrinking of tissue, which result from reduced estrogen levels.

Atrophic vaginitis—Thinning, drying, and inflammation of the vaginal walls due to reduced estrogen levels.

Embolism—The lodging of a blood clot somewhere in the veins of the vascular system.

Female hypogonadism—Dysfunction or failure of the ovaries resulting in lack of production of female hormones.

Hypopituitarism—Failure of the pituitary gland to produce normal amounts of the pituitary hormones.

Jaundice—The yellowing of the eyes and skin due to an excess of a chemical in blood cells called bilirubin. It occurs in certain diseases in which the liver cannot process old blood cells properly as they break down; this results in too much bilirubin being released into the bloodstream.

Palliative—Referring to any type of treatment that is given to relieve the symptoms of a disease rather than to cure it.

Perimenopause—The early years preceding menopause when the natural transition to infertility is just beginning and estrogen levels are reducing gradually.

Women with liver disease, bleeding disorders, abnormal or excessive vaginal bleeding, history of estrogen-dependent cancer (e.g., breast, uterine, ovarian, or thyroid cancer), or history of heart attack, stroke, or blood clot formation in the lungs or legs are advised not to take estradiol. Women who are allergic to any medications or food dyes are also advised not to take estradiol.

Before taking estradiol, the patient's healthcare provider should be made aware of any history of jaundice in pregnancy or while taking birth control pills, thyroid disorders, kidney disease, asthma, epilepsy, migraine headaches, gallbladder disease, uterine fibroid tumors or endometriosis, high or low calcium levels, and previous hysterectomy.

Since certain gynecologic cancers are related to excess estrogen, women taking estradiol are strongly advised to have regular physical examinations and

mammograms, per recommended guidelines, while using the drug.

Pregnant or breastfeeding

Pregnant women are advised not to take estradiol or other estrogen replacement therapies since they may increase the risk of developing conditions that can lead to uterine cancer. Estradiol can also cause birth defects; female children may develop vaginal adenosis and vaginal cancer later in life, and male children have a greater risk of developing urogenital abnormalities and testicular cancer. Estradiol and other oral estrogens are considered to be compatible with breastfeeding but may reduce the quantity or quality of the breast milk, so caution is advised when prescribing estradiol to breastfeeding mothers.

Side effects

Common side effects of estradiol may include breast pain, headache, vaginal itching or discharge, changes in the menstrual period or breakthrough bleeding or spotting, thinning scalp hair, and possibly nausea, vomiting, bloating, and stomach cramps.

High levels of calcium may develop in the blood circulation, producing symptoms such as nausea, vomiting, abdominal pain, loss of appetite, constipation, increased thirst or urination, muscle pain or weakness, joint pain, confusion, or feeling tired or restless. The appearance of any of these symptoms alone or together should be reported to the prescribing healthcare provider.

Allergic reactions to estradiol may occur, including hives, difficulty breathing, and swelling of the face, lips, tongue, or throat. Such reactions should be reported to the healthcare provider immediately. Emergency medical help may be needed.

Other signs that must be reported immediately include:

- heart attack symptoms such as chest pain, nausea, and sweating
- signs of stroke, such as sudden numbness or weakness on one side of the body, sudden severe headache, slurred speech, and disturbed vision or balance
- signs of a blood clot in the lung (pulmonary embolism), such as chest pain, sudden cough, wheezing, rapid breathing, or coughing up blood
- swelling or tenderness in the abdomen
- yellowing of the skin or eyes (jaundice)
- unusual vaginal bleeding
- a lump in breast tissue

- swelling of limbs and/or abdomen, or rapid weight gain that may indicate fluid retention

Interactions

Estradiol is known to interact with various drugs, herbs and supplements, and foods.

Drugs

Certain drugs may decrease the function of either naturally occurring estrogen or synthetic estrogens such as estradiol. Drugs that decrease estrogen levels include clomiphene, phenytoin, phenobarbital and other barbiturates, and rifampin. Other drugs may increase estrogen levels, including antifungal medications, certain antidepressants (e.g., **fluoxetine** [Prozac]), and antibiotics such as **erythromycin** and **clarithromycin**. **Raloxifene**, **tamoxifen**, corticosteroids like hydrocortisone and **prednisone**, and anticoagulation medications such as **warfarin** can increase the side effects of synthetic estrogens. Taking estradiol as prescribed by a healthcare provider for menopause symptoms, hypothyroidism, or diabetes treatment may affect blood levels of glucose and thyroid hormones, and these factors will likely be monitored regularly.

Herbs and supplements

St. John's wort is an herb known to decrease the function of estrogen.

Food and other substances

Grapefruit juice is known to decrease the function of estrogen.

Resources

PERIODICALS

DeVilliers, T. J., et al. "Updated 2013 International Menopause Society Recommendations for Menopausal Hormone Therapy and Preventive Strategies for Midlife Health." *Climacteric* 16 (2013): 316–37.

Luine, V. N. "Estradiol and Cognitive Function: Past, Present, and Future." *Hormone Behavior* 66, no. 4 (2014): 602–618.

Manson, J. E., et al. "The Women's Health Initiative Hormone Therapy Trials: Update and Overview of Health Outcomes During the Intervention and Post-Stopping Phases." *Journal of the American Medical Association* 310, no. 13 (2013): 1353–68.

North American Menopause Society. "The 2012 Hormone Therapy Position Statement of the North American Menopause Society." *Menopause* 19 (2012): 257–71.

WEBSITES

"Estradiol." Drugs.com. <http://www.drugs.com/estradiol.html> (accessed February 7, 2015).

MedlinePlus. "Estradiol Transdermal Patch." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a605042.html> (accessed February 10, 2015).

MedlinePlus. "Estrogen." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682922.html> (accessed February 7, 2015).

National Women's Health Resource Center. "Estrogen." HealthyWomen.org. <http://www.healthywomen.org/condition/estrogen> (accessed February 7, 2015).

ORGANIZATIONS

Office on Women's Health, U.S. Department of Health and Human Services, 200 Independence Avenue SW, Room 712E, Washington, DC 20201, (202) 690-7650, (800) 994-9662, Fax: (202) 205-2631, <http://www.womenshealth.gov/>.

L. Lee Culvert

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Estrogen/progestin see **Oral contraceptives**

Estrogens, conjugated see **Conjugated estrogens**

Eszopiclone

Definition

Eszopiclone is a sedative-hypnotic drug in the class of cyclopyrrolones. It is a Schedule IV controlled substance.

Purpose

Eszopiclone is used to treat insomnia when the main complaint is the inability to fall asleep. It is also used to improve sleep quality for patients who cannot sleep through the night. It is derived from and is chemically similar to the drug zopiclone (Zimovane, Imovane).

Description

Eszopiclone is a nonbenzodiazepine sedative-hypnotic, indicating that it does not work precisely like the commonly prescribed benzodiazepine psychoactive drugs used for treating insomnia, as well as anxiety, agitation, seizures, muscle spasms, and alcohol withdrawal. However, both eszopiclone and benzodiazepine act on the same cellular binding site, that of gamma-aminobutyric acid (GABA). Eszopiclone is reported to have a more benign side effect profile than the



Lunesta (eszopiclone), 3 mg. (© Cengage Learning®)

benzodiazepine drugs, but it is only slightly more effective for treating insomnia compared to placebo. Nevertheless, after taking the drug to fall asleep, many patients find that they are drowsy and not fully able to cope with activities that require careful attention when they wake up the next morning, including driving and performing certain tasks at work.

Eszopiclone is prescribed most often for elderly patients. However, newer drugs with different mechanisms of action and satisfactory safety profiles are now considered more appropriate for older adults.

U.S. brand names

Eszopiclone is sold in the United States under the trade name Lunesta.

Origins

Eszopiclone was approved by the U.S. Food and Drug Administration (FDA) in 2004 for treatment of insomnia.

Recommended dosage

Eszopiclone is available as 1, 2, and 3 milligram (mg) film-coated tablets. Dosage is determined

individually. One tablet of the prescribed dosage is usually taken at bedtime or after trying unsuccessfully to fall asleep. It should be taken with a full glass of water and should not be taken within the first hour after eating a heavy or high-fat meal.

Precautions

Since eszopiclone may cause daytime dizziness and drowsiness, activities that require being alert should be avoided, including driving motor vehicles or operating machinery of any kind. Alcohol consumption should also be avoided while taking eszopiclone regularly.

Physical and psychological dependence on eszopiclone has been reported. The risk of dependence is increased with increased dosage and duration of treatment. Patients who have a history of alcohol or drug abuse or a history of psychiatric illness are at greater risk of dependence. Discontinuing the use of eszopiclone abruptly may produce withdrawal symptoms such as anxiety, abdominal cramping, vomiting, sweating, or shakiness, particularly in patients using higher doses long term. To prevent withdrawal symptoms, it is best to reduce dosage gradually as advised by the physician.

More serious neuropsychiatric adverse effects may include confusion, agitation, depression, depersonalization, amnesia, hallucinations, suicidal thoughts, and aggressive behavior. Aggression, agitation, and changes in behavior may represent a severe allergic reaction and should be reported to the prescribing physician immediately.

Geriatric

Eszopiclone is prescribed most often for elderly patients who are having difficulty falling asleep or staying asleep. However, clinical trials in elderly patients revealed that 2.3% of patients receiving 2 mg tablets and 1.4% of patient receiving 1 mg tablets discontinued treatment due to having adverse reactions. Older adult patients more often report being confused, disoriented, dizzy, or sleepy during the day when they take eszopiclone at night.

Pregnant or breastfeeding

Eszopiclone has not been evaluated in adequate, well-controlled studies in pregnant women and should be used in pregnant women only if benefits justify potential risks to the fetus. It is unknown whether eszopiclone passes into breast milk. Patients who are pregnant or breastfeeding should consult with their physicians about risks versus the benefits of using eszopiclone.

KEY TERMS

Benzodiazepines—A class of drugs that have a hypnotic and sedative action, used mainly as tranquilizers to control symptoms of anxiety.

Dependence—A state in which a person requires a steady concentration of a particular substance in order to avoid withdrawal symptoms.

Drug schedule—A group of drugs including narcotics, sedatives, hallucinogens, and other drugs that are restricted under federal and state laws in the United States. Schedule I substances have no approved medical use, while Schedules II, III, and IV have approved uses. The higher the schedule, the lower the degree of restriction.

Gamma-aminobutyric acid (GABA)—GABA is an amino acid functioning as a neurotransmitter inhibitor in the human central nervous system. It acts to control motor function and to reduce excitability of nerves throughout the body.

Hypnotic—A hypnotic drug is a sedative that balances certain neurotransmitters (serotonin, dopamine, acetylcholine) in the brain.

Insomnia—Insomnia refers to the inability to initiate or maintain sleep.

Myasthenia gravis—Myasthenia gravis is an autoimmune or congenital neuromuscular disorder that involves muscles throughout the body and the nerves that control them. The main characteristics of the disease are muscular weakness and fatigue of any muscles people control themselves (voluntary control), including eye and facial muscles and muscles used in swallowing.

Placebo—A pill or liquid given during the study of a drug or dietary supplement that contains no medication or active ingredient. Usually study participants do not know if they are receiving a pill containing the drug or an identical-appearing placebo.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

Other conditions and allergies

Allergic reactions can result after taking eszopiclone, and some may be severe. Before taking eszopiclone, patients must inform their physicians of any known allergies and previous allergic reactions. Serious allergic

reactions to eszopiclone are rare; however, when taking eszopiclone, any signs of an allergic reaction such as hives, difficulty breathing, or swelling of the face, lips, tongue, or throat should be reported immediately, and patients should stop taking the drug.

Patients with a history of kidney or liver disease, breathing problems or lung diseases (e.g., sleep apnea, chronic bronchitis, chronic obstructive pulmonary disease [COPD]), mental or mood disorders (e.g., depression, anxiety, suicidal thoughts), alcohol or drug abuse, sleepwalking, or the muscle disorder myasthenia gravis are not always candidates for eszopiclone. The physician will consider risks versus benefits in such patients before prescribing eszopiclone.

Side effects

The main side effects of eszopiclone are daytime sleepiness and sedation. Other side effects may include:

- headache
- chest or back pain
- cold symptoms
- dry mouth, bitter or metallic taste
- dizziness, light-headedness
- upset stomach, heartburn
- decreased sexual desire
- painful menstruation
- rashes, itching
- swelling of hands, feet, ankles, or lower legs
- painful or frequent urination

Allergic reactions may include daytime drowsiness, dizziness, hives, difficulty breathing, and swelling of the face, lips, tongue, or throat. Any of these signs or symptoms should be reported to the prescribing physician immediately.

Patients who do not go to sleep after taking eszopiclone may experience light-headedness, problems with coordination, and possibly hallucinations or amnesia if they get up within a few hours of taking the medication.

Interactions

Eszopiclone has been known to interact with other medications. The healthcare provider should be informed of all other medications, supplements, vitamins, and over-the-counter drugs being taken.

Drugs

Certain medications taken during the same time period as eszopiclone may either reduce or increase the

PATIENT PROFILE

A 55-year-old man with a stressful occupation was troubled by insomnia and wondered if a sleeping medication might help. He was finding it difficult to fall asleep and was only sleeping for three or four hours each night, which was affecting his job performance. His doctor suggested several possible treatment options for inducing sleep, including eszopiclone (Lunesta), which is prescribed specifically for short-term treatment of insomnia when the main complaint is being unable to fall asleep. His doctor informed him that the drug is a sedative-hypnotic drug but that it has fewer and less serious side effects than the type of sedative-hypnotic drugs used for treating anxiety, agitation, and seizures. His doctor explained that while eszopiclone is mildly effective for insomnia, it is also a short-acting narcotic and can be habit-forming.

A low initial dose of 1 mg was prescribed for the patient, and he was instructed to take one tablet at bedtime or after trying unsuccessfully to fall asleep. The doctor recommended taking the dose with a full glass of water at least two hours after finishing his evening meal. Eszopiclone works to induce sleep by balancing certain neurotransmitters in the brain, resulting in a sedative effect. The patient was advised to get up cautiously if he woke during the night, since the peak sedative effect occurred within 1 to 1.5 hours and could result in dizziness or drowsiness prior to sleeping a full 7 or 8 hours. He was urged to report any unusual symptoms that might appear after taking the medication, and to return in four weeks for re-evaluation.

During the first ten days of using eszopiclone, the man noticed a slight difference in the time that it took him to fall asleep. His doctor increased the dosage to 2 mg per day, taken at bedtime with a full glass of water. The increased dose promptly improved the patient's ability to fall asleep and stay asleep, and he was still able to remain alert during his workday. However, he began to notice an extremely dry mouth and a bitter or metallic taste. At his follow-up visit, his doctor explained that dry mouth (xerostomia) and metallic taste (dysgeusia) are common side effects of this class of drugs; the dryness was due to reduced saliva production and the metallic taste was a combination of lack of saliva and a digestive imbalance caused by metabolism of the drug in the liver. Given the patient's age and overall good health status, the doctor recommended continuing with the medication but returning to the original dose of one 1 mg tablet per night, which might correct the metallic taste. In addition, he advised that frequent and thorough brushing of the teeth and rinsing the mouth with peppermint mouth wash would also help minimize the metallic taste. He reminded the patient that drinking sufficient water is important both day and night and could help relieve both dry mouth and the metallic taste sensation. The modest adjustments of a reduced dose of eszopiclone with good hydration and mouth hygiene worked together effectively for this patient, providing a good night's sleep, reduced oral symptoms, and greater comfort. The patient agreed to continue the regimen for another four weeks and then begin a gradual reduction of eszopiclone dosage, while also focusing on stress reduction.

sedative effects and unwanted side effects of eszopiclone. Patients should inform their physicians if they are taking rifampin (Rifadin, Rifamate), ketoconazole (Nizoral), or any antidepressants, anti-anxiety medications, or medications given for seizures.

Cimetidine and erythromycin have been found to inhibit the metabolism of nonbenzodiazepines such as eszopiclone and enhance their sedative effects.

Drugs that cause drowsiness or dizziness should be avoided, including antihistamines such as **diphenhydramine**; sleeping aides and anti-anxiety medications such as **alprazolam**, **diazepam**, and **zolpidem**; muscle relaxants such as **baclofen**, **cyclobenzaprine**, **methocarbamol**, and **diazepam** (Valium); and narcotic pain relievers such as codeine, meperidine, **morphine**, or **oxycodone**, among others. To help avoid interactions, patients should inform their physicians about all prescription and

nonprescription drugs being taken, including over-the-counter medications and herbs or supplements.

Food and other substances

Alcohol consumption should be avoided.

Resources

BOOKS

American Society of Health System Pharmacists. *AHFS Drug Information 2015*. Bethesda: ASHP, 2015.

PERIODICALS

Bertisch, S. M., et al. "National Use of Prescription Medications for Insomnia: NHANES 1999–2010." *Sleep* 37, no. 2 (2014): 343–49.

Greenblatt, D. J., and G. K. Zimmet. "Pharmacokinetic Evaluation of Eszopiclone: Clinical and Therapeutic

Implications.” *Expert Opinion in Drug Metabolism and Toxicology* 8, no. 12 (2012): 1609–18.

Krystal, A. D., et al. “Eszopiclone Treatment for Insomnia: Effect Size Comparisons in Patients with Primary Insomnia and Insomnia with Medical and Psychiatric Comorbidity.” *Primary Care Companion CNS Disorders* 14, no. 4 (2012). <http://dx.doi.org/10.4088/PCC.11m01296> (accessed March 6, 2015).

Stranks, E. K., and S. F. Crowe. “The Acute Cognitive Effects of Zopiclone, Zolpidem, Zaleplon, and Eszopiclone: A Systematic Review and Meta-Analysis.” *Journal of Clinical and Experimental Neuropsychology* 36, no. 7 (2014): 691–700.

WEBSITES

AHFS Consumer Medication Information. “Eszopiclone.” American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a605009.html> (accessed March 6, 2015).

Lunesta.com. <http://www.lunesta.com/index.html> (accessed March 6, 2015).

National Sleep Foundation. “Insomnia.” <http://sleepfoundation.org/sleep-disorders-problems/insomnia> (accessed March 6, 2015).

Physicians’ Desk Reference. “Lunesta.” PDR Health. <http://www.pdrhealth.com/drugs/lunesta> (accessed March 6, 2015).

U.S. Food and Drug Administration. “Eszopiclone Containing Sleep Aids: Drug Safety Communication—Can Cause Next-Day Impairment.” <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm397536.htm> (accessed March 6, 2015).

ORGANIZATIONS

National Sleep Foundation, 1010 N. Glebe Road, Suite 310, Arlington, VA 20221, (703) 243-1697, nsf@sleepfoundation.org, <http://sleepfoundation.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

L. Lee Culvert

REVIEWED BY JAMES E. WAUN, MD, RPH

Etanercept

Definition

Etanercept is a tumor necrosis factor (TNF)-alpha inhibitor that is used to treat autoimmune disorders, such as arthritis and psoriasis, by blocking the action of TNF-alpha, an immune system protein that produces widespread inflammation. Etanercept is in a medication class called biologics, because it is based on naturally

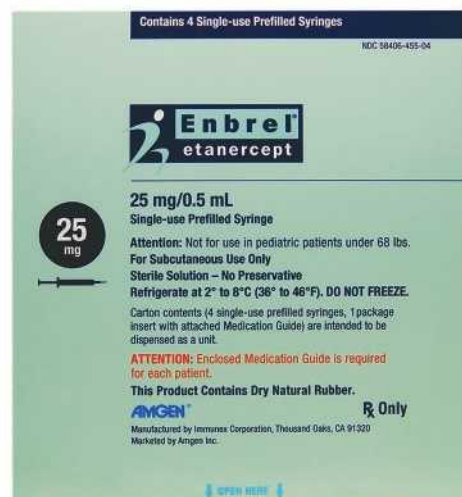
occurring proteins. Because it is used to treat rheumatoid arthritis (RA), it is also classified as a disease-modifying antirheumatic drug (DMARD).

Purpose

Autoimmune disorders are caused by immune system attacks on the body’s own healthy tissues, leading to inflammation, swelling, pain, loss of function, and permanent damage. TNF inhibitors, such as etanercept, do not cure autoimmune disorders, but they can control symptoms, prevent progressive structural damage, and reduce severe complications, hospitalizations, and surgeries. Etanercept is used alone or in combination with other medications to treat:

- RA
- juvenile idiopathic arthritis (JIA) that can delay growth and development
- chronic plaque psoriasis, in which red, scaly patches form on the skin
- psoriatic arthritis (PsA), a serious complication of plaque psoriasis
- ankylosing spondylitis, RA of the joints of the spine

The combination of etanercept with **methotrexate** (MTX), a nonbiologic DMARD, prevents the progression of structural damage and deterioration of function in arthritis patients who have not responded adequately to MTX alone. Etanercept can induce arthritis remission.



Etanercept (Enbrel). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Prolonged maintenance therapy reduces severe complications and improves patient quality of life.

Description

Biologics such as etanercept are similar to antibodies made by the body's own immune system, but they are produced in cell cultures in the laboratory. Etanercept is a protein made by fusing together the portion of the human TNF receptor p75 that binds TNF and a portion of a human immunoglobulin (antibody). In the body, etanercept binds to TNF-alpha, thereby blocking its binding to its normal receptor and preventing it from exerting inflammatory effects on the joints, skin, and spine. Etanercept binds to membrane-bound TNF similarly to the TNF inhibitors **infliximab** and **adalimumab**, but it binds more strongly to soluble TNF than those biologics.

Etanercept and other TNF-alpha inhibitors are among the ten bestselling drugs in the United States. They effectively treat conditions that are both common and chronic and so are generally used long term. For example, RA affects about 1% of the U.S. population, with a peak onset in patients in their 40s. Moderate-to-severe plaque psoriasis affects 1.5 million people in the United States. Extensive direct-to-consumer advertising has probably also played a role in sales of these drugs. Although they are highly effective, etanercept and other TNF inhibitors are very expensive. Etanercept can cost almost \$2,500 per month. It is not clear whether disease remission can be maintained without the drug.

International brand names

Etanercept is marketed under the brand name Enbrel in most countries worldwide. A biologically similar DMARD was launched in India in 2013 under the brand name Etacept.

Recommended dosage

Like other biologics, etanercept is a very large, complex protein—about 1,000 times larger than most chemically synthesized drugs—so it must be administered by injection. Etanercept is available as:

- 50-milligram (mg) single-use prefilled syringes containing 0.98 milliliters (mL) of a 50 mg/mL solution
- 50 mg single-use prefilled SureClick Autoinjectors containing 0.98 mL of a 50 mg/mL solution
- 25 mg single-use prefilled syringes containing 0.51 mL of a 50 mg/mL solution
- 25 mg multiple-use vials of powder to be mixed with the provided liquid

The recommended dosage for adult RA, PsA, and ankylosing spondylitis is 50 mg once a week. For adult

plaque psoriasis, the dosage is 50 mg twice weekly for three months, followed by a maintenance dosage of 50 mg once per week. Missed doses should be injected as soon as possible unless it is almost time for the next dose, in which case the dose should be skipped.

Etanercept is injected under the skin (subcutaneously). The first injection is given in the doctor's office, and the patient or a family member or friend is taught to inject subsequent doses. The medication is injected into the front of the middle thigh. It can also be injected into the lower stomach below the navel, at least 2 in. (5 cm) away from the navel. An assistant may inject the medication into the upper arm. The skin of the stomach or upper arm must be stretched to create a firm surface. Each injection should be made into healthy skin at a different site from previous injections. Prefilled syringes and automatic-injection devices are used only once, even if there is liquid remaining, and are disposed of in a puncture-proof container. Vials with powder that are mixed with solution may have enough for more than one complete dose; in this case, after the first injection, the vial must be refrigerated within four hours after mixing and the remainder used within 14 days. Contents of multiple vials should not be combined to make a complete dose. Etanercept should be kept in its original container in the refrigerator away from light. Refrigerated doses should be warmed by sitting out at room temperature for 15–30 minutes before use.

Pediatric

The recommended dosage for JIA is 50 mg once per week for children weighing at least 138 lb. (63 kg). For children weighing less than 138 lb., the dosage is 0.8 mg/kg (2.2 lb.) of body weight once a week.

Precautions

Patients should discuss the risks of etanercept with their doctor. Etanercept comes with a boxed warning:

- It can decrease the body's ability to fight infection and increase the risk of severe or life-threatening fungal, bacterial, and viral infections that could spread through the body.
- Doctors should be informed of any infections, including open cuts or sores, intermittent infections such as cold sores, or chronic infections, and patients should be monitored for any signs of infection before, during, and after treatment.
- Doctors should be informed of any current or past conditions or medications that affect the immune system, including diabetes and HIV/AIDS, and whether patients have ever lived in areas such as the Ohio or

KEY TERMS

Adalimumab—Humira. A tumor necrosis factor inhibitor similar to etanercept.

Ankylosing spondylitis—Rheumatoid arthritis of the spine.

Antibody—A specific protein produced in response to a specific protein, such as tumor necrosis factor.

Autoimmune disorders—Conditions caused by inappropriate immune system activity.

Biologics—Naturally occurring compounds in the human body, usually proteins, that are used to treat disease.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Chronic—A disease or condition that progresses slowly but persists or reoccurs over time.

Disease-modifying antirheumatic drug (DMARD)—A drug such as etanercept that suppresses the immune system to decrease inflammation from rheumatoid arthritis.

Inflammation—An immune system response mediated by TNF-alpha.

Infliximab—Remicade. A tumor necrosis factor inhibitor that is similar to etanercept.

Juvenile idiopathic arthritis (JIA)—A type of autoimmune arthritis that affects children aged 16 and younger and that can delay growth and development.

Methotrexate (MTX)—A drug used to treat severe psoriasis and rheumatoid arthritis.

Plaque psoriasis—An autoimmune disorder that causes patches of inflamed skin.

Psoriatic arthritis (PsA)—Joint inflammation that develops in some psoriasis patients.

Receptor—A molecule, such as a protein, inside or on the surface of a cell, that binds a specific substance.

Rheumatoid arthritis (RA)—A chronic autoimmune disease that causes pain, stiffness, inflammation, swelling, and sometimes destruction of joints.

Tuberculosis (TB)—A highly variable chronic bacterial infection that affects the lungs and can spread to other parts of the body.

Tumor necrosis factor (TNF)-alpha—A protein called a cytokine that mediates inflammation throughout the body and activates immune system cells. Inhibited by etanercept.

Mississippi River valleys where fungal infections are common.

- Patients should be tested for inactive tuberculosis (TB) and hepatitis B infection before treatment. Doctors should be informed if patients have ever had TB, ever been in a country where TB is common, or been around someone who has had TB.
- Doctors should be informed immediately of any of the following symptoms before, during, or shortly after treatment: sweating; sore throat; cough; coughing up bloody mucus; fever; weight loss; weakness; loss of muscle tone; yellowing of the skin or eyes; loss of appetite; nausea or vomiting; muscle aches; dark urine; clay-colored bowel movements; chills; stomach pain; rash; extreme tiredness; diarrhea; warm, red, or painful skin; painful, difficult, or frequent urination; other signs of infection.

There are various other precautions:

- Etanercept should not be stopped without consulting the doctor.

- Doctors and laboratory personnel should be notified about etanercept injection before performing any laboratory tests.
- Doctors and dentists should be informed of etanercept treatment before performing any type of surgery.
- Patients should not have any **vaccinations** without talking to their doctor.
- Patients should call their doctors immediately if they are exposed to chickenpox while receiving etanercept injections.
- Adults using etanercept may be at greater risk for lymphoma, leukemia, skin cancer, and other types of cancer.

Pediatric

If possible, children should receive all of their required vaccinations before beginning etanercept. Some children and adolescents administered etanercept have developed severe or life-threatening cancers, including lymphoma.

Pregnant or breastfeeding

Etanercept is in the FDA low-risk pregnancy category B. Although etanercept has not been well-studied during pregnancy, there have been no reports of increased risk of birth defects or miscarriage in pregnant women treated with etanercept or other TNF inhibitors. Significant amounts of etanercept are not expected to reach the placenta until the second or third trimester of pregnancy. Etanercept is being studied to determine whether it can improve the success of some fertility treatments in certain women. Nevertheless, women who are pregnant or breastfeeding, planning to become pregnant, or become pregnant while receiving etanercept should consult with their doctors. On average, it takes about three weeks after the last injection for etanercept to completely clear the body. Babies whose mothers received etanercept during pregnancy may need to have some vaccinations delayed.

Because etanercept is a large protein, very little will pass into breast milk, and breast milk levels appear to be very low. Furthermore, etanercept is not well absorbed by the gut, so any of the medication in breast milk would not be well absorbed by the baby's digestive system. Premature infants with underdeveloped digestive systems may absorb more.

Other conditions and allergies

Patients should inform their doctors and pharmacists if they are allergic to etanercept or any of its ingredients or any other medications and whether the patient or person injecting the drug is allergic to latex or rubber. Doctors should be informed if patients have ever had seizures, numbness or tingling in any part of the body, or any disease that affects the nervous system such as multiple sclerosis, transverse myelitis, optic neuritis, bleeding problems, liver disease, or heart failure.

Side effects

Patients should contact their physician if any of the following side effects are severe or long-lasting:

- redness, itching, pain, or swelling at the injection site
- headache
- nausea
- vomiting
- heartburn
- stomach pain
- weakness
- cough

In addition to the symptoms listed in the boxed warning, side effects that are medical emergencies include:

- seizures
- bruising
- bleeding
- pale skin
- blistering skin
- rash
- rash on the face and arms that worsens in the sun
- hives
- itching
- swelling of the eyes, face, lips, tongue, throat, arms, hands, feet, ankles, or lower legs
- difficulty breathing or swallowing
- numbness or tingling
- vision problems
- weakness in the arms or legs
- dizziness
- red, scaly patches or pus-filled bumps on the skin

Interactions

Patients should tell their doctors and pharmacists about all of their prescription and nonprescription medications, vitamins, nutritional supplements, and herbal products.

Drugs

Medications that decrease immune system activity and may require changing etanercept dosages or monitoring for side effects include:

- abatacept
- anakinra
- azathioprine
- MTX
- steroids such as dexamethasone, **methylprednisolone**, **prednisone**, or prednisolone

Other drugs that may require changing dosages or careful monitoring for side effects include diabetes medications and cyclophosphamide.

Resources

BOOKS

- Koo, John Y. M., et al, eds. *Moderate to Severe Psoriasis*, 4th ed. Boca Raton, FL: CRC Press, 2014.
- Zhou, Honghui, and Bernd Meibohm, eds. *Drug-Drug Interactions for Therapeutic Biologics*. Hoboken, NJ: John Wiley & Sons, 2013.

PERIODICALS

- Curtis, Jeffrey R., et al. "Estimating Effectiveness and Cost of Biologics for Rheumatoid Arthritis: Application of a Validated Algorithm to Commercial Insurance Claims." *Clinical Therapeutics* 36, no. 7 (2014): 996–1004.
- Emery, Paul, et al. "Sustained Remission with Etanercept Tapering in Early Rheumatoid Arthritis." *New England Journal of Medicine* 371, no. 19 (2014): 1781–92.
- Shader, Richard I. "Rheumatoid Arthritis and More." *Clinical Therapeutics* 36, no. 7 (July 2014): 993–94.
- Tanaka, Yoshiya, and Shintaro Hirata. "Is It Possible to Withdraw Biologics from Therapy in Rheumatoid Arthritis?" *Clinical Therapeutics* 35, no. 12 (2013): 2028–35.
- Tkacz, Joseph, et al. "Utilization and Adherence Patterns of Subcutaneously Administered Anti-Tumor Necrosis Factor Treatment among Rheumatoid Arthritis Patients." *Clinical Therapeutics* 36, no. 5 (2014): 737–47.

WEBSITES

- Agency for Healthcare Research and Quality. "Medicines for Psoriatic Arthritis: A Review of the Research for Adults." Effective Health Care Program. <http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1312> (accessed January 22, 2015).
- Organization of Teratology Information Specialists. "Etanercept (Enbrel) and Pregnancy." Raising Mom's Awareness. Reducing Baby's Risk: OTIS. <http://www.mohtortobaby.org/files/Etanercept.pdf> (accessed January 22, 2015).
- U.S. Food and Drug Administration. "Medication Guide Enbrel (en-brel) (Etanercept)." <http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088590.pdf> (accessed January 22, 2015).
- U.S. National Library of Medicine. "Etanercept Injection." MedlinePlus. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a602013.html> (accessed January 22, 2015).

ORGANIZATIONS

- Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, 301-427-1364, <http://www.ahrq.gov/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, 888-INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

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tuberculosis (TB), *Mycobacterium tuberculosis*, as well as related species *Mycobacterium avium* and *Mycobacterium kansasii*, which can infect immunocompromised individuals (people with an impaired immune system), such as people with human immunodeficiency virus (HIV).

Purpose

Ethambutol is an antibacterial agent, also called an antituberculosis agent, that works specifically to eliminate certain types of infectious bacteria, mainly the mycobacteria strain that causes pulmonary TB. It can be used both to treat tuberculosis and to prevent it from spreading from one person to another. Ethambutol is often used in combination with other medications (e.g., isoniazid, rifampicin, and pyrazinamide) that are also used to treat tuberculosis. It is an important medication worldwide, since pulmonary TB is still prevalent in many developed and developing countries.

Other uses for ethambutol may include treating opportunistic HIV infections such as those caused by *Mycobacterium avium* and *Mycobacterium kansasii*.

Description

The activity of bacteriostatic drugs is different from commonly used antibiotic agents called bactericides, which kill bacteria directly on contact. As a bacteriostat, ethambutol works by interfering with the DNA replication and cellular metabolism of actively growing tubercular



Ethambutol hydrochloride, 400 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Ethambutol

Definition

Ethambutol (ethambutol dihydrochloride) is an antimycobacterial drug that stops certain bacteria from reproducing, including the mycobacteria that cause pulmonary

bacteria. It then works in conjunction with the body's immune system to eliminate the bacteria from the body. This activity stops the targeted bacteria from growing in the body, and the elimination of the bacteria helps to prevent the spread of TB to otherwise healthy individuals.

Ethambutol is taken orally and is absorbed by the gastrointestinal tract, from where it is then distributed throughout the body. It concentrates primarily in the lungs, kidneys, saliva, and red blood cells, and it is excreted mainly in urine. This type of antibiotic only works against bacteria, not against viruses.

TB can be either active, when it produces active symptoms and can spread to other individuals, or latent, when the tubercular bacilli (bacteria) are present but are not producing symptoms. Mycobacteria such as *Mycobacterium tuberculosis* are especially slow growing and can grow within body cells almost as a parasite would grow. The cell walls of the mycobacterium uniquely protect it from the body's immune system activity, allowing the bacteria to spread to any body organ that has a good supply of oxygen (e.g., lungs, kidneys, and bones). This makes ethambutol particularly effective, since its activity is directed to the cell wall of the bacteria.

Pulmonary tuberculosis attacks the tissue cells of the lungs and is the most common form of TB. However, other forms of tuberculosis may affect the skin (cutaneous tuberculosis) or may appear as small infected sores or lesions in various sites throughout the body (miliary tuberculosis). It can develop in the pharynx (pharyngeal tuberculosis) or in a joint (hip tuberculosis). Ethambutol may be the treatment of choice for any type of tuberculosis, but it is most commonly applied to treat pulmonary tuberculosis.

U.S. brand names

Ethambutol is sold in the United States under the brand name Myambutol.

International brand names

Ethambutol is sold internationally under the brand name Servambutol.

Recommended dosage

A powdered form of ethambutol dihydrochloride is prepared as a tablet to be administered orally. It is available in 100 and 400 milligram (mg) tablets.

The dosage for ethambutol is determined based on the patient's age, weight, overall health status, and response to treatment. For initial treatment of pulmonary TB, the recommended dose is 15 mg per kilogram (kg, or 2.2 lb.) of body weight per day. It is usually taken for

KEY TERMS

Antimycobacterial—A bacteriostatic drug that specifically targets mycobacteria to eliminate them from the body.

Bactericide—An antibacterial drug that acts to kill bacteria in the body and thereby to stop infection from becoming worse or spreading.

Bacteriostat—An antibacterial drug that acts to stop specific bacterial cells from reproducing, thereby stopping infection and preventing the spread of the bacteria from one person to another.

Diabetic retinopathy—Diabetic retinopathy represents several eye conditions that develop as complications of diabetes mellitus. It can involve damage to the blood vessels in the retina of the eye and may result in cataract or glaucoma.

Human immunodeficiency virus (HIV)—The virus that causes acquired immune deficiency syndrome (AIDS).

Hyperuricemia—An abnormally high level of uric acid in the blood due to an imbalance in the amount of purines ingested as food or due to the activity of certain drugs that may decrease the excretion of uric acid. Excess uric acid is associated with gout and gouty arthritis.

Mycobacteria—*Mycobacterium* is in the family of Mycobacteriaceae and a genus of Actinobacteria. These bacteria cause serious diseases in humans and other mammals, including tuberculosis and leprosy.

Nystagmus—A condition of the eyes that is characterized by involuntary eye movement and results in reduced or limited vision.

60 days in combination with another antituberculosis drug, most commonly isoniazid (Hyzyd, Laniazid). In certain cases, ethambutol may be taken initially for two months and then followed by four to seven months of combination treatment. Other drugs may be added to the regimen if the patient appears to be resistant to the ethambutol/isoniazid combination treatment.

Ethambutol is taken by mouth, usually once daily at the same time every day. With appropriate changes in dosage by the healthcare provider, it can be taken twice weekly or three times per week. It can be taken either with or without food. However, ethambutol may cause upset stomach in some people; if that occurs, it may be controlled by taking it with food.

Antibiotics work best when the amount of the drug is maintained in the body, which means that ethambutol should be taken at evenly spaced intervals. If a dose of ethambutol is missed, it should be taken as soon as possible. If it is close to the time for the next dose, skip the missed dose and maintain the regular dosing schedule. Two pills should never be taken at the same time. Patients should take the entire prescription even if symptoms are relieved before the pills are gone.

Precautions

With ethambutol and other bacteriostatic drugs, the targeted bacteria will come back and start growing again if the treatment is not maintained for the recommended time period. Patients should be sure to take the entire prescription, even if symptoms subside.

Individuals who are taking any prescription drugs or nonprescription medicines, herbal preparations, or dietary supplements should also inform their healthcare providers so that possible interactions can be avoided.

Pediatric

The safety and efficacy of ethambutol has not been confirmed in children younger than 13 years of age. Ethambutol should not be given to children younger than 13.

Pregnant or breastfeeding

Ethambutol carries the FDA pregnancy category C, which means that adequate studies have not been performed in pregnant women. However, there have been reports of ophthalmic abnormalities in infants born to women who had been treated with ethambutol while pregnant. Pregnant women should consult with their doctors about the safety of the drug for the baby. Ethambutol is released in breast milk, but studies have shown no evidence of harmful effects when breastfeeding. The benefits and risks of using ethambutol must be considered based on the individual case.

Other conditions and allergies

Individuals who have cataracts, recurrent inflammation of the optic nerve, or eye problems associated with diabetes (diabetic retinopathy) may not be candidates for ethambutol because these conditions will mask vision changes caused by the drug, which can result in damage to the eyes if not treated.

Certain medical conditions may interfere with ethambutol and reduce its effectiveness against tuberculosis, including kidney or liver problems and gouty arthritis or attacks of gout. Patients should inform their

healthcare providers of any history of such illnesses as well as any allergies to medicines, foods, or other substances. Ethambutol should not be taken by individuals who are allergic to any ingredients in the drug.

Side effects

Common side effects of ethambutol may include upset stomach, loss of appetite, vomiting, dizziness, general body discomfort, and skin rash or itching. Taking ethambutol with food may help patients avoid stomach upset.

Vision problems may occur when taking ethambutol, including sudden changes in vision, blurred vision, limited vision (vertical nystagmus), and inability to see the colors red and green (red-green colorblindness). Optical neuritis, an inflammation of the optic nerve, may develop.

Acute gout, or hyperuricemia, may occur in some individuals when taking ethambutol. Therefore, the drug should not be used to treat anyone who has previously had gouty arthritis or acute gout.

The presence of persistent nausea and vomiting, unusual fatigue or weakness, loss of appetite, abdominal pain, and dark urine, with or without yellowing of the eyes or skin, may indicate liver disease. Such symptoms should be reported to the healthcare provider as soon as they are noticed.

Other potentially severe side effects can occur, such as the loss of sensation in the limbs (peripheral neuropathy). Any such side effects that occur, such as tingling in the hands or arms or loss of sensation in the arms or legs, should be reported to the physician.

Pediatric

In children under the age of six, ethambutol can cause optical neuritis (an inflammation of the optic nerve). For this reason, ethambutol should not be used for children younger than six years old.

Interactions

The use of ethambutol is contraindicated (should not be taken) if a patient has received live bacillus Calmette–Guérin (BCG) vaccine. Serious or life-threatening interactions may occur as a result of the combination.

Drugs

The activity of certain other drugs may be compromised when taking ethambutol, including **allopurinol**, febuxostat, and probenecid, which are used to treat gout, and sodium picosulfate/magnesium, which is a laxative.

Antacid medications that contain aluminum hydroxide are known to interfere with the activity of ethambutol, which reduces its effectiveness against tuberculosis. Aluminum hydroxide and aluminum hydroxide/magnesium should be avoided. If antacids are necessary, they must be taken two hours before or four hours after taking ethambutol.

Certain other medications may also cause dizziness when taken in combination of ethambutol.

Food and other substances

Ethambutol may cause dizziness, which can be worsened by consumption of alcohol. Alcohol should be avoided while taking ethambutol.

Resources

BOOKS

American Society of Health-System Pharmacists. *AHFS Drug Information 2011*. Bethesda, MD: American Society of Health-System Pharmacists, 2011.

Porter, Robert S., ed. "Pulmonary Disorders." In *The Merck Manual of Diagnosis and Therapy*. 19th ed. 1823–2014. Whitehouse Station, NJ: Merck Research Laboratories, 2011.

Shetty, N., J. W. Tang, and J. Andrews. *Infectious Disease: Pathogenesis, Prevention, and Case Studies*. Hoboken, NJ: Wiley-Blackwell, 2009.

WEBSITES

AHFS Consumer Medication Information. "Ethambutol." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682550.html> (accessed February 10, 2015).

"Ethambutol." Drugs.com. <http://www.drugs.com/cdi/ethambutol.html> (accessed February 8, 2015).

Lexi-Comp. "Ethambutol." Merck Manual (Professional Edition). <http://www.merckmanuals.com/professional/lexicomp/ethambutol.html> (accessed February 10, 2015).

Micromedex. "Ethambutol (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/ethambutol-oral-route/description/drg-20063728> (accessed February 10, 2015).

ORGANIZATIONS

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Ethinyl estradiol/etonogestrel see

Etonogestrel/ethinyl estradiol

Ethinyl estradiol/norelgestromin see

Norelgestromin/ethinyl estradiol

Etodolac

Definition

Etodolac is a prescription pain killer (analgesic) that belongs to the family of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs).

Purpose

Etodolac is used to treat acute and chronic symptoms of osteoarthritis, rheumatoid arthritis, and juvenile idiopathic arthritis.

Description

Etodolac is available in the following formulations:

- oral capsules: 200 and 300 milligrams (mg)
- oral tablets: 400 mg and 500 mg
- extended-release tablets: 400 mg, 500 mg, and 600 mg

U.S. brand names

Etodolac was previously sold in the United States under the brand name Lodine, but as of early 2015 this brand was discontinued. However, many generics are available.

Canadian brand names

In Canada, etodolac is sold under the names Ulradol and Apo-Etodolac.



Etodolac, 500 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Acute—Having a sudden onset and lasting a short time.

Analgesic—A drug used to control pain.

Ankylosing spondylitis—A type of arthritis in the spine that leads to stiffening and fusion of the vertebral (spinal) bones.

Boxed warning—This is a notification required by the U.S. Food and Drug Administration (FDA) that a drug carries the potential for a disabling or life-threatening adverse reaction, and its benefits must be weighed against this risk. The serious adverse reaction may be prevented or its frequency reduced with proper patient management (e.g., proper assessment of the individual's health status, avoidance of drugs with known interactions), or the FDA may have approved the drug only with restrictions on its distribution and use.

Bronchiole—A very small, thin-walled air passage in the lungs that branches off from a bronchus.

Bronchospasm—Constriction of the muscles surrounding the bronchioles, or air passages in the lungs.

Bursitis—Inflammation of a fluid-filled sac within a joint.

Chronic—A disease or condition that progresses slowly but persists or reoccurs over time.

Gout—A condition in which the deposition of uric acid crystals in the joints causes swelling and pain.

Parkinsonism—A progressive nervous system disorder that affects normal movement.

Pregnancy class—A system of classifying drugs for their use during pregnancy. Class A: Controlled human studies have identified no fetal risk. Class B: Animal studies indicate no fetal risk but no human studies exist, or adverse effects have been found in animals but not in well-controlled human studies. Class C: No adequate animal or human data is available, or adverse effects have been found in animal studies but no human data is available. Class D: Evidence of fetal risks, but benefits outweigh risks. Class X: Evidence of fetal risks, and risks outweigh any benefits.

Rhinitis—An inflammation of the mucous membranes that line the nasal passages.

Tendinitis—Inflammation of a tendon.

Tolerance—A decrease in tolerance to a drug, requiring an individual to take more and more of the drug to achieve the same effect.

International brand names

Etodolac is sold under several brand names internationally.

Recommended dosage

The recommended dose ranges for adults and geriatric patients are as follows:

- acute pain, immediate-release formulation: 200–400 mg per dose, every 6–8 hours (maximum dose per 24 hours is 1,000 mg).
- rheumatoid arthritis and osteoarthritis: 300–500 mg per dose, every 12 hours.
- immediate-release formulation, general: 400 mg twice daily, 300 mg two to three times per day, or 500 mg twice daily (depending on specific pill being taken)
- extended-release formulation: 400–1,000 mg daily

Pediatric

If used in pediatric patients (6–16 years) to treat juvenile idiopathic arthritis, the dose is determined by weight:

- children weighing 20–30 kg (approximately 44–66 lb.): 400 mg dose once per day
- children 31–45 kg (~68–99 lb.): 600 mg once per day
- children 46–60 kg (~101–132 lb.): 800 mg once per day
- children over 60 kg (132 lb.): 1,000 mg once per day

Other conditions and allergies

In the case of mild to moderate kidney impairment, no dosage adjustment is recommended. However, in the case of severe kidney impairment, etodolac use is not recommended.

No dosage adjustment is recommended in the case of liver impairment.

Precautions

The following precautions apply to all individuals.

- Etodolac should not be taken by individuals who are hypersensitive to it or other nonsteroidal anti-inflammatory medications, or who have the following cluster

of three factors: bronchial asthma, aspirin intolerance, and rhinitis.

- Individuals who have experienced bronchospasm, asthma, rhinitis, or hives while taking **aspirin** or other NSAIDs should not take etodolac.
- A boxed warning is included with this product stating that individuals should be aware of an increased risk of life-threatening heart attack or stroke with the use of etodolac. The risk elevates with prolonged use over time or if other cardiovascular risk factors or conditions are present.
- A boxed warning is included with this product stating that individuals should be aware of an increased risk of life-threatening gastrointestinal irritation, inflammation, ulceration, bleeding, or perforation. Patients with a history of these problems; elderly individuals; smokers; heavy alcohol drinkers; or people using aspirin, blood thinners, or steroid medications should use particular caution or take an alternate drug. The gastrointestinal risks may be decreased if etodolac is taken with food.
- A boxed warning is included with this product stating that etodolac should not be given to patients who have had a recent coronary artery bypass graft (CABG) due to a greatly increased risk of heart attack or stroke.
- Etodolac may cause headache, dizziness, and confusion.
- Etodolac may cause vision problems, including blurring, decreased vision, blind spots, and problems discerning color. If these symptoms occur, patients should stop use of etodolac and go to an eye doctor (ophthalmologist).
- Etodolac increases bleeding time, so patients with clotting disorders or who are taking anticoagulant medications such as blood thinners or aspirin should use particular caution and undergo regular monitoring for the development of anemia. Individuals who are scheduled to have dental or surgical procedures should avoid the use of etodolac in the week prior to the procedure.
- Etodolac can cause an increased blood level of potassium, especially in older people, patients with kidney disease or diabetes, or individuals taking other drugs that can increase potassium levels.
- Etodolac can cause skin reactions, including rashes, welts, hives, blisters, and separation or peeling of the skin layers. If this occurs, etodolac use should be immediately stopped.

Geriatric

The elderly are at particular risk of complications from etodolac use, especially bleeding, heart attack, and

stroke. Etodolac should be used with extreme caution and close monitoring in older patients.

Pregnant or breastfeeding

Etodolac is considered a pregnancy category C drug up to 30 weeks gestation and a pregnancy category D drug after 30 weeks gestation. Pregnancy category C means that the risk of adverse effects to a fetus cannot be ruled out in pregnant women. If at all possible, use of this drug should be avoided. Pregnancy category D means that studies have shown risks to a developing fetus. Etodolac should not be used by women in the last trimester of pregnancy.

Research has not fully determined whether etodolac passes into breast milk, so it should be avoided by breastfeeding women.

Other conditions and allergies

Etodolac should be avoided in people with specific conditions, including:

- people with asthma (may cause severe bronchospasm and wheezing)
- patients who have undergone recent coronary artery bypass graft (CABG) surgery
- patients with liver disorders (may cause hepatitis, liver failure)
- individuals with high blood pressure
- individuals with kidney impairment

Etodolac may prompt the onset of kidney problems in the elderly or individuals who are dehydrated, have heart or liver failure, or are taking diuretic medications or ACE inhibitors (used to treat hypertension).

Side effects

The most common side effects of etodolac treatment include:

- upset stomach
- abdominal pain
- indigestion
- nausea and vomiting
- gas
- constipation or diarrhea
- dizziness
- anxiety
- ringing in the ears
- itching, rash, or hives
- headache, dizziness, or drowsiness
- seizures

- blood test evidence of bone marrow suppression, including low white blood cell counts, low platelets, and low hematocrit (red blood cell levels)
- blood test evidence of liver damage
- blood test evidence of kidney damage
- blood in the urine

Rare but serious signs of a significant allergic reaction to etodolac should prompt individuals to seek immediate medical care. These include:

- difficulty breathing or swallowing
- hoarse voice
- wheezing, shortness of breath, or cough
- fever
- pain in the abdomen
- blue skin or lips
- yellow cast to the skin or the whites of the eyes (symptoms of jaundice)
- severe headache
- stiff neck
- confusion
- seizures
- swollen face, lips, tongue, or throat
- rash, hives, or blisters or peeling skin

Interactions

Pharmaceutical drugs may interact with other drugs, herbal and dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Concomitant use of etodolac may increase potential toxic effects of the following drugs:

- 5-ASA derivatives
- antiplatelet drugs
- aminoglycoside antibiotics
- anticoagulants
- bisphosphonate derivatives
- collagenase
- cyclosporine
- desmopressin
- digoxin
- haloperidol

- lithium
- **methotrexate**
- salicylates
- **tacrolimus**
- tenofovir
- vancomycin

The risk of potential adverse effects from etodolac may be increased with concomitant use of the following drugs:

- ACE inhibitors
- angiotensin II receptor blockers
- tricyclic antidepressants
- corticosteroids
- dextetodolac
- **diclofenac**
- floctafenine
- **ketorolac**
- probenecid
- selective serotonin reuptake inhibitors (SSRIs)
- serotonin/norepinephrine reuptake inhibitors (SNRIs)
- treprostinil

Use of etodolac may hamper the effectiveness of the following drugs:

- aliskiren
- beta blockers
- eplerenone
- hydralazine
- loop diuretics
- potassium-sparing diuretics
- thiazide diuretics

Use of bile acid sequestrants may hamper the effectiveness of etodolac.

Resources

BOOKS

- Aronson, J. K. *Meyler's Side Effects of Analgesics and Anti-inflammatory Drugs*. Oxford: Elsevier, 2010.
- Benzon, Honorio T. *Essentials of Pain Medicine*. 3rd ed. Philadelphia: Saunders, 2011.
- Smith, Howard S. *Current Therapy in Pain*. Philadelphia: Saunders, 2009.
- Waldman, Steven D. *Pain Management*. 2nd ed. Philadelphia: Saunders, 2011.

WEBSITES

- AHFS Consumer Medication Information. "Etodolac." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a692015.html> (accessed February 9, 2015).

Physicians' Desk Reference. "Etonogestrel." PDR Health. <http://www.pdrhealth.com/drugs/etonogestrel> (accessed February 9, 2015).

U.S. National Library of Medicine. LactMed (Drugs and Lactation Database). <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm> (accessed February 9, 2015).

ORGANIZATIONS

American Chronic Pain Association, PO Box 850, Rocklin, CA 95677, (800) 533-3231, APAC@theacpa.org, <http://www.theacpa.org>.

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

National Pain Foundation, 14828 West 6 Avenue, Suite 16-B, Room 1, Golden, CO 80401-5000, (720) 541-6808, Fax: (720) 541-6809, <http://www.thenationalpainfoundation.org>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rosalyn S. Carson-Dewitt, MD

REVIEWED BY KEVIN GLAZA, RPh

Etonogestrel/ethinyl estradiol

Definition

Etonogestrel/ethinyl estradiol is a contraceptive that prevents pregnancy by suppressing ovulation. It is prepared as a flexible vaginal ring that is inserted easily into the vaginal canal, where it releases the steroidal hormones estrogen and progestin. Etonogestrel is also available as a progestin-only subdermal implant that is placed under the skin of the upper arm by injection.

Purpose

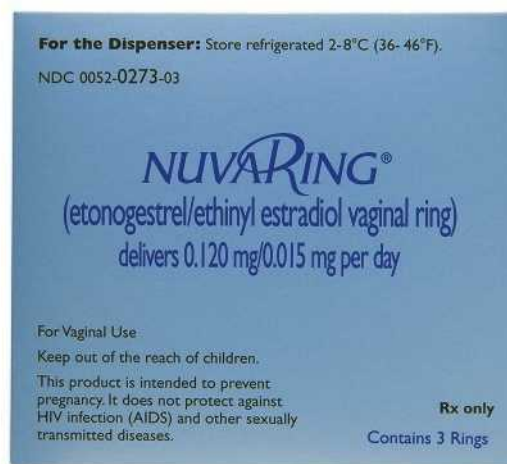
Etonogestrel/ethinyl estradiol is a balanced combination of low-dose estrogen and progestin hormones formulated as a flexible vaginal ring. It contains a fixed dose of ethinyl estradiol, a form of estrogen, and the steroidal progestin etonogestrel. Etonogestrel is the active form of the hormone desogestrel, a derivative of progestin. The ring is easily placed into the upper vaginal canal by the user, where it continuously releases the hormonal medication to protect against pregnancy. The continuous release of hormones by the ring maintains dosages of estrogen and progestin that are significantly lower than in some other contraceptives. However, the risk of blood clot formation is associated with contraceptive use. No other contraceptive measures are needed when using the etonogestrel ring.

Description

The etonogestrel ring provides continuous contraception if used as recommended. The hormonal medications in the etonogestrel birth control ring work by preventing the release of eggs by the ovaries. This is the result of increases in the hormone levels, which signal the brain to stop the ovaries from releasing eggs. The presence of the hormones also thickens the cervical mucus and the lining of the uterus so that it becomes more difficult for sperm to reach the uterus in time to fertilize an egg. At the same time, it also becomes more difficult for an egg that does become fertilized to adhere to the uterine lining.

Effective monthly protection from pregnancy requires that the etonogestrel ring remains in place in the vaginal canal for three weeks. The ring is then removed for seven days and a new ring is inserted on the same day of the week and same time that the previous ring was inserted in order to maintain continuous protection. The woman's menstrual period usually starts during the seven-day ring-free period, and the new ring is inserted on the correct day whether or not bleeding has stopped. No daily dosing is necessary and the ring is reported to be 98% effective in preventing pregnancy, similar to the effective rate of the birth control pill.

Most women can become pregnant fairly quickly after use of the etonogestrel ring has been discontinued.



NuvaRing (etonogestrel/ethinyl estradiol). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

U.S. brand names

The etonogestrel ring is sold in the United States under the brand name NuvaRing. Etonogestrel is also available as a progestin-only subdermal implant (placed under the skin of the upper arm by injection) and sold under the brand names Implanon and Nexplanon.

Canadian brand names

The etonogestrel ring is sold in Canada under the brand name NuvaRing.

International brand names

The etonogestrel ring is sold internationally under the brand names Cirlet and NuvaRing. The progestin-only subdermal implant is sold internationally under the brand names Implanon, Implanon NXT, and Nexplanon.

Recommended dosage

The dosage of etonogestrel is standardized within the ring (11.7 mg etonogestrel, 2.7 mg ethinyl estradiol) and a correct daily dose is delivered continuously. As long as the ring is left in place, there is no concern about missed dosages or overdosing.

Precautions

Women using the etonogestrel ring may experience changes in the timing of their menstrual cycles and possibly in the amount of menstrual bleeding. Any heavy or long-lasting menstrual periods should be reported to a healthcare provider. If periods stop, the patient should be evaluated for possible pregnancy.

Women with a history of blood clots, heart attack or stroke, or any disease associated with blood clot formation should not use the etonogestrel ring, as the hormones in the ring are known to contribute to the development of blood clots, just as with other hormonal contraceptives. The risk of developing blood clots may be higher with etonogestrel than with certain low-dose, progestin-only contraceptives.

The etonogestrel ring should not be used by women with diabetes and concomitant kidney, eye, nerve, or blood vessel damage. Etonogestrel should also not be used by women with certain types of migraine headaches, liver disease or liver tumors, a history of breast cancer, or any estrogen-dependent gynecologic cancer (e.g., endometrial cancer).

The etonogestrel ring does not protect women from infection by sexually transmitted diseases, including HIV and AIDS. The use of condoms is still the only protection from these diseases.

KEY TERMS

Estrogen—A female hormone produced by the ovaries that stimulates the growth of the lining of the uterus.

Jaundice—Yellowing of the eyes and skin due to an excess of bilirubin, a chemical in blood cells. Jaundice occurs with certain diseases in which the liver cannot process the breakdown of old blood cells properly, which results in too much bilirubin being released into the bloodstream.

Progestin—A synthetic steroid hormone, or progestogen, that has the same effects as naturally occurring sex hormones.

Pregnant or breastfeeding

Pregnant women should not use the etonogestrel ring, so a pregnancy test must be done to rule out pregnancy before inserting the ring.

Side effects

The etonogestrel ring is associated with certain side effects, including menstrual cramps, changes in the menstrual cycle, mild headache, dizziness, mood changes or nervousness, vaginal itching or discharge, breast pain, acne, problems with contact lenses, mild nausea or stomach pain, back pain, sore throat or flu-like symptoms, and weight gain. These are usually not serious side effects and may clear up spontaneously.

More serious side effects that should be reported as soon as they are noticed include:

- sudden numbness or weakness on one side of the body
- severe cramping in the pelvic area
- pain, swelling, warmth, or redness in one or both legs
- sudden severe headache, confusion, pain behind the eyes, or problems with vision or balance
- sudden cough, wheezing, rapid breathing, coughing up blood
- pain or heaviness in the chest, pain spreading to the arm or shoulder, nausea, and sweating
- swelling of hands, ankles, or feet
- yellowing of the skin or eyes (jaundice)
- depression, manifesting as trouble sleeping, fatigue, weakness, and mood changes
- sudden severe high blood pressure, manifesting as severe headache, blurred vision, buzzing in the ears,

anxiety, confusion, chest pain, shortness of breath, irregular heartbeat, or seizures

Interactions

Etonogestrel/ethinyl estradiol is known to interact with various drugs and supplements.

Drugs

Certain drugs may interfere with the contraceptive action of the etonogestrel ring, resulting in pregnancy. Drugs that affect the hormonal activity of the ring include bosentan (Tracleer), dexamethasone (Cortastat, Dexasone, Solurex, DexPak), **griseofulvin** (Fulvicin, Grifulvin), rifabutin (Mycobutin), **rifampin** (Rifadin, Rifater, Rifamate), and rifapentine (Priftin), as well as drugs used to treat hepatitis C, HIV, or AIDS. Antifungal medications (itraconazole or **ketoconazole**) and barbiturates (phenobarbital, secobarbital, pentobarbital) also interfere with the effectiveness of etonogestrel and should be avoided.

Seizure medications such as **carbamazepine** (Carbatrol, Equetro, Tegretol), felbamate (Felbatol), **oxcarbazepine** (Trileptal), and primidone (Mysoline) should be avoided. Taking these drugs while using the etonogestrel ring may result in pregnancy.

Herbs and supplements

The herb St. John's wort can reduce the effectiveness of etonogestrel contraception and should not be taken.

Resources

PERIODICALS

- Brache, V., L. J. Payán, and A. Faundes. "Current Status of Contraceptive Vaginal Rings." *Contraception* 87, no. 3 (2013): 264–72. <http://dx.doi.org/10.1016/j.contraception.2012.08.037> (accessed February 10, 2015).
- Caruso, S., et al. "Quality of Sexual Life of Women Using the Contraceptive Vaginal Ring in Extended Cycles: Preliminary Report." *European Journal of Contraception and Reproductive Health Care* 19, no. 4 (2014): 307–14. <http://dx.doi.org/10.3109/13625187.2014.914488> (accessed February 10, 2015).
- Dinger, J., S. Möhner, and K. Heinemann. "Cardiovascular Risk Associated with the Use of an Etonogestrel-Containing Vaginal Ring." *Obstetrics and Gynecology* 122, no. 4 (2013): 800–808. <http://dx.doi.org/10.1097/AOG.0b013e3182a5ec6b> (accessed February 10, 2015).
- Roumen, F. J., and D. R. Mishell Jr. "The Contraceptive Vaginal Ring, NuvaRing®, A Decade after Its Introduction." *European Journal of Contraception and Reproductive Health Care* 17, no. 6 (2012): 415–27. <http://dx.doi.org/10.3109/13625187.2012.713535> (accessed February 10, 2015).

WEBSITES

- Micromedex. "Ethinyl Estradiol and Etonogestrel (Vaginal Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/ethinyl-estradiol-and-etonogestrel-vaginal-route/description/DRG-20061925> (accessed February 10, 2015).
- National Women's Health Resource Center. "Contraception." HealthyWomen.org. <http://www.healthywomen.org/condition/contraception> (accessed February 8, 2015).
- Planned Parenthood. "Birth Control Vaginal Ring (NuvaRing)." <http://www.plannedparenthood.org/health-info/birth-control/birth-control-vaginal-ring-nuvaring> (accessed February 8, 2015).
- U.S. National Library of Medicine. "Implanon." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=50ed7e31-b9b7-4f0a-8e36-91ed5af86b81> (accessed February 10, 2015).
- U.S. National Library of Medicine. "NuvaRing." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=017343fb-86c4-45ab-9c47-52cc5b9f3a02> (accessed February 10, 2015).

ORGANIZATIONS

- American Society for Clinical Pharmacology and Therapeutics, 528 N Washington Street, Alexandria, VA 22314, (703) 836-6981, info@ascpt.org, <http://www.ascpt.org/>.
- Office on Women's Health, U.S. Department of Health and Human Services, 200 Independence Avenue SW, Room 712E, Washington, DC 20201, (202) 690-7650, (800) 994-9662, Fax: (202) 205-2631, <http://www.womenshealth.gov/>.
- Planned Parenthood Federation of America, 434 West 33rd Street, New York, NY 10001, (212) 541-7800, (800) 230-PLAN (7526), Fax: (212) 245-1845, <http://www.plannedparenthood.org/>.

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Evista see **Raloxifene**

Evra see **Norelgestromin/ethinyl estradiol**

Exelon see **Rivastigmine**

Exforge see **Amlodipine/valsartan**

Ezetimibe

Definition

Ezetimibe is a drug in the class of cholesterol absorption inhibitors, which are used to reduce the amount of cholesterol absorbed by the body.

Purpose

Ezetimibe is used to reduce high circulating levels of cholesterol in the blood. It is often given with other cholesterol-lowering drugs called statins (e.g., **atorvastatin**, cerivastatin, fluvastatin, **pravastatin**, or **simvastatin**). Combination cholesterol-lowering drug therapy is part of a complete program of diet, exercise, and weight control intended to support a healthy heart and vascular system.

Description

Ezetimibe inhibits the absorption of cholesterol in the small intestine. The drug is metabolized in the small intestine and the liver and then, as ezetimibe-glucuronide, it binds to protein and is distributed within the body.

Ezetimibe may be given to patients with high cholesterol (hypercholesterolemia). High cholesterol may include elevated total cholesterol, elevated low-density lipoprotein (LDL) cholesterol, or non-high-density lipoprotein (HDL) cholesterol, triglycerides, and apolipoprotein B. Elevated levels of these fats (lipids) are an indication of a person's risk of developing cardiovascular disease, including angina, heart attack, and stroke.

Reducing circulating levels of cholesterol to normal is essential to maintaining overall health and is especially important in preventing cholesterol from combining with other substances in the blood to form plaque on the walls of blood vessels, a condition known

as atherosclerosis. Plaque is a hard substance that can accumulate in veins and arteries; pieces of plaque sometimes break off and lodge in blood vessels of the heart or brain, causing heart attack or stroke. Elevated cholesterol can be a result of genetic tendencies in the metabolism of fats or of consuming a high-fat, high-carbohydrate diet and not engaging in sufficient exercise. Studies have shown that using ezetimibe as adjunctive (additional) therapy to diet and exercise can effectively reduce cholesterol levels.

Sometimes non-statin agents like ezetimibe are added to the regimens of statin agents (HMG-CoA reductase inhibitors). The American Heart Association reported the results of a clinical trial showing that the combination of ezetimibe and simvastatin lowered LDL cholesterol significantly in patients with acute coronary syndrome. The results of that clinical trial also showed that reducing LDL cholesterol prevented cardiovascular adverse events.

U.S. brand names

Ezetimibe is sold in the United States under the brand name Zetia. A combination product containing both ezetimibe and atorvastatin is sold under the brand name Liptruzet.

Canadian brand names

Ezetimibe is sold in Canada under the brand name Ezetrol.

Recommended dosage

Ezetimibe is available as a pill to be taken orally. The recommended dosage of ezetimibe is 10 milligrams (mg) by mouth once a day. The same dosage applies to adults of all ages. It can be taken with or without food, and may be taken alone or in combination with other lipid-lowering drugs.

Pediatric

The regular adult dosage of 10 mg once a day applies to children 10 years of age and older.

Precautions

Cholesterol levels will likely be monitored regularly while taking ezetimibe. Liver and kidney function tests may also be evaluated periodically, especially in patients with any previous liver or kidney issues.

In rare cases, ezetimibe may cause a breakdown of skeletal muscle tissue (rhabdomyolysis) that can lead to kidney failure. The presence of symptoms such as muscle pain or tenderness, muscle weakness, fever, flu



Zetia (ezetimibe), 10 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Apolipoproteins—Proteins that bind with fats (lipids) to form lipoproteins. Detection of these apolipoproteins indicates risk of developing cardiovascular disease.

Cardiovascular disease—A structural or functional abnormality of the heart, or of the blood vessels supplying the heart, that impairs its normal function.

Cholesterol—A fat-soluble steroid alcohol (sterol) found in animal fats and oils and in egg yolks. The human body needs cholesterol to produce vitamin D, but too much cholesterol may lead to heart disease and other conditions.

Hypercholesterolemia—High cholesterol in the blood.

Hyperlipidemia—High levels of lipids in the blood, including elevated total cholesterol, LDL cholesterol, non-HDL cholesterol and apolipoproteins.

Plaque—A compound made up of fat, cholesterol, calcium, and other substances found in the blood. It can stick to the walls of arteries, partially or totally blocking blood flow.

Rhabdomyolysis—A condition in which muscle tissue breakdown releases muscle fiber contents into the blood, which may result in kidney damage.

Statin—Statins, also known as HMG-CoA reductase inhibitors, are drugs used to reduce cholesterol levels by blocking the enzyme HMG-CoA, which helps produce cholesterol in the liver.

symptoms, or dark urine may indicate that skeletal muscles have been affected and are releasing muscle fiber into the bloodstream, which can harm the kidneys. Such symptoms should be reported to the healthcare provider as soon as they are noticed.

Pregnant or breastfeeding

Ezetimibe carries the FDA pregnancy category C, meaning that it has not been investigated in humans whether ezetimibe is harmful to the developing fetus, but animal studies have shown that ezetimibe crosses the placenta and certain effects have been noted on fetal skeletal structure. Consequently, cholesterol absorption inhibitors such as ezetimibe carry a warning against use

by pregnant women. Pregnant women or nursing mothers should consult with their healthcare providers before taking ezetimibe.

Other conditions and allergies

Ezetimibe should not be taken by patients with liver disease. Patients with kidney disease or thyroid disease may require dosage adjustments of ezetimibe. Patients with liver disease or elevated serum levels of liver enzymes (transaminases) should not take ezetimibe combined with other cholesterol-lowering drugs called HMG-CoA reductase inhibitors.

Patients with allergies should report the sources of allergies to their healthcare provider before taking ezetimibe. Ezetimibe should not be taken if the patient is allergic to the drug itself or any of its ingredients.

Side effects

Common side effects of ezetimibe include:

- fatigue
- headache
- dizziness
- diarrhea
- abdominal pain
- nausea
- hives or rash
- pain in the legs or joints
- upper respiratory symptoms such as sore throat, runny nose, and sneezing
- sinusitis

More serious side effects may include gallbladder disease or gallstones and, rarely, elevated liver enzymes, or hepatitis.

Interactions

Ezetimibe is known to interact with other drugs.

Drugs

Ezetimibe cannot be taken at the same time as certain other cholesterol-lowering medications, including cholestyramine (Prevalite, Questran), colestipol (Colestid), or **colesevelam** (Welchol). Patients who are taking ezetimibe should wait at least four hours after taking any of these other cholesterol medications before taking ezetimibe, or should take ezetimibe two hours before taking the other medication. However, ezetimibe may be taken at the same time as **fenofibrate**, sold as Antara, Lipofen, Lofibra, Tricor, or Triglide, or statin

drugs such as atorvastatin (Lipitor), cerivastatin (Baycol), fluvastatin (Lescol), pravastatin (Pravachol), or simvastatin (Zocor).

Certain drugs may affect the activity of ezetimibe, decreasing its effectiveness. Antacids containing aluminum, magnesium, and bile acid sequestrants (e.g., cholestyramine) may reduce the effectiveness of ezetimibe. Cimetidine, **cyclosporine**, and fibrin acid drugs (e.g., fenofibrate, **gemfibrozil**) may increase concentrations of ezetimibe. Patients taking these drugs while taking ezetimibe should be monitored for any adverse reactions.

Patients who are taking steroid medications (e.g., cortisone) or hormones of any kind, including **oral contraceptives**, should take ezetimibe with caution. Dosage adjustments may be required to safely take ezetimibe with these medications.

Resources

BOOKS

American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda, MD: ASHP, 2015.

Porter, Robert S., and Justin L. Kaplan, editors. "Cardiovascular Disorders." In *The Merck Manual of Diagnosis and Therapy*. 19th ed, 2015–2242. Whitehouse Station, NJ: Merck Research Laboratories, 2011.

WEBSITES

AHFS Consumer Medication Information. "Ezetimibe." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a603015.html> (accessed March 6, 2015).

Micromedex. "Ezetimibe (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/ezetimibe-oral-route/description/drg-20067172> (accessed March 6, 2015).

UK National Health Service (NHS). "Ezetrol (Ezetrol 10mg Tablets)." <http://www.nhs.uk/medicine-guides/pages/MedicineOverview.aspx?condition=Cholesterol&medicine=Ezetrol&preparation=Ezetrol%2010mg%20tablets> (accessed March 6, 2015).

ORGANIZATIONS

American College of Cardiology, Heart House, 2400 N Street NW, Washington, DC 20037, (202) 375-6000(800) 253-4636 x8603, (202) 375-7000resource@acc.org, <http://www.acc.org/>.

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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F

Famciclovir

Definition

Famciclovir is an oral antiviral agent used to treat herpesvirus infections, including cold sores, genital herpes, and shingles. It is in a drug class called purine nucleoside analogs.

Purpose

Famciclovir is used to treat infections with herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) and herpes zoster or shingles caused by reactivation of the varicella zoster virus (VZV) that causes chickenpox. Famciclovir does not cure herpes infections, but it can decrease itching, burning, tingling, tenderness, and pain caused by herpes outbreaks, help sores heal faster, and prevent new sores from forming. Famciclovir may also be prescribed for other purposes.

Description

HSV-1, also known as herpes labialis or oral herpes, is a very common infection of the mouth and surrounding tissue. Following the initial infection, the virus becomes inactive (dormant) in nerve tissues in the face. Sometimes the virus reactivates, causing small, painful blisters called cold sores or fever blisters. HSV-2 is a sexually transmitted infection that causes genital herpes and can also spread to the mouth and cause oral herpes. Famciclovir is used to treat recurrent outbreaks of HSV-1 and HSV-2 in people with healthy immune systems (immunocompetent), as well as in people infected with the human immunodeficiency virus (HIV). Famciclovir shortens the course and severity of herpes symptoms, and it can prevent further outbreaks of genital herpes. Famciclovir also may help prevent transmission of the virus to others. Famciclovir is most effective when started within six hours of the first sign of recurrent genital herpes, such as pain or blisters.

Shingles is a reactivation of dormant VZV in people who have had chickenpox (varicella) or the varicella vaccine. It usually affects seniors, and about 50% of people in the United States will have had shingles by age 80. Shingles causes localized itching, blistery rash, and painful nerve inflammation. It sometimes results in painful, long-lasting post-herpetic neuralgia (PHN). Famciclovir treats the symptoms of shingles, shortening the illness and decreasing its severity. Famciclovir is most effective when started as soon as possible—within 48 hours of the first appearance of the shingles rash. The earlier treatment is started, the faster the recovery and the lower the risk of PHN. Both famciclovir and the similar drug **valacyclovir** significantly reduce the risk of PHN compared to **acyclovir**, the third antiviral agent used for treating herpes infections. Famciclovir treatment is especially important for shingles that affects the eyes (herpes zoster ophthalmicus). Shingles is not contagious; however, direct contact with sores can transmit VZV to people—usually children—who have not had chickenpox or been immunized against it, causing them to develop chickenpox, not shingles.

Unlike shingles, which rarely recurs, outbreaks of genital herpes may recur often. People who have few symptoms of recurrent genital herpes and/or infrequent outbreaks may not require treatment, especially if they are not sexually active and so are not at risk for transmitting HSV to an uninfected partner. Episodic therapy treats genital herpes only when outbreaks occur. It may be recommended for people who have fewer than six outbreaks per year. Episodic therapy can decrease the duration and severity of genital herpes outbreaks by hours or a few days but does not reduce the frequency of outbreaks. People with recurrent genital herpes are often advised to keep a supply of medication for use at the first signs of pain, tingling, or a blister. Suppressive therapy is low-dose treatment with a daily antiviral to prevent or decrease the frequency and duration of outbreaks. Suppressive therapy may be recommended for people who have at



Famciclovir, 250 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

least six outbreaks per year, have severe symptoms, or have a weakened immune system from HIV/AIDS, immune-suppressing drugs, or other conditions. Suppressive therapy also reduces the risk of transmitting the virus to an uninfected sexual partner who has no history of genital herpes or has had a blood test that indicates a lack of HSV-1 or HSV-2 antibodies. Some experts recommend periodically suspending suppressive therapy every few years to determine whether it is still needed; it can be restarted if outbreaks recur.

Famciclovir is supplied as 125, 250, and 500 milligram (mg) tablets that are stored at room temperature away from moisture (not in the bathroom).

U.S. brand names

Famciclovir is marketed as Famvir in the United States.

Canadian brand names

In Canada, famciclovir is marketed as Famvir, CO Famciclovir, PMS-Famciclovir, Sandoz Famciclovir, and Apo-Famciclovir.

International brand names

Famciclovir is marketed as Famvir in the majority of countries worldwide. It is also sold as Apo-Famciclovir in Australia.

Origins

Famvir (famciclovir) tablets were first approved by the U.S. Food and Drug Administration (FDA) in 1994 for treatment of acute herpes zoster, treatment and/or suppression of genital herpes in immunocompetent people, and treatment of recurrent HSV infections of mucous membranes in HIV-infected people. In 2006, the FDA approved Famvir as the first one-day antiviral treatment for recurrent genital herpes, as well as for treatment of cold sores in people with healthy immune systems. Previously, genital herpes required five days of low-dose treatment, and Famvir was not FDA approved for treating cold sores in people without HIV/AIDS. Single-day Famvir must be started within six hours of the first sign of itching, burning, or the appearance of sores. This is because the virus replicates fastest during the first hours of an outbreak.

Generic famciclovir became available in the United States in 2007.

Recommended dosage

Antivirals are most effective if begun within 72 hours of the first symptoms. Recommended adult dosages of famciclovir are:

- treatment of recurrent genital herpes—1,000 mg twice for one day
- suppression of recurrent genital herpes—250 mg twice a day for up to one year
- initial episode of genital herpes (off label)—250 mg every eight hours for seven to ten days
- treatment of recurrent cold sores—a single 1,500 mg dose
- treatment of recurrent HSV infections in HIV-infected people—500 mg twice a day for seven days
- prevention HSV reactivation in HIV-infected adults—500 mg twice a day
- shingles and herpes zoster ophthalmicus (HZO)—500 mg every eight hours for seven days

Famciclovir is taken by mouth, with or without food. A missed dose should be taken as soon as possible, but if it is almost time for the next dose, the missed dose should be skipped, and the regular dosing schedule resumed.

Pediatric

Off-label treatment of genital herpes may be considered for adolescents. The recommended dosages for an initial episode and suppressive therapy are the same as for adults. Recurrent episodes may be treated with 125 mg every 12 hours for three to five days.

KEY TERMS

Acyclovir—An antiviral medication similar to famciclovir.

Cold sores—Fever blisters; itching, burning, or painful lesions, usually in or around the mouth, caused by reactivation of herpes simplex virus type 1.

Episodic therapy—Antiviral treatment at the first sign of a genital herpes outbreak.

Genital herpes—Infection of the genitals with herpes simplex virus type 2.

Herpes labialis—Oral herpes; herpes simplex virus affecting the lips and nose.

Herpes simplex virus type 1 (HSV-1)—The virus that is usually responsible for cold sores.

Herpes simplex virus type 2 (HSV-2)—The virus that causes genital and sometimes oral herpes.

Herpes zoster ophthalmicus—Shingles that affects the eyes.

Human immunodeficiency virus (HIV)—The virus that causes acquired immune deficiency syndrome (AIDS).

Immunocompetent—Having a healthy immune system.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Penciclovir—The active antiviral agent that is formed from famciclovir in the body.

Post-herpetic neuralgia (PHN)—Pain that continues or recurs after the shingles rash has healed.

Shingles—Herpes zoster; a blistering rash and nerve pain that primarily affects older adults and is caused by reactivation of the varicella zoster virus that causes chickenpox.

Suppressive therapy—Low-dose antiviral therapy to prevent outbreaks and transmission of genital herpes.

Valacyclovir—An antiviral medication similar to famciclovir.

Varicella zoster virus (VZV)—The virus that causes chickenpox and remains dormant in the nerves where its reactivation causes shingles.

Other conditions and allergies

Dosages require adjustment for patients with kidney impairment.

Precautions

Certain precautions should be taken while using famciclovir:

- The entire course of famciclovir should be taken to fully clear the infection even if symptoms disappear.
- Famciclovir can cause drowsiness, dizziness, confusion, or disorientation: patients should not drive or operate machinery until they know how the drug affects them.
- Lab tests may be ordered to monitor response to famciclovir.
- Genital intercourse should be avoided during a genital herpes outbreak, and the virus can still be transmitted to sexual partners even in the absence of symptoms.

Pediatric

The safety and effectiveness of famciclovir have not been established in children under age 18.

Pregnant or breastfeeding

Famciclovir is in the FDA pregnancy category B for all trimesters. This means that the drug has not been studied in pregnant women, but animal studies have not indicated any harm to the embryo or fetus. Nevertheless, unnecessary use of famciclovir during pregnancy should be avoided. It is not known whether famciclovir is excreted in human breast milk, but it is excreted in the milk of lactating rats. Famciclovir should only be used while breastfeeding if the potential benefits outweigh the potential risks to the baby.

Other conditions and allergies

The doctor and pharmacist should be informed of allergies to famciclovir, penciclovir cream (Denavir), acyclovir (Zovirax), any other medications, or lactose. The doctor should be informed if the patient has ever had:

- immune system problems such as HIV/AIDS
- galactose intolerance or glucose-galactose malabsorption— inherited intolerance of lactose
- kidney or liver disease

Side effects

The most commonly reported side effects of famciclovir are headache and nausea. Pain, burning,

numbness, or tingling in the hands and feet should be reported to the doctor immediately. The doctor should be notified if any of the following symptoms are severe or persistent:

- headache
- nausea
- vomiting
- diarrhea or loose stools
- gas
- stomach pain
- tiredness
- rash
- itching
- painful menstrual periods

Interactions

It is important that the doctor and pharmacist be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Drugs

Famciclovir may interact with probenecid (Benemid).

Resources

PERIODICALS

Avalos, Lyndsay A., et al. "The Prevalence and Trends of Antiviral Medication Use During Pregnancy in the US: A Population-Based Study of 664,297 Deliveries in 2001–2007." *Maternal and Child Health Journal* 18, no. 1 (2014): 64–72.

WEBSITES

Albrecht, Mary A. "Patient Information: Genital Herpes (Beyond the Basics)." UpToDate.com. <http://www.uptodate.com/contents/genital-herpes-beyond-the-basics?view=print> (accessed February 7, 2015).

"Famvir." Drugs.com <http://www.drugs.com/cons/famvir.html> (accessed February 7, 2015).

MedlinePlus. "Herpes—Oral." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/ency/article/000606.htm> (accessed February 7, 2015).

MedlinePlus. "Shingles." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/tutorials/shingles/htm/index.htm> (accessed February 7, 2015).

U.S. Food and Drug Administration. "Novartis: Full Prescribing Information." <http://www.accessdata.fda.gov/>

drugsatfda_docs/label/2011/020363s037lbl.pdf (accessed February 7, 2015).

Zachary, Kimon C. "Famciclovir: An Overview." UpToDate.com. http://www.uptodate.com/contents/famciclovir-an-overview?source=see_link (accessed February 7, 2015).

ORGANIZATIONS

National Shingles Foundation, 603 West 115th Street, #371, New York, NY 10025, (212) 222-3390, Fax: (212) 222-8627, Shingles@ShinglesFoundation.org, <http://shinglesfoundation.org/>.

U.S. Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30329, (800) CDC-INFO (232-4636), cdcinfo@cdc.gov, <http://www.cdc.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY GREGORY A. PRATT, RPH

Famotidine

Definition

Famotidine is a medication that is available in an over-the-counter formula to help relieve heartburn or ulcers related to gastroesophageal reflux disease (GERD) or as a prescription tablet. It also is available as a fluid



Famotidine, 20 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

that a healthcare provider gives intravenously through a needle or catheter. Famotidine is in a class of drugs called histamine 2 blockers, or histamine 2 receptor antagonists, which decrease how much acid is produced in the stomach.

Purpose

People who have GERD have symptoms such as pain near the breast bone that burns, especially when they lie down or bend over. The burning is caused by acid created in the stomach to break down food. In GERD, some of the acid backs up into the esophagus, which is called reflux. The constant reflux of acid can eventually damage the thin lining of the esophagus and cause ulcers, or sores, in the lining. Famotidine also can be taken to treat ulcers in the esophagus or stomach and intestine.

Description

Famotidine is a medication that comes in several strengths and formulas, depending on the severity of GERD symptoms and the intended use. Over-the-counter products may combine famotidine with an antacid to provide faster heartburn relief while the famotidine begins to work. Another formula is taken before meals to prevent heartburn. The oral tablets are available in 20 and 40 milligram (mg) strengths and come in chewable forms. The doctor may recommend use of over-the-counter famotidine or a prescription formula to treat ulcers or GERD.

U.S. brand names

In the United States, famotidine is sold as Pepcid and Pepcid AC. Generic versions of famotidine also are available. Duexis is a medicine that combines famotidine with the nonsteroidal anti-inflammatory drug ibuprofen and Pepcid Complete combines famotidine with antacids.

Recommended dosage

To prevent heartburn, it is advised to take 10–20 mg of famotidine by mouth within 15 to 60 minutes of eating foods that usually cause heartburn, taking no more than two tablets every 12 hours. To treat symptoms of GERD, doctors usually recommend that adults take 20 mg of famotidine by mouth every 12 hours for six weeks. Adults should not take more than two tablets within 24 hours. Dosage varies for treatment of ulcers but may be given in increments of 20 or 40 mg by oral tablet or intravenously at bedtime for four to eight weeks until symptoms improve. To maintain healing, patients usually continue taking 20 mg of famotidine at bedtime.

Doses for children are lower, and most children aged 1 to 16 take 1 mg per kilogram (kg, or 2.2 lb.) of

KEY TERMS

Gastroesophageal reflux disease—Abbreviated GERD, it is the passage of stomach acid back into the esophagus through the small muscle that normally allows food to travel down from the esophagus into the stomach. GERD can cause heartburn and lead to ulcers in the esophagus.

Intravenous—Within a vein; usually referring to how a drug is placed, or administered, through a needle or catheter into a vein and therefore into the blood system.

Ulcer—A sore or break in the skin or lining of an organ.

body weight of famotidine per day, divided into two doses. The total dose should not exceed 40 mg per day. Children may also take the medicine for peptic ulcers, at a dose of 0.5 mg/kg/day, not to exceed 40 mg/day at bedtime. There is a liquid form of the medicine that can be given to young children.

The medicine can be given to infants with GERD at a dose of 0.5 mg/kg/day for up to eight weeks in those less than 3 months old, and twice a day for infants between 3 and 12 months old.

Other conditions and allergies

People who have kidney disorders and impaired kidney function may experience severe side effects from famotidine and should receive lower doses than other patients or undergo longer time periods between doses.

Precautions

Injected famotidine should never be used if the solution appears to be discolored or has any material floating in the liquid. The medicine always should be used as directed by the doctor.

Pediatric

Effectiveness of famotidine for treating heartburn in children younger than 12 years old has not been established. Babies who use the medicine may become fussy as a side effect.

Geriatric

Famotidine is generally as safe and effective in older adults as in the general adult population, but some older individuals may be more sensitive to the drug's effects.

Pregnant or breastfeeding

Famotidine is a pregnancy category B drug, which means that animal studies have found no adverse effects on a fetus, but no controlled studies have been performed in pregnant women. It should be used during pregnancy only if clearly needed. The drug has been found in breast milk, and mothers who want to nurse their infants should either discontinue famotidine while breastfeeding or choose not to breastfeed their infants if they want to continue using the drug.

Other conditions and allergies

Anyone allergic to famotidine, along with other histamine 2 blockers such as cimetidine (Tagamet) or **ranitidine** (Zantac), should inform the doctor.

Famotidine can cause serious central nervous system side effects in people who have problems with kidney function.

Side effects

Side effects of famotidine may include:

- dizziness
- headache
- diarrhea or constipation

Certain side effects of famotidine can be more severe. Even though they are not common, they should be reported to a doctor. Serious side effects of the drug include:

- rash or hives
- itching
- swelling of the throat, tongue, lips, face, hands, or lower limbs
- problems breathing or swallowing

In addition, people who receive famotidine intravenously may develop an infection where the drug is injected. Signs of infection at the injection site include:

- warmth or redness
- swelling
- pain or irritation
- drainage

Interactions

It is important to tell the doctor about any medications or herbal or vitamin supplements being taken before using famotidine.

Drugs

When drugs interact with one another, it can affect how well one drug or another works or increase the side effects of a drug. Famotidine can cause moderate or

minor reactions with many drugs and more severe ones with some drugs used to treat human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS). It also interacts with a drug called **tizanidine** (Zanaflex), which is used to treat multiple sclerosis.

Resources

PERIODICALS

Lightdale, Jennifer R., and David A. Gremse. "Gastroesophageal Reflux: Management Guidance for the Pediatrician." *American Academy of Pediatrics* 131, no. 5 (2013): e1684–95.

Sugano, Kentaro. "Single-Tablet Double-Dose Famotidine plus Ibuprofen Decreases Endoscopic Upper GI Ulcers Compared with Ibuprofen Alone." *Evidence-Based Medicine* 18, no. 1 (2013): 26–7.

Resources

WEBSITES

"Famotidine." Drugs.com. <http://www.drugs.com/famotidine.html> (accessed February 7, 2015).

McNeil Consumer Pharmaceuticals. Pepcid.com. <http://www.pepcid.com/> (accessed February 7, 2015).

MedlinePlus. "Famotidine." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a687011.html> (accessed February 7, 2015).

MedlinePlus. "Famotidine Injection." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601142.html> (accessed February 7, 2015).

ORGANIZATIONS

American Gastroenterological Association, 4930 Del Ray Avenue, Bethesda, MD 20814, (301) 654-2055, Fax: (301) 654-5920, <http://www.gastro.org/>.

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, 1501 Bethlehem Pike, Flourtown, PA 19031, (215) 233-0808, naspgan@naspgan.org, <http://www.naspgan.org/>.

Teresa G. Odle, BA, ELS

REVIEWED BY KEVIN GLAZA, RPh

Famvir see **Famciclovir**

Fenofibrate

Definition

Fenofibrate is one of the members of the class of fibrates, a group of carboxylic acid drugs used to lower high blood cholesterol levels. It is therefore considered an antilipidemic agent.



Tricor (fenofibrate), 48 mg. (© Cengage Learning®.)

Purpose

Fenofibrate is used as monotherapy to lower the patient's risk of pancreatitis (inflammation of the pancreas) by lowering the levels of triglycerides in the blood. It is also used together with statins to lower a patient's risk of atherosclerosis and fatal heart attacks by lowering the level of LDL ("bad") cholesterol in the blood and raising the level of HDL ("good") cholesterol. It can be used by itself to treat high blood cholesterol levels in patients who are allergic to or otherwise cannot tolerate statins. Fenofibrate works by increasing the production of an enzyme called lipoprotein lipase that helps to break down triglyceride molecules and speed their removal from the body. Fenofibrate also slows down the production of cholesterol in the liver.

Off-label use

Fenofibrate is used off label to prevent diabetic peripheral neuropathy, a condition in which patients with poorly controlled diabetes develop pain, tingling sensations, dizziness, muscular weakness, and other symptoms in the parts of the body supplied by peripheral nerves (nerves outside the central nervous system). The reason for this off-label use is that fenofibrate appears to lower insulin resistance in patients whose dyslipidemia is associated with type 2 diabetes.

Description

Fenofibrate is available as tablets or capsules to be taken by mouth. The drug is dispensed as 40, 54, 120, and 160 milligram (mg) tablets; and as 50 mg, 67 mg, 134 mg, 150 mg, and 200 mg capsules. Fenofibrate tablets are usually white and oval shaped; the capsules come in various colors depending on the manufacturer and the dosage. The capsules contain micronized formulations of the drug.

U.S. brand names

Fenofibrate is sold by Abbott in the United States under the brand name TriCor. Other U.S. brand names include Antara, Triglide, Fenoglide, Lipofen, Lofibra, and Triplix. Generic forms are also available.

Canadian brand names

Canadian brand names include Lipidil Supra, Lipidil EZ, and Lipidil Micro; they are marketed by Fournier Pharma. Other Canadian brand names include Apo-Fenofibrate (Apotex), Sandoz Fenofibrate-S, and Apteor (Solvay).

International brand names

Generic versions of fenofibrate are sold by more than 20 different pharmaceutical companies worldwide, under such names as Adfen-160, Antilip, Catalip, Durafenat, Fenardin, Fenatrol, Fenobate, Fenox, Fibrufen, Lipibrat, Lipifen, Promeral, Qualipantyl, Secalip, Tigicon, and Yosenob.

Origins

Fenofibrate was originally approved by the U.S. Food and Drug Administration (FDA) in 1993; it went off patent in 2007. In 2012, the FDA approved new versions of fenofibrate known as micronized formulations. Micronization refers to the reduction of the particles of the drug to very small dimensions, often on the level of a nanometer (one billionth of a meter). One reason for this change is to increase the bioavailability of fenofibrate; the drug is nearly insoluble in water, and micronization allows the body to absorb the drug more efficiently.

Recommended dosage

In most cases, the patient's doctor will recommend a diet low in fats, sugars, and cholesterol to maximize the benefit of fenofibrate. The dosage of fenofibrate in adults depends on the specific brand as well as the purpose of the medication:

KEY TERMS

Atherosclerosis—Thickening and hardening of the walls of an artery as the result of accumulations of white blood cells, cholesterol, and triglycerides (fats).

Bile acid sequestrants—A group of drugs used to bind certain components of bile within the digestive tract. They are often used to lower blood cholesterol levels.

Bioavailability—The fraction of an unchanged administered drug that reaches the systemic circulation. The bioavailability of drugs administered intravenously is usually close to 100% but that of drugs taken by mouth is usually significantly lower.

Dyslipidemia—The medical term for an abnormal level of lipids (cholesterol and other fats) in the blood. Most dyslipidemias are hyperlipidemias; that is, the level of lipids is abnormally high rather than abnormally low.

Fibrates—A group of carboxylic acid drugs used to lower blood cholesterol levels and thus reduce the patient's risk of atherosclerosis. Fenofibrate is one of the older medications in this class.

Hypolipidemics—A group of drugs used to lower the levels of cholesterol and other lipids (fatty substances) in the blood. The fibrates are one type of antilipidemic agents.

Monotherapy—The use of a single drug or treatment by itself.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Pancreatitis—Inflammation of the pancreas, either acute (sudden and episodic) or chronic, usually caused by excessive alcohol intake or gallbladder disease.

Peripheral neuropathy—A disease affecting the portion of the nervous system outside the brain and spinal cord. One or more nerves can be involved, causing sensory loss, muscle weakness and shrinkage, and decreased reflexes.

Rhabdomyolysis—A condition in which damaged skeletal muscle undergoes rapid breakdown. It is a rare but potentially serious effect of taking statins together with fibrates.

Triglycerides—Chemical compounds derived from glycerol (a sweet-tasting sugar alcohol) and three fatty acid molecules. They are the most abundant fatty molecules found in most animals, including humans. High levels of triglycerides in the blood are a major risk factor for pancreatitis and atherosclerosis.

- TriCor: For hypercholesterolemia or mixed dyslipidemia, the initial dose is 145 mg by mouth once per day. For hypertriglyceridemia, the initial dose is 48–145 mg by mouth once per day. Dosage may be adjusted every four to eight weeks but should not exceed 145 mg/day.
- Triglide: For hypercholesterolemia or mixed dyslipidemia, the initial dose is 160 mg by mouth once per day. For hypertriglyceridemia, the initial dose is 50–160 mg by mouth once per day.
- Lipofen: For hypercholesterolemia or mixed dyslipidemia, the initial dose is 150 mg by mouth once per day. For hypertriglyceridemia, the initial dose is 50–150 mg by mouth once per day.
- Lofibra: For hypercholesterolemia or mixed dyslipidemia, the initial dose is 160 mg by mouth once per day. For hypertriglyceridemia, the initial dose is 54–160 mg by mouth once per day.
- Fenoglide: For hypercholesterolemia or mixed dyslipidemia, the initial dose is 120 mg by mouth once per

day. For hypertriglyceridemia, the initial dose is 40–120 mg by mouth once per day.

TriCor, Triglide, and Lofibra tablets can be taken with or without meals, as the patient prefers. Lipofen should be taken with meals. The patient should take fenofibrate tablets or capsules at the same time each day, and should swallow them whole; the tablets or capsules should not be chewed or crushed. Fenofibrate tablets and capsules should be stored at room temperature, kept from freezing, and kept away from heat, moisture, and direct light.

Patients who are also taking bile acid sequestrants (cholestyramine, **colesevelam**, or colestipol) should not take these drugs at the same time as fenofibrate; they should take them either four hours before taking fenofibrate or one hour after taking it.

Pediatric

Fenofibrate is not recommended for use in children.

Geriatric

Dosage adjustments should be made for older adults being treated for hypercholesterolemia, mixed dyslipidemia, or hypertriglyceridemia (the recommended dosages are the same for all three conditions):

- TriCor: initial dose of 48 mg/day; patient should be evaluated before dosage is increased
- Triglide: initial dose of 50 mg/day
- Lipofen: no more than 50 mg/day
- Lofibra: initial dose of 54 mg/day
- Fenoglide: initial dose of 40 mg/day

Other conditions and allergies

Adult patients with impaired kidney function should receive the following dosages of fenofibrate, depending on the specific brand:

- TriCor: initial dose of 48 mg/day; patient should be evaluated before dosage is increased
- Triglide: initial dose of 50 mg/day
- Lipofen: no more than 50 mg/day
- Lofibra: initial dose of 54 mg/day
- Fenoglide: initial dose of 40 mg/day

Precautions

Treatment with fenofibrate should be discontinued if the patient shows no benefit after two to three months of treatment, if liver enzyme values persist at a level three times above the upper limit of normal, or if gallstones are detected in the patient's gallbladder.

Pregnant or breastfeeding

Fenofibrate is classified as a pregnancy category C drug, which means that the drug has been shown to harm the fetus in animal studies but that no data from human studies are available. There are no accurate studies of risks to nursing infants if this drug is used by nursing mothers; however, most doctors advise nursing mothers against using fenofibrate because the drug can pass into breast milk.

Other conditions and allergies

Patients with any of the following conditions should not use fenofibrate:

- known allergy to fibrates or to any of the ingredients used to formulate the tablets or capsules
- gallbladder disease
- severe kidney disease
- undergoing dialysis

- liver disease
- elevated levels of liver enzymes

Patients with a history of pancreatitis, heart disease, diabetes, bleeding disorders, alcoholism, muscle weakness, or a thyroid disorder should inform their doctor before taking fenofibrate.

Side effects

Fenofibrate is generally well tolerated. Common side effects include:

- upset stomach
- headache
- constipation or mild diarrhea
- mild itching
- runny or stuffy nose
- increased levels of liver enzymes on liver function tests

Less common side effects include:

- flatulence (digestive gas)
- increased sensitivity of the skin to sunlight
- back pain
- emotional agitation
- insomnia
- joint pain

Patients who have any of the following symptoms should contact their doctor at once:

- signs of a severe allergic reaction (hives; itching; sudden and unexplained swelling of the lips, mouth, or throat; difficulty breathing)
- jaundice, dark-colored urine, pain in the upper abdomen, or other signs of a liver disorder
- severe upper abdominal pain accompanied by nausea, vomiting, and lightheadedness, which may indicate pancreatitis
- severe stomach pain with nausea and vomiting, which may indicate gallstones
- severe muscle pain or tenderness accompanied by fever and unusual tiredness, which may indicate rhabdomyolysis (sudden breakdown of muscle tissue); more likely to occur in patients taking statins along with fenofibrate
- severe skin reactions, including blistering, peeling, itching, rashes, sores, ulcers, or white spots in the mouth or on the lips
- unexplained changes in urine output
- chills, fever, sore throat, or other symptoms of an infection, which can result from low white blood cell counts caused by fenofibrate

Interactions

Individuals should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs and supplements, before starting treatment with fenofibrate.

Drugs

Fenofibrate interacts with the following drugs or drug classes:

- bile sequestrants (colestipol, colestevlam, cholestyramine)
- **colchicine** (drug used to treat gout); increases risk of rhabdomyolysis
- statin medications (**lovastatin**, **pravastatin**, rosuvastatin, **simvastatin**, **atorvastatin**, etc.); increase risk of rhabdomyolysis
- **cyclosporine**; increases risk of kidney disorders
- **warfarin** and other blood thinners
- insulins (**insulin glargine**, **insulin detemir**, **insulin aspart**, insulin lispro); fenofibrate intensifies the effects of insulin, increasing the patient's risk of hypoglycemia
- tolbutamide, **glipizide**, and other oral antidiabetic drugs; increased risk of hypoglycemia

Food and other substances

Patients taking fenofibrate should avoid consuming alcohol, as alcohol can raise triglyceride levels and increase the risk of liver damage.

Resources

BOOKS

- Guthrie, Robert M. *Hypertension and Dyslipidemia Management Essentials*. Sudbury: Physicians' Press/Jones and Bartlett Publishers, 2010.
- Opie, Lionel H., and Bernard J. Gersh. *Drugs for the Heart*. 8th ed. Philadelphia: Elsevier/Saunders, 2013.
- Ramrakha, Punit, and Jonathan Hill, eds. *Oxford Handbook of Cardiology*. 2nd ed. New York: Oxford University Press, 2012.

PERIODICALS

- d'Emden, M. C., et al. "Favourable Effects of Fenofibrate on Lipids and Cardiovascular Disease in Women with Type 2 Diabetes: Results from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study." *Diabetologia* 57, no. 11 (2014): 2296–303.
- Hamilton, S. J., and G. F. Watts. "Atherogenic Dyslipidemia and Combination Pharmacotherapy in Diabetes: Recent Clinical Trials." *Review of Diabetic Studies* 10, no. 2–3 (2013): 191–203.
- Tenenbaum, A., and E. Z. Fisman. "Fibrates Are an Essential Part of Modern Anti-dyslipidemic Arsenal: Spotlight on

Atherogenic Dyslipidemia and Residual Risk Reduction." *Cardiovascular Diabetology* 11 (2012): 125.

Weissig, V., T. K. Pettinger, and N. Murdock. "Nanopharmaceuticals (Part I): Products on the Market." *International Journal of Nanomedicine* 9 (2014): 4357–73.

WEBSITES

- "Fenofibrate." Drugs.com. <http://www.drugs.com/fenofibrate.html> (accessed February 28, 2015).
- Medscape. "Fenofibrate (Rx)." <http://reference.medscape.com/drug/tricor-lofibra-tablets-fenofibrate-342451> (accessed February 28, 2015).
- Micromedex. "Fenofibrate (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/fenofibrate-oral-route/description/drg-20068427> (accessed February 28, 2015).

ORGANIZATIONS

- American College of Cardiology (ACC) Heart House, 2400 N Street NW, Washington, DC 20037, (202) 375-6000, ext. 5603, Fax: (202) 375-7000, (800) 253-4636, ext. 5603, resource@acc.org, <http://www.cardiosource.org/>.
- American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Rebecca J. Frey, PhD

REVIEWED BY GREGORY A. PRATT, RPH

Fentanyl

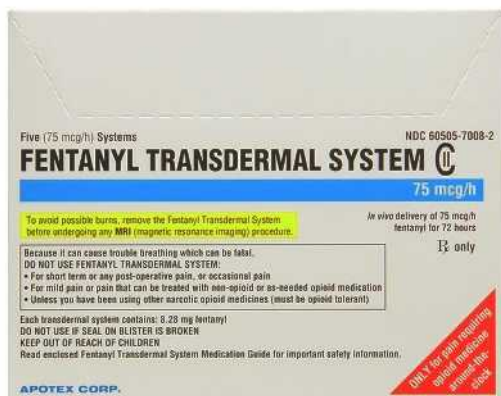
Definition

Fentanyl is a prescription-only painkiller (analgesic) that belongs to the family of drugs called opioid analgesics. Fentanyl is a type of synthetic narcotic drug.

Purpose

Fentanyl is used to treat moderate to severe pain, as a pretreatment prior to surgery, and as a supplementary drug during surgery.

Many of the formulations of fentanyl (lozenges, sublingual and buccal formats, intranasal sprays) are designed for use by cancer patients with severe breakthrough pain that their usual baseline pain medications are not able to cover. They should not be used by patients who are not already habituated (tolerant) to narcotic medications.



Fentanyl patch. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

Fentanyl is classified by the U.S. Drug Enforcement Administration (DEA) as a Schedule II drug. This means that fentanyl:

- is medically accepted as a therapeutic agent
- carries a high potential for abuse (although less so than Schedule I drugs)
- carries a high potential of initiating severe psychological or physical dependence
- possesses a side effect profile that is potentially dangerous

Fentanyl is available in a variety of formulations allowing for varied delivery, including as an oral lozenge, a sublingual spray (a tablet that melts under the tongue, or a spray that is applied under the tongue), a buccal film (a film that is placed inside the cheek and melts), a transdermal patch (a patch that goes on the skin and releases small amounts of fentanyl over time), an intranasal spray (delivered through a nose spray), an intravenous solution, or an intramuscular injection.

Each formulation is available in a variety of strengths:

- buccal film—200, 400, 600, 800, and 1,200 micrograms (mcg)
- injection solutions—available in a variety of volumes, with a dosage strength of 0.05 milligrams (mg) of active drug per milliliter (mL) of injection volume

- sublingual spray—100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg
- oral lozenges—200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,200 mcg, and 1,600 mcg
- transdermal patch—12.5 mcg, 25 mcg, 50 mcg, 75 mcg, or 100 mcg of active drug per hour worn
- intranasal spray—100 mcg or 400 mcg per spray
- buccal tablets—100 mcg, 200 mcg, 400 mcg, 600 mcg, or 800 mcg
- sublingual tablets—100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, and 800 mcg

U.S. brand names

Fentanyl is sold in the United States under the brand names Abstral, Actiq, Duragesic, Fentora, Lazanda, Onsolis, and Subsys.

Canadian brand names

Fentanyl is sold in Canada under the brand names Abstral, Apo-Fentanyl Matrix, Co-Fentanyl, Duragesic MAT, Fentanyl Citrate Injection USP, Fentora, Mylan-Fentanyl Matrix Patch, PMS-Fentanyl MTX, RAN-Fentanyl Matrix Patch, Sandoz Fentanyl Patch, and Teva-Fentanyl.

International brand names

Fentanyl is sold under several hundred brand names internationally, including Abstral (Germany), Durotep (Japan), Epufen (Slovenia), Fendivia (Spain), Matrifen (Italy), Demogyl (Greece), Tanyl (Israel), and Bufyl (United Kingdom). In some countries, fentanyl is only one component of the medication, and there are other medications included in the formulation. In some locations, it is only available for veterinary, not human, use.

Recommended dosage

Because fentanyl has the capacity to depress breathing to a potentially life-threatening degree, dosing of fentanyl is complicated. Dosing depends on the specific formulation/delivery system to be used, the patient's previous experience with narcotic drugs, the patient's current tolerance to narcotic medications, the patient's current narcotic medication regimen, and whether or not the patient is going to be mechanically ventilated. The dosage formats below are examples of possible dosing, but they do not completely cover the full range of possibilities for safe dosing.

- oral lozenges: 200 mcg melted in mouth over 15 minutes, repeated no more than every 4 hours

KEY TERMS

Analgesic—A drug used to control pain.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Buccal—The lining of the inside of the cheek.

Intramuscular—Into the muscle.

Intranasal—In the nose.

Intravenous—Into a vein.

Narcotic—A class of chemical that contains opium or opium-derivatives. These drugs decrease pain, often cause drowsiness, may induce a sense of euphoria or well-being, and have profound side effects that include respiratory depression in overdoses and addictive potential.

Opioid—A substance that resembles opium and binds to the same types of receptors in the body, producing similar effects in pain relief, pleasure, and addictiveness. Does not actually contain opium, but is synthetically produced to mimic its therapeutic benefits.

Sublingual—Under the tongue.

Tolerance—A decrease in tolerance to a drug so that an individual must take more and more of the drug to achieve the same effect.

- sublingual tablet or spray: 100 mcg under the tongue; if pain relief is not achieved, can repeat in 30 minutes but should not be repeated any more than every 2 hours
- buccal tablets: initial dose 100 mcg
- buccal film: started with 200 mcg film to be placed on inner surface of cheek
- transdermal patch: strength of patch depends on current use of narcotic pain medications; patches generally applied every 48–72 hours
- intranasal spray: treatment initiated with a single spray in one nostril, which delivers 100 mcg of active drug

For intravenous or intramuscular injection, appropriate dosing is highly varied depending on individual patient characteristics, including whether the patient is mechanically ventilated or breathing autonomously. The adult dose prior to surgery ranges from 0.05 mg to 0.1 mg per dose via intravenous or intramuscular injection. Anesthetic dosing is 0.5–20 mcg per kilogram (kg, or

2.2 lb.) of body weight per dose. A maintenance infusion ranges from 1–2 mcg/kg/hour.

Pediatric

The pediatric dosing via intravenous or intramuscular injection (for children two years and older) is 2–3 mcg/kg/dose.

Other conditions and allergies

The transdermal dose should be reduced by about 50% in the event of mild to moderate kidney or liver impairment. Individuals with severe kidney or liver impairment should not use the transdermal delivery system.

Precautions

Boxed warnings are included with this product that cover the following topics:

- Fentanyl has the potential to cause life-threatening respiratory depression. Particular care should be taken in patients who have demonstrated previous intolerance to opioid pain medications. Additionally, using more than one type of medication that has the potential for respiratory depression can greatly increase the threat of respiratory failure.
- Fentanyl carries serious risk for medication errors. Blood levels achieved by various delivery systems are different, and substitutions between delivery formulations cannot be made without recomputing the appropriate dose of active drug for an individual patient.
- Use of fentanyl carries increased risk of misuse, abuse, addiction, and overdose.

The transdermal form has additional boxed warnings regarding the dangers of:

- accidental exposure to the drug (especially by children)
- use with CYP3A4 inhibitor drugs, which may increase the potentially dangerous side effects of fentanyl when taken concurrently
- in-utero exposure leading to neonatal abstinence syndrome after birth
- exposing the patch to heat (e.g., via sauna, hot water bottle, heating pad, electric blanket), which can lead to dangerously higher blood levels of the drug

Fentanyl buccal tablets and films, lozenges, sublingual tablets, sublingual spray, transdermal patches, and nasal spray should not be used for treatment of acute pain, postoperative pain, or in patients who are not already habituated to opioid drugs.

Fentanyl can cause drowsiness and can impair physical abilities as well as mental processing and alertness.

Because of fentanyl's addictive potential, sudden discontinuation of the drug can lead to symptoms of withdrawal, including nausea, vomiting, diarrhea, teary eyes, runny nose, severe sweating, itchy skin, twitchy muscles, and uncontrollable yawning.

Geriatric

Elderly and debilitated patients are at particular risk of complications from fentanyl use, especially effects on the central nervous system and respiratory system and constipating effects. Fentanyl should be used with extreme caution and close monitoring in this population.

Fentanyl's potential for life-threatening respiratory depression is increased in the elderly, debilitated patients, and individuals with preexisting respiratory conditions. Using more than one type of medication that has the potential for respiratory depression can greatly increase the threat of respiratory failure.

Pregnant or breastfeeding

Fentanyl carries the FDA pregnancy category C, meaning that risk cannot be ruled out in pregnant individuals. If possible, use of this drug should be avoided. Babies who have been exposed to fentanyl acutely before birth may be born with decreased respiratory drive and a weak suck. Babies who have been exposed to fentanyl chronically before birth may experience withdrawal syndrome (neonatal abstinence syndrome) after birth when they no longer receive fentanyl through the placenta. These babies may require treatment to avoid severe symptoms of withdrawal.

Fentanyl is known to pass into breast milk. It should be avoided by breastfeeding women.

Other conditions and allergies

Fentanyl should be avoided in people with specific conditions, including:

- Adrenal problems—fentanyl can exacerbate these conditions, leading to symptoms such as sexual problems, problems with fertility, mood issues, and weak bones.
- Gall bladder problems—fentanyl can cause spasms in one of the gall bladder valves, resulting in severe pain.
- Slow heart rates (bradycardia)—fentanyl may further slow the heart rate.
- History of substance abuse or alcoholism—individuals with a prior history of addiction may have an increased risk of becoming addicted to fentanyl due to the drug's high abuse potential.

- Head injury—fentanyl and other opioid drugs may complicate assessment and course of traumatic brain injuries and other causes of brain swelling.
- Oral mucositis—individuals with ulcers or inflammation of the lining of the mouth may have more rapid absorption of the oral forms of fentanyl (e.g., lozenges, sprays, films), which may increase the risk of respiratory depression.

Fentanyl should not be given to individuals with known sensitivity to fentanyl or other ingredients within a specific delivery formulation.

Fentanyl transdermal patches should not be used in patients with severe respiratory problems including asthma (unless the patient is concurrently mechanically ventilated), or who have a functional bowel obstruction (paralytic ileus).

Side effects

The most common side effects of fentanyl treatment include:

- slow heart rate
- swelling
- headache, drowsiness, confusion, unclear thinking, depression
- sweating, itching
- dehydration
- constipation
- dry mouth
- stiff or weak muscles
- shortness of breath, respiratory depression
- euphoria
- agitation, hallucinations
- upset stomach, nausea, vomiting

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

The following may increase fentanyl's side effects:

- alpha- and beta-agonists
- opioid analgesics

- amphetamines
- anticholinergic agents
- antiemetics
- **aripiprazole**
- antipsychotic agents
- cannabis
- crizotinib
- droperidol
- hydrocodone
- **hydroxyzine**
- magnesium sulfate
- methotrimeprazine
- mifepristone
- **zolpidem**

Drugs classified as CYP3A4 inhibitors have a profound effect on fentanyl and may greatly increase the risk of potentially fatal side effects. There are many drugs in this group, including:

- amiodarone
- anastrozole
- **azithromycin**
- cannabinoids
- cimetidine
- **clarithromycin**
- clotrimazole
- **cyclosporine**
- danazol
- delavirdine
- dexamethasone
- diethyldithiocarbamate
- **diltiazem**
- disulfiram
- entacapone
- **erythromycin**
- ethinyl estradiol
- **fluconazole**
- **fluoxetine**
- **fluvoxamine**
- gestodene
- indinavir
- isoniazid
- **ketoconazole**
- **metronidazole**
- mibefradil
- miconazole
- nefazodone

- nelfinavir
- nevirapine
- norfloxacin
- norfluoxetine
- **omeprazole**
- oxiconazole
- **paroxetine**
- propoxyphene
- quinidine
- quinine
- **ranitidine**
- ritonavir
- saquinavir
- sertindole
- **sertraline**
- troglitazone
- troleandomycin
- **valproic acid**

Fentanyl may increase the side effects of the following:

- opioid analgesics
- antiemetics
- antipsychotic agents
- beta blockers
- buprenorphine
- calcium channel blockers
- desmopressin
- diuretics
- hydrocodone
- hydroxyzine
- monoamine oxidase inhibitors (MAOIs)
- methotrimeprazine
- **metoclopramide**

Herbs and supplements

Kava kava may increase the side effects of fentanyl.

Fentanyl may increase the side effects of cannabis and kava kava.

Food and other substances

Ingesting over a quart of grapefruit juice per day may increase fentanyl levels and therefore the risk of side effects.

Fentanyl may increase the side effects of alcohol.

Resources

BOOKS

- Aronson, J. K. *Meyler's Side Effects of Analgesics and Anti-inflammatory Drugs*. Oxford: Elsevier, 2010.
- Benzon, Honorio T. *Essentials of Pain Medicine*. 3rd ed. Philadelphia: Saunders, 2011.
- Smith, Howard S. *Current Therapy in Pain*. Philadelphia: Saunders, 2009.
- Waldman, Steven D. *Pain Management*. 2nd ed. Philadelphia: Saunders, 2011.

WEBSITES

- "Fentanyl Injection." Drugs.com. <http://www.drugs.com/fentanyl.html> (accessed February 13, 2015).
- Mayo Clinic Staff. "Fentanyl (Buccal Mucosa Route, Oromucosal Route, Sublingual Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/fentanyl-buccal-mucosa-route-oromucosal-route-sublingual-route/description/drg-20063888> (accessed February 13, 2015).
- MedlinePlus. "Fentanyl." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a605043.html> (accessed February 13, 2015).
- U.S. National Library of Medicine. "LactMed: Fentanyl." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+356> (accessed February 13, 2015).

ORGANIZATIONS

- American Chronic Pain Association, PO Box 850, Rocklin, CA 95677, (800) 533-3231, APAC@theacpa.org, <http://www.theacpa.org/>.
- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- National Pain Foundation, 14828 W 6 Avenue, Suite 16-B, Room 1, Golden, CO 80401-5000, (720) 541-6808, Fax: (720) 541-6809, <http://www.thenationalpainfoundation.org/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rosalyn S. Carson-Dewitt, MD

REVIEWED BY KEVIN GLAZA, RPh

Fexofenadine

Definition

Fexofenadine (Allegra) is an antihistamine, which means it is used to relieve the symptoms of seasonal allergies. The full name of the drug is fexofenadine hydrochloride.



Allegra-D 12 hour (fexofenadine/pseudoephedrine, 60 mg/120 mg). (© Cengage Learning®.)

Purpose

People who have seasonal allergies, often called hay fever, can experience many bothersome symptoms. The symptoms, such as runny nose, itchy and watery eyes, and sneezing, can simply make it difficult to carry on everyday activities and sleep well, or they can become more serious. For example, some people already have problems breathing because they have asthma or other chronic respiratory diseases, and seasonal allergies make breathing and other symptoms worse. Anyone with severe allergies can develop a sinus infection or ear infection from the constant running or thickening of mucus in tiny cavities.

The reason people with seasonal allergies experience symptoms is because they have a high sensitivity to pollen from certain plants. The sensitivity causes the body's immune system to release histamine, a natural chemical that causes capillaries in the body to expand, along with other reactions. Fexofenadine is a histamine H1-receptor antagonist. This means that the drug's active ingredient helps control the body's release of histamine and resulting symptoms. Fexofenadine also may be used to treat a condition called chronic idiopathic urticaria, which causes itching, redness, and wheals.

Description

Fexofenadine is taken orally. It comes in liquid and tablet form and in strengths that last 12 or 24 hours. Although it is used primarily to help people manage seasonal allergies, the drug also is used for certain types of itching, hives, and other purposes. The drug used to be available only with a prescription, but in 2011, the U.S. Food and Drug Administration (FDA) switched approval of the drug for over-the-counter availability. One form also contains a decongestant, which helps to relieve congestion in the nose and other upper respiratory areas. Some formulations of fexofenadine are designed for children, coming in either melting orange-flavored tablets or a raspberry-flavored liquid.

U.S. brand names

In the United States, fexofenadine is sold as:

- Allegra (12-hour and 24-hour)
- Allegra-D (decongestant in 12-hour and 24-hour)
- Allegra Children's Meltable Tablets
- Allegra Children's Liquid

Recommended dosage

Adults can take up to two 60 milligram (mg) Allegra 12-hour tablets a day to relieve allergy symptoms, and no more than two tablets in a 24-hour period. Adults and children older than age 12 can take one 24-hour Allegra tablet each day; the pill is not recommended for anyone under age 12. Fexofenadine tablets should be swallowed with water.

Allegra Meltable Tablets should be placed on the tongue. Adults and children older than 12 can take two meltable tablets every 12 hours on an empty stomach; they should not take more than four tablets in a 24-hour period.

The liquid form of Allegra can be taken by adults and children age 12 and older as two teaspoonfuls (10 mL) every 12 hours, and no more than four teaspoonfuls (20 mL) in a 24-hour period.

Pediatric

The 12- and 24-hour tablets are not recommended for children younger than 12 years old. Children between 6 and 12 years old can take one meltable tablet every 12 hours on an empty stomach, and no more than two tablets in a 24-hour period. These tablets should not be given to children younger than 6 years old.

For the liquid form, children from ages 2–12 can take one teaspoon (5 mL) every 12 hours and

KEY TERMS

Capillaries—A tiny branching blood vessel that connects small arteries and veins.

Chronic idiopathic urticaria—The near daily occurrence of hives, or wheals, and itching, caused by a problem in a person's autoimmune system that releases histamine and other substances into the body.

Histamine—A chemical found naturally in the body that produces inflammation and increases blood flow; the uncomfortable symptoms of an allergy attack or an allergic reaction are generally caused by the release of histamine.

Wheal—A welt, or small swollen and red area on the skin's surface that can itch and burn.

should not exceed two teaspoons (10 mL) in a 24-hour period. Parents should consult a doctor before giving the liquid form of fexofenadine to children younger than 2 years old.

Geriatric

Anyone older than age 65 should talk to a doctor before using fexofenadine in any form.

Precautions

Anyone with drug allergies should inform their doctor or pharmacist of these allergies before using this drug, as these allergies could indicate a problem with fexofenadine. An allergic reaction to fexofenadine usually causes hives; facial, tongue, and throat swelling; and trouble breathing. If a person has these symptoms or has taken too much of the drug, they should stop its use and seek emergency care.

Pediatric

H1-antihistamines such as fexofenadine are among the medicines used most often in children. In general, fexofenadine should not be given to children under age 2. The oral form of Allegra may be recommended for children between 2 months and 2 years old to relieve the symptoms of chronic idiopathic urticaria, but only with a doctor's instructions for use. Studies have been done to demonstrate its effectiveness for very young children for managing urticaria symptoms. Studies also have documented safe use of fexofenadine in children from 6 to 11 years old.

Geriatric

Trials on the safety and use of fexofenadine have not involved enough older patients to test whether seniors might react differently to effects from the drug. In general, it is assumed safe for older patients, as long as they have no kidney disease or doctors monitor the patient's kidney health.

Pregnant or breastfeeding

Fexofenadine is pregnancy category C, meaning it is not known whether the drug harms a fetus. Doctors do not know if the active ingredient in Allegra can pass into breast milk from a mother taking the drug, so anyone who is pregnant or breastfeeding should check with a doctor before using any form of Allegra. Pregnant women should only use fexofenadine when the benefits outweigh the risks of its use.

Other conditions and allergies

People with kidney disease should not use fexofenadine or may need reduced doses of the drug.

Side effects

Fexofenadine can cause side effects, and the most reported adverse effect is vomiting. Other reported side effects are less common and include:

- dizziness
- headache
- diarrhea
- pain, especially in the arms, legs, and back, or during menstruation
- coughing
- ringing in the ear
- ear redness or swelling
- unusual tiredness or weakness

More serious side effects could indicate an allergic reaction to the drug. These should be reported to a doctor immediately:

- rash
- hives
- trouble breathing or swallowing
- facial swelling
- swelling of the tongue, hands, feet, or lower legs

Interactions

Fexofenadine may interact with prescription drugs and over-the-counter medications, including some vitamins,

herbal products, and nutritional supplements. The medicine also can interact with some foods.

Drugs

Fexofenadine is known to interact with the antibiotic erythromycin (Erythrocin, E-Mycin, E.E.S.) and an antifungal medication called **ketoconazole** (Nizoral). More than 60 drugs can interact with fexofenadine, which can lessen the effect of one of the medicines or cause unwanted side effects. Some of the common medicines that interact with fexofenadine are listed below, but anyone using the drug should consult their doctor or pharmacist about other drugs taken.

- **aspirin**
- **duloxetine** (Cymbalta)
- **fluticasone** nasal (Flonase)
- **esomeprazole** (Nexium)
- **montelukast** (Singulair)
- **levothyroxine** (Synthroid)

Food and other substances

It is recommended that anyone taking fexofenadine avoid consuming large amounts of some fruit juices while on the medication, because the juices can decrease the amount of the active ingredient in the body. These include grapefruit, orange, and apple juices. Drinking plenty of water with the drug helps the body absorb the medication better.

Resources

PERIODICALS

Fitzsimons, Roisin, et al. "Antihistamine Use in Children." *Archives of Disease in Childhood* (August 21, 2014): e-pub ahead of print. <http://dx.doi.org/10.1136/archdischild-2013-304446> (accessed February 19, 2015).

WEBSITES

"Allegra." Drugs.com. <http://www.drugs.com/allegra.html> (accessed January 5, 2015).

MedlinePlus. "Fexofenadine." National Library of Medicine, U.S. National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a697035.html> (accessed January 5, 2015).

Sanofi. "Allegra." Allegra.com. <http://www.allegra.com> (accessed January 5, 2015).

U.S. Food and Drug Administration. "Prescription to Over-the-Counter (OTC) Switch List." <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm106378.htm> (accessed April 8, 2015).

ORGANIZATIONS

American Academy of Allergy, Asthma & Immunology, 555 East Wells Street, Suite 1100, Milwaukee, WI 53202, (414) 272-6071, <http://www.aaaai.org/home.aspx>.

National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, MSC 9806, Bethesda, MD 20892-9806, (301) 496-5717, (866) 284-4107, Fax: (301) 402-3573, TTY: (800) 877-8339, <http://www.niaid.nih.gov/>.

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Finasteride

Definition

Finasteride is a drug that belongs to the class of androgen inhibitors, which means that it blocks the production of male sex hormones. Finasteride inhibits the body's production of an enzyme called 5-alpha reductase, which is needed to convert testosterone to another androgen called 5-alpha dihydrotestosterone (DHT).

Purpose

Finasteride has two main purposes: the treatment of urinary problems in men caused by benign prostatic hyperplasia (BPH) or enlargement of the prostate gland, and the stimulation of new hair growth in men with male pattern baldness. This drug may be used alone or in combination with the drug doxazosin (Cardura) to treat BPH.



Finasteride, 5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Alopecia—The medical term for baldness.

Androgens—A group of hormones that produce masculine characteristics.

Benign prostatic hyperplasia (BPH)—A noncancerous swelling of the prostate.

Dysuria—Painful or difficult urination.

Incontinence—Inability to control urination or defecation.

Nocturia—Excessive need to urinate at night.

Prostate—A gland in males below the bladder that surrounds the urethra. Enlargement of the prostate may cause problems in urination.

Finasteride works to relieve such symptoms of prostate enlargement as urinary urgency, the need to urinate frequently at night (nocturia), inability to completely empty the bladder, incontinence, or painful urination (dysuria) by blocking the production of DHT. DHT causes the prostate gland to grow and increase pressure on the bladder. As the swollen prostate gradually shrinks, the patient finds it easier to pass urine without discomfort and to empty the bladder completely before going to sleep.

Results of a large clinical trial called the Prostate Cancer Prevention Trial, which were released in 2010, revealed that finasteride (Proscar) reduced the risk for prostate cancer by as much as 25% in men (ages 55 and older) enrolled in the trial. In the near future, men with an increasing prostate-specific antigen (PSA) level who are considered by their physicians to be at high risk for the development of prostate cancer may be prescribed finasteride to decrease their risk for developing prostate cancer.

Off-label use

Some doctors prescribe finasteride as pretreatment for prostate surgery, as it lowers the risk of severe bleeding during the operation.

Description

U.S. brand names

Finasteride is sold in the United States (and Canada) under the brand names Proscar (indicated for the treatment of BPH) and Propecia (indicated for the treatment of male pattern baldness). Both Proscar and

PATIENT PROFILE

Finasteride (Proscar) was prescribed for an otherwise healthy 62-year-old man who had been diagnosed with noncancerous enlargement of the prostate (benign prostatic hypertrophy or BPH). For about six months prior to being diagnosed, the patient had experienced urinary symptoms on and off, including increased frequency of urination and sometimes difficult urination. A few times he was also unable to urinate, even after feeling the urge to empty his bladder. Urinary flow tests and transrectal ultrasound images revealed that the prostate glands were somewhat, but not markedly, enlarged and were pressing on the urethra, which was most likely responsible for his symptoms. A biopsy revealed that cells from the prostate glands were normal and that no cancer was present. The patient was informed that BPH does not increase the risk of cancer, but that prostate cancer may still develop.

Finasteride was prescribed as a 5 mg tablet to be taken orally once a day with or without food and at the same time each day. Finasteride works by blocking the conversion of the male hormone testosterone to dihydrotestosterone, the male hormone that is responsible for enlargement of the prostate glands. When taken regularly, finasteride reduces the symptoms of frequent urination or difficult urination and also reduces the likelihood of acute urinary retention, which was the cause of the patient's sudden inability to urinate. Experience with this drug has shown that it decreases the chance that the patient will require prostate surgery. However, the patient was advised that, although this medication is able to control prostate enlargement, it is not a cure for BPH and also does not prevent the development of cancer.

After taking finasteride for one month, the patient reported at his four-week follow-up visit that his urinary symptoms had not recurred, but that he had new symptoms that were much more upsetting to him. He told his doctor that his sexual desire was diminished significantly and that he could not perform normally in having intercourse with his wife. The doctor informed him that these side effects did occur in some men when taking finasteride and sometimes, but not always, disappeared after stopping the drug. It then became a question of which symptoms affected the patient's quality of life more and which symptoms he wanted to correct. In a conference with the patient and his wife, the doctor explained that the patient's BPH was fairly mild and did not indicate a need for surgery at that time. Finasteride also presents a risk of prostate cancer development even while relieving symptoms. Therefore, the doctor suggested that, because the patient only had lower urinary tract symptoms and had never had urinary tract infection or bladder complications, they could apply "watchful waiting" with regular tests for prostate-specific antigen (PSA) rather than continue with finasteride treatment. Eventually, a procedure called transurethral resection of the prostate (TURP) could possibly be performed to correct bladder outlet obstruction (BOO) caused by the enlarged prostate. Although medical therapy with finasteride or other drugs effective for treating lower urinary tract symptoms are usually applied prior to considering TURP, the patient would need to decide which route to follow. While meeting with the doctor, the patient and his wife expressed that the effects and risks associated with finasteride treatment outweighed the benefits for them, and they would continue to watch the BPH for the time being but not treat it medically.

Propecia are manufactured as coated tablets to be taken by mouth.

Origins

Finasteride was first approved by the U.S. Food and Drug Administration (FDA) in 1992 under the trade name Proscar as a treatment for BPH. It received a second FDA approval in December 1997 under the trade name Propecia for the treatment of hair loss in men.

Recommended dosage

Finasteride for treatment of an enlarged prostate is taken once a day as a 5 milligram (mg) tablet. The pill may be crushed or broken if the patient finds it hard to swallow.

Finasteride for hair regrowth is taken once a day as a 1 mg tablet. The drug may be taken with or without meals.

Precautions

Finasteride should be stored in a dry place and kept at a temperature between 59°F and 86°F (15°C–30°C). Heat and moisture may cause the drug to lose its potency.

Patients should be advised that finasteride takes several months to reach its full effect—as long as six months for BPH and three months for hair regrowth. In addition, the drug's effects on the body are not permanent; the prostate will start to enlarge again or the hair growth will be lost if the patient stops taking the drug.

Proscar can affect the results of a prostate-specific antigen (PSA) test for cancer of the prostate.

Finasteride is not indicated for the treatment of hair loss in women in the United States.

Pregnant or breastfeeding

Tablets, especially crushed or broken tablets, should not be touched by pregnant women, as the drug can be absorbed through the skin. If the woman is carrying a male fetus, the drug can cause abnormalities in the baby's sex organs. The FDA issued a warning in 2003 that men taking finasteride should not donate blood until one month after the final dose of the drug, on the grounds that their blood could contain high enough levels of the medication to cause birth defects in a male baby if given to a pregnant woman.

Other conditions and allergies

Finasteride should be used cautiously by men with liver disorders.

Side effects

Reported side effects from using finasteride include:

- impotence or loss of interest in sex
- lumps or pain in the breast or a discharge from the nipple
- skin rash, itching, or hives
- swelling of the lips or face
- a smaller quantity of ejaculate during intercourse (which does not affect fertility)
- headaches, dizziness, or diarrhea
- pain in the testicles

These side effects are more common with the 5 mg dose but usually disappear when the drug is discontinued.

Interactions

Finasteride has not been reported to cause significant interactions with other medications.

Resources

BOOKS

Vallerand, April H., and Cynthia A. Sanoski. *Davis's Drug Guide for Nurses*. 14th ed. Philadelphia: F.A. Davis, 2014.

PERIODICALS

Chaudhary, U.B., and J.S. Turner. "Finasteride." *Expert Opinion on Drug Metabolism and Toxicology* 6, no. 7 (July 6, 2010): 873–81.

Groves-Kirkby, N. "Chemotherapy: Optimizing Finasteride Chemoprevention for Prostate Cancer." *National Review of Clinical Oncology* 7, no. 5 (May 2010): 242.

Smith, A.B., and C.C. Carson. "Finasteride in the Treatment of Patients with Benign Prostatic Hyperplasia: A Review."

Journal of Therapeutics and Clinical Risk Management 5, no. 3 (June 2009): 535–45.

OTHER

"Proscar [prescribing information]." Merck.com. http://www.merck.com/product/usa/pi_circulars/p/proscar/proscar_pi.pdf (accessed February 23, 2015).

WEBSITES

Micromedex. "Finasteride (Oral Route)." <http://www.mayoclinic.org/drugs-supplements/finasteride-oral-route/description/drg-20063819> (accessed February 23, 2015).

National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC). "Prostate Enlargement: Benign Prostatic Hyperplasia." <http://kidney.niddk.nih.gov/kudiseases/pubs/prostateenlargement/> (accessed February 23, 2015).

U.S. Food and Drug Administration. "Propecia (Finasteride) 1 mg Tablet." <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm208701.htm> (accessed February 23, 2015).

ORGANIZATIONS

National Kidney and Urologic Diseases Information Clearinghouse, 3 Information Way, Bethesda, MD 20892–3580, (800) 891–5390, Fax: (703) 738–4929, TTY: (866) 569–1162, nkudic@info.niddk.nih.gov, <http://kidney.niddk.nih.gov/>.

Rebecca J. Frey, PhD

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REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Fioricet see **See Butalbital/acetaminophen/caffeine**

Flagyl see **Metronidazole**

Flexeril see **Cyclobenzaprine**

Flomax see **Tamsulosin**

Flonase see **Fluticasone**

Flovent HFA see **Fluticasone**

Fluconazole

Definition

Fluconazole is an oral or injected drug for treating or suppressing fungal infections. Fluconazole is in the triazole family of antifungal agents.

Purpose

Fluconazole is on the World Health Organization's (WHO) list of essential medicines. It is used to treat both common localized fungal infections and potentially



Fluconazole, 200 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

life-threatening opportunistic infections that can spread through the body. Fluconazole is used to treat:

- common localized yeast infections (candidiasis) of the vagina, mouth (oral thrush), throat, esophagus, abdomen, lungs, blood, urinary tract, and other organs caused by *Candida* spp., especially *C. albicans* (but not infections caused by *C. krusei* or *C. glabrata*)
- systemic (body-wide), invasive, or disseminated candida infections (candidemia) that have traveled through the bloodstream to other parts of the body
- superficial infections by *Epidermophyton* spp. or *Trichophyton* spp. that cause tinea cruris (“jock itch,” an infection of the groin or perineum), tinea pedis (athlete’s foot), or onychomycosis (infection of the nail bed of the fingernails or toenails)
- tinea corporis (ringworm of the skin) and tinea capitis (ringworm of the scalp) caused by *Microsporum* spp.
- tinea versicolor—a chronic fungal infection of the trunk
- sporotrichosis—skin infection by a fungus in the genus *Sporothrix* or *Sporotrichum*
- coccidioidomycosis or valley fever, a rare disease caused by inhaling microscopic spores of the soil fungus *Coccidioides immitis* or cocci, which is on the increase in the southwestern United States
- cryptococcosis—a serious disease caused by yeast-like fungi of the genus *Cryptococcus*, especially *C. neoformans*

- meningitis—life-threatening inflammation of the membranes surrounding the brain and spinal cord caused by cocci or *Cryptococcus* infection that has spread to the central nervous system
- fungal pneumonia
- blastomycosis—a potentially very serious disease of the skin, lymph nodes, and lungs, caused by yeast-like fungi of the genus *Blastomyces*
- histoplasmosis—respiratory disease caused by the fungus *Histoplasma capsulatum*

Fluconazole is also used to prevent or suppress yeast infections in patients with suppressed immune systems because of HIV/AIDS, cancer, organ transplants, or chemotherapy or radiation therapy prior to bone-marrow transplantation. This is because fungal infections treated with fluconazole are often opportunistic, only causing illness in people with compromised immune systems. Fluconazole may be prescribed for other uses.

Description

Fluconazole was the first drug in a new subclass of synthetic triazole antifungal agents. It works by interfering with fungal membranes to suppress the growth and reproduction of the pathogens. In some cases, especially with *Cryptococcus*, fluconazole may destroy the fungus and cure the infection. In other cases, it may need to be taken for the rest of a patient’s life to prevent recurrence of the infection.

U.S. brand names

The U.S. brand name of fluconazole is Diflucan. Fluconazole is also available from generic manufacturers.

Canadian brand names

The Canadian brand names for fluconazole are Diflucan and CanesOral.

International brand names

There are many international generic and brand names for fluconazole, including:

- Baten
- Diflazon
- Diflucan
- Efac
- Exomax
- Flucess
- Flucon
- Flucoric
- Forcan

KEY TERMS

Antifungal—A medicine used to treat infections caused by a fungus.

Blastomycosis—Either of two infectious diseases (North American and South American) caused by yeast-like fungi of the genus *Blastomyces*.

Candidemia—Invasive or disseminated candidiasis. *Candida* infection that spreads from the bloodstream to other parts of the body.

Candidiasis—A yeast infection caused by *Candida* spp. For example, overgrowth of *C. albicans*, which is normally present in the vagina, causes vaginitis.

Coccidioidomycosis—Valley fever. A disease caused by the fungus *Coccidioides immitis* or *cocci*.

Cryptococcus—A genus of yeast-like fungi that can cause serious illness, especially in immunocompromised patients.

Histoplasmosis—A respiratory disease with flu-like symptoms caused by the fungus *Histoplasma capsulatum* that is endemic to the Mississippi and Ohio River valleys.

Meningitis—Inflammation of the meninges—membranes covering the brain and spinal cord—that can be caused by fungi.

Onychomycosis—A fungal disease of the fingernails or toenails.

Opportunistic infection—An organism that normally only causes disease in patients with compromised immune systems such as with HIV/AIDS.

Pathogen—A disease-causing organism.

Pregnancy category—A system of classifying drugs according to their established risks for use during

pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk but no human studies exist, or adverse effects have been seen in animals but not in well-controlled human studies. Category C: No adequate human or animal studies exist, or adverse fetal effects have occurred in animal studies but there is no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk, and risks outweigh any benefits.

Prophylaxis—Treatment to prevent disease.

Ringworm—Any of several contagious fungal diseases of the skin, hair, or nails characterized by ring-shaped patches.

Sporotrichosis—Skin infection with a fungus in the genus *Sporothrix* or *Sporotrichum*.

Suppress—Prevent recurrence.

Systemic—Having effects throughout the body, as with a disseminated infection.

Thrush—Infection with the fungus *Candida albicans* that causes white patches in the oral cavity.

Tinea capitis—A contagious fungal infection (ringworm) of the scalp.

Tinea corporis—A fungal infection (ringworm) of the skin.

Tinea cruris—A fungal infection of the groin and perineum; also referred to as “jock itch.”

Tinea pedis—Ringworm of the feet; also referred to as “athlete’s foot.”

Tinea versicolor—A chronic skin infection caused by the fungus *Pityrosporum orbiculare*.

- Fungolon
- Funzol
- Medoflucon
- Mutum
- Mycomax
- Mycosyst
- Stabilanol
- Stalene
- Triflucan
- Zenafluk

Recommended dosage

Fluconazole injections are 100 or 200 milliliter (mL) sterile solutions with 2 milligrams (mg) fluconazole per mL in 0.9% sodium chloride (saline) or 5% dextrose. The liquid is well shaken to mix evenly and injected slowly (infused) into a vein through a needle or catheter over one to two hours, at a rate of about 200 mg per hour. Infusions are performed in a medical facility or at home at about the same time each day. A missed dose should be infused as soon as possible, but if it is almost time for the next dose, the missed dose should be skipped and the regular schedule resumed. Glass containers are stored at 5°C–30°C (41°F–86°F). Plastic containers are stored at

5°C–25°C (41°F–77°F). The solution must be discarded after two weeks.

Fluconazole dosages and treatment duration depend on the condition and patient response. Unless otherwise noted, fluconazole is administered once daily. The first day's dose is generally double the regular dose (a loading or induction dose). The dose is the same for oral tablets or suspensions and intravenous (IV) administration.

Usual adult dosages are:

- blastomycosis: 400–800 mg taken orally for at least 6 to 12 months
- candida infection of the bones or joints (osteoarticular): 400 mg (IV or orally) for 6 weeks to 12 months
- candida urinary tract infection and peritonitis: 50–400 mg (IV or orally)
- candidemia, disseminated candidiasis, or pneumonia: 800 mg (IV or orally) on day one, followed by 400 mg until 14 days after negative blood tests and resolution of symptoms
- cardiovascular candida: 400–800 mg (IV or orally); may be taken for weeks, months, or as lifelong suppressive therapy
- central nervous system candidiasis after initial treatment with amphotericin B: 400–800 mg (IV or orally) until all signs, symptoms, and abnormalities have resolved
- complicated vulvovaginal candidiasis: 150 mg orally, taken every 72 hours for two or three doses
- recurrent vulvovaginal candidiasis: 100–200 mg orally, taken every 72 hours for three doses or for 10–14 days; maintenance dosage is 100–200 mg orally taken once weekly for six months
- uncomplicated vaginal candidiasis: one 150 mg oral dose
- oropharyngeal candidiasis: 200 mg (IV or orally) on day one, followed by 100 mg for at least two weeks thereafter
- esophageal candidiasis: 200–400 mg (IV or orally) on day one, followed by 100 mg for at least 14–21 days thereafter or at least two weeks after symptoms resolve
- coccidioidomycosis: 400–800 mg (IV or orally) for 3 to 6 months for uncomplicated pneumonia and at least one year for more serious disease
- coccidioidomycosis meningitis: 400–1,000 mg orally; may need to take 400 mg orally lifelong
- cryptococcosis: 400 mg orally for 6 to 12 months
- cryptococcal meningitis: 400 mg (IV or orally) on day one, followed by 200 mg taken for 10 to 12 weeks after tests return negative or 400–800 mg orally for eight weeks followed by 200 mg orally for 6 to 12 months
- disseminated histoplasmosis: 200–800 mg (IV or orally) for at least 12 months
- onychomycosis: 150–300 mg orally once a week for 3 to 6 months for fingernail infection and 6 to 12 months for toenails
- sporotrichosis: 400–800 mg (IV or orally) for 2 to 4 weeks after all lesions have resolved (usually 3 to 6 months total)

Pediatric

Pediatric doses of 3, 6, and 12 mg per kilogram (kg, or 2.2 lb.) of body weight are generally equivalent to adult doses of 100, 200, and 400 mg, respectively. The maximum pediatric dose is usually 600 mg/day.

Specific doses include:

- candida urinary tract infection: 3–6 mg/kg (IV or orally) for two weeks
- candidemia, systemic candidiasis, disseminated fungal infections: for children two weeks or younger, 6–12 mg/kg (IV or orally) every 72 hours; older children, 6–12 mg/kg/day (IV or orally) for at least two weeks after negative blood cultures and resolution of symptoms (much longer for chronic disseminated candidiasis and candida osteoarticular infection; months to lifelong for candida cardiovascular infection)
- esophageal candidiasis: two weeks or younger, 3 mg/kg (IV or orally) every 72 hours; older than two weeks, 6–12 mg/kg (IV or orally) on day one, then 3 mg/kg (maximum 600 mg/dose) for at least three weeks and at least two weeks after symptoms resolve
- oral thrush: two weeks or younger, 3 mg/kg (IV or orally) every 72 hours; older than two weeks, 6 mg/kg (IV or orally) on day one, then 3 mg/kg once daily for at least two weeks
- cryptococcosis (disseminated disease after induction therapy): 10–12 mg/kg/day orally in two daily doses for eight weeks; 6–12 mg/kg orally for 6 to 12 months for cryptococcal pneumonia
- cryptococcal meningitis: two weeks and younger, 6 mg/kg (IV or orally) every 72 hours; older than two weeks, 12 mg/kg (IV or orally) on day one, then 6 mg/kg (IV or orally) for 10–12 weeks after negative test results; higher doses and longer duration for HIV-exposed and infected children
- fungal infection prevention: 12 mg/kg (IV or orally) on day one, followed by 6 mg/kg (IV or orally)

Doses for HIV-exposed or infected children and adolescents include:

- candidemia, systemic candidiasis, disseminated fungal infections: 12 mg/kg IV (maximum 600 mg/dose) for invasive disease
- esophageal candidiasis: 100–400 mg (IV or orally) for 14–21 days, followed by 100–200 mg orally once daily for suppression
- oral thrush: younger children, 6–12 mg/kg orally (maximum 400 mg/dose) for 7 to 14 days; adolescents, 100 mg orally for 7 to 14 days and 100 mg orally once daily or three times per week thereafter
- vaginal candidiasis: uncomplicated, single 150 mg oral dose; severe, 100–200 mg orally for at least seven days, followed by 150 mg orally once weekly for suppression
- coccidioidomycosis: 6–12 mg/kg (IV or orally) up to 400–800 mg/dose for one year
- coccidioidomycosis meningitis: 12 mg/kg (IV or orally) up to 800 mg/dose; 6 mg/kg orally up to 400 mg/dose for life
- cryptococcosis (disseminated disease after induction therapy): 6 mg/kg orally for maintenance therapy
- histoplasmosis in HIV-exposed and infected: acute pulmonary infection, 3–6 mg/kg orally, 200 mg/dose maximum; mild disseminated, 5–6 mg/kg (IV or orally) twice daily, 300 mg/dose maximum, for 12 months; prevention, 3–6 mg/kg orally, 200 mg/dose maximum; adolescents, 800 mg orally for at least 12 months, then 400 mg orally for suppression

Other conditions and allergies:

HIV/AIDS patients usually require maintenance or suppressive therapy for recurrent candidiasis and meningitis:

- cryptococcal meningitis: 800–2,000 mg orally for 6 to 12 weeks in HIV-infected and organ-transplant patients; 200 mg (IV or orally) for suppression of relapse in AIDS patients
- esophageal candidiasis: 100–400 mg (IV or orally) for 14–21 days; 100–200 mg orally once daily for suppression
- initial oropharyngeal candidiasis: 100 mg orally for 7–14 days; moderate-to-severe, 100–200 mg (IV or orally) for 7–14 days; suppressive therapy, 100 mg orally once daily or three times per week
- severe or recurrent vulvovaginal candidiasis: 100–200 mg orally for at least seven days; 150 mg orally once per week for suppression

For fungal infection prevention in bone marrow transplant patients, the dose is 400 mg (IV or orally) for seven days after neutrophil (white blood cell) count has risen.

No adjustment is required for single-dose therapy in kidney-impaired patients. Adjustments when more than one dose is needed may be determined by a patient's creatinine clearance rate (CrCl). Creatinine is a waste material that is filtered out of the body by the kidneys. Measuring the amount of creatinine in a patient's urine helps determine kidney function. For a CrCl of 50 mL/min or less, the loading dose is 50–400 mg IV or orally, followed by 50% of the usual daily dose. Dialysis patients should receive the usual dose following dialysis.

Precautions

When taking fluconazole, the entire prescribed course should be used, even if symptoms disappear, to prevent recurrence of the infection. Patients should contact their doctor if symptoms do not improve or worsen. Doctors and dentists should be informed of fluconazole use before patients undergo any type of surgery.

Fluconazole can cause dizziness or seizures. Patients should not drive or operate machinery until they know how the drug affects them.

Symptoms of overdose include hallucinations and extreme fear of harm from other people.

Geriatric

Kidney function should be considered when prescribing fluconazole for elderly patients.

Pregnant or breastfeeding

In 2011, the FDA changed the fluconazole pregnancy category from C to D, because doses of 400–800 mg per day during the first trimester of pregnancy may be associated with birth defects, although the potential benefits to women with serious or life-threatening infections may outweigh the risk. Single-dose treatment of vaginal candidiasis remains in category C. Studies indicate that single low-dose fluconazole during pregnancy does not increase the risk of birth defects or miscarriage. Fluconazole takes, on average, six to nine days to completely clear the body.

Although fluconazole enters breast milk, the infant's dose is far below that for treating infant infections. The American Academy of Pediatrics considers fluconazole to be compatible with breastfeeding. Breastfeeding can be continued during oral fluconazole treatment for a yeast infection in the breast if a topical antifungal is ineffective. In the case of such infection, the infant must be treated for oral thrush.

Other conditions and allergies

Patients must tell their doctors and pharmacists if they are allergic to fluconazole, fluconazole ingredients, other antifungal medications, or any other medications. Liver function should be monitored, especially in patients with liver disease. The doctor should be informed if the patient has ever had:

- cancer
- HIV/AIDS
- irregular heartbeat
- low blood levels of calcium, sodium, magnesium, or potassium
- heart, kidney, or liver disease
- rare, inherited intolerance of lactose or sucrose

Side effects

The doctor should be notified if any of the following side effects are severe or persistent:

- headache
- dizziness
- diarrhea
- stomach pain
- heartburn
- changes in taste

The following side effects require immediately notifying the doctor or obtaining emergency treatment:

- nausea
- vomiting
- lack of energy
- extreme tiredness
- unusual bruising or bleeding
- loss of appetite
- pain in the upper right stomach
- yellowing of the skin or eyes
- flu-like symptoms
- dark urine
- pale stools
- rash
- hives
- itching
- skin peeling
- seizures
- swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs
- difficulty breathing or swallowing

Interactions

The doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient, as well as any new medications taken within seven days of fluconazole. Patients should bring a list of medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

A large number of drugs can interact with fluconazole. Fluconazole should not be used by patients taking:

- astemizole
- cisapride
- **erythromycin**
- pimozide
- quinidine
- terfenadine

Medications that may require altering dosages or monitoring for side effects include:

- **amitriptyline**
- amphotericin B
- anticoagulants such as **warfarin**
- benzodiazepines such as midazolam
- calcium channel blockers such as **amlodipine**, felodipine, isradipine, and **nifedipine**
- **carbamazepine**
- **celecoxib**
- cholesterol-lowering medications (statins)
- **clopidogrel**
- cyclophosphamide
- **cyclosporine**
- diuretics such as **hydrochlorothiazide**
- **fentanyl**
- isoniazid
- **losartan**
- **methadone**
- nevirapine
- nonsteroidal anti-inflammatories such as **ibuprofen** and naproxen
- **oral contraceptives**
- oral medication for diabetes such as **glipizide**, **glyburide**, and tolbutamide
- **nortriptyline**
- **phenytoin**
- **prednisone**

- rifabutin
- **rifampin**
- saquinavir
- sirolimus
- **tacrolimus**
- theophylline
- tofacitinib
- **triazolam**
- **valproic acid**
- vinblastine
- vincristine
- voriconazole
- zidovudine

Herbs and supplements

Vitamin A may interact with fluconazole.

Food and other substances

Fluconazole may be taken with or without food.

Resources

BOOKS

Herrera, Santiago, and Joaquin Acosta. *Fluconazole: Pharmacology, Clinical Uses, and Health Effects*. New York: Nova Science Publishers, 2013.

OTHER

Organization of Teratology Information Specialists. "Fluconazole and Pregnancy." <http://www.mothertobaby.org/files/Fluconazole.pdf> (accessed January 22, 2015).

WEBSITES

- American Academy of Pediatrics. "Fungal Diseases." HealthyChildren.org. <http://www.healthychildren.org/English/health-issues/conditions/infections/pages/Fungal-Diseases.aspx> (accessed January 23, 2015).
- American Academy of Pediatrics. "Thrush and Other Candida Infections." HealthyChildren.org. <http://www.healthychildren.org/English/health-issues/conditions/infections/pages/Thrush-and-Other-Candida-Infections.aspx> (accessed January 23, 2015).
- American Society of Health-System Pharmacists. "Fluconazole." MedlinePlus. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a690002.html> (accessed January 22, 2015).
- American Society of Health-System Pharmacists. "Fluconazole Injection." MedlinePlus. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601143.html> (accessed January 22, 2015).
- "Fluconazole Dosage." Drugs.com. <http://www.drugs.com/dosage/fluconazole.html> (accessed January 22, 2015).

ORGANIZATIONS

American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, IL 60007-1098, (847) 434-4000, Fax: (847) 434-8000, info@healthychildren.org, <http://www.healthychildren.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

World Health Organization, Avenue Appia 20, 1211 Geneva 27, Switzerland, +41 22 791 21 11, Fax: +41 22 791 31 11, info@who.int, <http://www.who.int/en>.

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REVIEWED BY JAMES E. WAUN, MD, RPH

Fluorouracil

Definition

Fluorouracil is a medication that kills cancer cells. It is also known as 5-FU or 5-fluorouracil.

Purpose

5-FU may be used in combination with other chemotherapy agents to treat cancers of the breast, stomach, colon, rectum, and pancreas.

Description

5-FU is a cytotoxic drug. 5-FU kills cells by interfering with the activities of DNA and RNA, which



Fluorouracil cream. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Cancer—A disease caused by uncontrolled cell growth.

Cytotoxic drug—A medicine that kills (cancer) cells.

DNA—A molecule found in all living cells that contains tiny bits of genetic information.

Infusion therapy—Administration of a medication as a liquid through an intravenous (IV) device.

RNA—A molecule found in all living cells that plays a role in transmitting information from the DNA to the protein-forming system of the cell.

are molecules in the cells important in expressing genetic material.

U.S. brand names

Fluorouracil is sold under the brand name Adrucil.

Recommended dosage

Most frequently, 5-FU is given as an injection into the vein (intravenous injection or IV). Many different doses and regimens are used depending on the cancer diagnosis, and patients should discuss the dose with their physician based on the individual protocol used. A sample dose is 500–1,000 milligrams (mg) per square meter (m^2) of body surface area, given as a 24-hour infusion for four to five days every three weeks. A dose of 425 mg/m^2 per day for five days given along with the drug leucovorin is also common.

Precautions

Patients with an allergic reaction to 5-FU should not be administered this drug. It is also inadvisable for pregnant women. 5-FU should be administered with caution to patients with impaired liver or kidney function, or in patients with a history of heart problems.

Side effects

The amount of drug given and the duration of which it is given during a single session greatly influences the side effects seen. For example, when given as a 24-hour continuous infusion, the most common side effects are diarrhea and mouth ulcers. If 5-FU is given as a bolus infusion (a high quantity of the drug all at once), the most common side effect is bone marrow suppression; this results in a decrease of the white blood cells responsible

for fighting infections, the platelets responsible for blood clotting, and the red blood cells responsible for providing oxygen to the cells of the body.

The severity of the side effects is increased when 5-FU is given with the drug leucovorin. Vomiting, diarrhea, nausea, and loss of appetite (anorexia) may occur, regardless of how 5-FU is administered. The diarrhea side effect may be severe in some patients, and it is important for them to alert their doctor immediately so that appropriate medications for the diarrhea can be prescribed.

5-FU may cause rashes, increased sensitivity to sunlight, changes in skin color, changes to the fingernails, and redness and swelling in the palms of the hands and soles of the feet. Patients who have had heart disease before starting therapy with 5-FU may have problems with blood flow to the heart. Rarely, 5-FU may cause an allergic reaction, dry eyes, sleepiness, confusion, headache, changes in walking gait, involuntary rapid movement of the eyes, and difficulty speaking. When 5-FU is applied directly on the skin, there are usually no side effects except for those to the skin itself. These may include burning sensations, pain, and darkening of the skin color.

Some authorities recommend discontinuation of 5-FU therapy as soon as mild side effects are observed as a way of reducing the extent of injury to the digestive tract. Administration may then be restarted at a lower dose after the side effects have stopped.

Interactions

People taking fluorouracil should consult their doctor before taking any other prescription drug, over-the-counter drug, or herbal remedy.

Resources

BOOKS

- Chu, Edward, and Vincent T. DeVita Jr. *Physicians' Cancer Chemotherapy Drug Manual 2014*. Burlington, MA: Jones & Bartlett Learning, 2014.
- Wilkes, Gail M., and Margaret Barton-Burke. *2013 Oncology Nursing Drug Handbook*. Burlington, MA: Jones & Bartlett Learning, 2013.

WEBSITES

- American Cancer Society. "Fluorouracil (5-FU)." <http://www.cancer.org/treatment/treatmentsandsideeffects/guideto-cancerdrugs/fluorouracil> (accessed February 20, 2015).
- Cancer Research UK. "Fluorouracil." <http://www.cancerresearchuk.org/about-cancer/cancers-in-general/treatment/cancer-drugs/fluorouracil> (accessed February 20, 2015).

ORGANIZATIONS

- American Cancer Society, 250 Williams Street NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org/>.

National Cancer Institute, 9609 Medical Center Drive, BG 9609
MSC 9760, Bethesda, MD 20892-9760, (800) 4-CANCER
(422-6237), <http://www.cancer.gov/>.

Bob Kirsch

REVIEWED BY KEVIN GLAZA, RPh

Fluoxetine

Definition

Fluoxetine is an antidepressant. It is within the drug class known as selective serotonin reuptake inhibitors (SSRIs). It is sold in the United States under the brand names Prozac and Sarafem.

Purpose

Fluoxetine is used to treat depression, premenstrual syndrome, bulimia, panic disorders, and obsessive-compulsive disorder (OCD). It is approved for use in children with major depressive disorder (MDD) who are eight years and older and in children seven years and older who have obsessive-compulsive disorder (OCD). Sarafem is not approved for use in children.

Off-label use

Some clinicians have prescribed fluoxetine as a treatment for autism, although it has not been approved

by the U.S. Food and Drug Administration (FDA) for this purpose. While some studies have been conducted, their value has been limited by small sample sizes and inconclusive results. In 2014, Australia and New Zealand began a large scale, randomized, placebo-controlled study of fluoxetine for this use, which should lead to a better understanding of the drug's applications (if any) in treating disorders that fall within the autistic spectrum.

Description

Serotonin is a neurotransmitter—a brain chemical that carries nerve impulses from one nerve cell to another. Researchers think that depression and certain other mental disorders may be caused, in part, because there is not enough serotonin being released and transmitted in the brain. Like the other SSRI antidepressants—fluvoxamine (Luvox), sertraline (Zoloft), **citalopram** (Celexa), **escitalopram** (Lexapro), vilazodone (Viibryd), and **paroxetine** (Paxil)—fluoxetine increases the level of brain serotonin (also known as 5-HT). Increased serotonin levels in the brain may be beneficial in patients with OCD, alcoholism, certain types of headaches, post-traumatic stress disorder (PTSD), premenstrual tension and mood swings, and panic disorder.

Fluoxetine (marketed as Prozac) is available in 10, 20, and 40 milligram (mg) capsules; 10 mg tablets; and in a liquid solution with 20 mg of active drug per 5 milliliters (mL). Prozac Weekly capsules are a time-release formula containing 90 mg of active drug. Sarafem is available in 10 and 20 mg capsules.

Origins

Fluoxetine was the first of the SSRIs to be approved for use in the United States. It was approved by the U.S. Food and Drug Administration (FDA) in 2000 for use in treating premenstrual dysphoric disorder (PMDD).

Recommended dosage

Fluoxetine therapy in adults is started as a single 20 mg dose, initially taken in the morning. Depending on the patient's response after four to six weeks of therapy, this dose can be increased up to a total of 80 mg per day. Doses over 20 mg per day can be given as equally divided morning and afternoon doses.

The benefits of fluoxetine develop slowly over a period of several weeks. Patients should be aware of this and continue to take the drug as directed, even if they feel no immediate improvement.

Precautions

Fluoxetine carries a boxed warning, which is the most severe warning issued by the FDA. In studies,



Fluoxetine, 20 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Depression—A mental state of depressed mood characterized by feelings of sadness, despair, and discouragement. Depression ranges from normal feelings of the blues through dysthymia to major depression. Clinical depression impairs everyday function and can lead to lethargy, anxiety, pain, and sleep disorders.

Diabetes—A disease in which sugar is not metabolized properly. People with diabetes need to monitor their blood or urine sugar carefully if they are taking fluoxetine, because this drug affects blood sugar.

Monoamine oxidase inhibitor (MAOI)—An older class of antidepressants. These drugs act by preventing the metabolism of stimulatory neurohormones, but are no longer widely used because they have potentially serious food and drug interactions.

Obsessive-compulsive disorder—An anxiety disorder in which people have unwanted and repeated thoughts, feelings, ideas, sensations (obsessions), or behaviors that make them feel driven to do something (compulsions). Often the person carries out the behaviors to get rid of the obsessive thoughts, but this only provides temporary relief. Not doing the obsessive rituals can cause great anxiety.

Premenstrual syndrome—A combination of emotional, physical, psychological, and mood disturbances that occur after ovulation and normally end with the onset of the menstrual flow.

Selective serotonin reuptake inhibitors—A group of drugs that are used to treat depression and related conditions. They act by maintaining the level of the neurotransmitter serotonin. Normally, serotonin goes from one nerve cell to another, but if it is not transferred, it is taken up by the cell that first released it. SSRIs prevent this reuptake so that the serotonin can move from cell to cell.

Serotonin—A brain chemical that carries nerve impulses from one nerve cell to another.

fluoxetine and other antidepressant drugs increased the risk of suicidal thoughts and tendencies in children and adults (up to 24 years) with major depressive disorder (MDD) and other psychiatric disorders. Patients taking fluoxetine should be monitored closely for insomnia, anxiety, mania, significant weight loss, seizures, and thoughts of suicide. Fluoxetine use should not be stopped abruptly.

Caution should also be exercised when prescribing fluoxetine to patients with impaired liver or kidney function, the elderly (over age 60), children, individuals with known manic-depressive disorder or a history of seizures, people with diabetes, and individuals expressing ideas of committing suicide.

Until an individual understands the effects that fluoxetine may have, he or she should avoid driving, operating dangerous machinery, or participating in hazardous activities. Alcohol should not be used while taking fluoxetine.

Pregnant or breastfeeding

Care should be taken to weigh the risks and benefits of this drug in women who are or wish to become pregnant, as well as those who are breastfeeding. Fluoxetine falls within pregnancy category C, which means that adverse effects on a fetus have been found in

animal studies, but there have been no adequate studies on humans.

Other conditions and allergies

People with diabetes should monitor their blood or urine sugar more carefully, since fluoxetine can affect blood glucose levels.

Side effects

Common side effects include:

- decreased sexual drive
- restlessness
- difficulty sitting still
- skin rash, hives, and itching

Less common side effects include fever and/or chills and pain in joints or muscles.

Rare side effects include:

- pain or enlargement of breasts and/or abnormal milk production in women
- seizures
- fast heart rate
- irregular heartbeat

- red or purple spots on the skin
- low blood sugar and its symptoms (anxiety, chills, cold sweats, confusion, difficulty concentrating, drowsiness, excess hunger, rapid heart rate, headache, shakiness or unsteadiness, severe fatigue)
- low blood sodium and its symptoms (confusion, seizures, drowsiness, dry mouth, severe thirst, decreased energy)
- serotonin syndrome (usually at least three of the following: diarrhea, fever, sweatiness, mood or behavior changes, overactive reflexes, fast heart rate, restlessness, shivering or shaking)
- excitability, agitation, irritability
- pressured talking
- difficulty breathing
- odd body or facial movements

Interactions

Fluoxetine interacts with many other medications. People who may be starting this drug should review the other medications they are taking with their physician and pharmacist for possible interactions. Patients should always inform all of their healthcare providers, including dentists, that they are taking fluoxetine.

Drugs

Individuals should not take monoamine oxidase inhibitors (MAOIs) during fluoxetine therapy. Severe, fatal reactions have occurred when fluoxetine is given along with MAOIs. Individuals who are already taking an MAOI will need to stop taking the drug (according to their healthcare provider's instructions) and will need to wait before starting treatment with fluoxetine. Patients should wait at least five weeks after stopping fluoxetine therapy before taking MAOIs.

When taken with fluoxetine, blood levels of the following drugs may increase, raising the risk of toxicity:

- benzodiazepines
- beta blockers
- carbamazepine
- dextromethorphan
- haloperidol
- atorvastatin
- lovastatin
- simvastatin
- phenytoin
- tricyclic antidepressants

The following drugs may increase the risk of serotonin syndrome:

- dexfenfluramine

- fenfluramine
- tryptophan

Additional interactions include:

- When **buspirone** is taken with fluoxetine, the therapeutic effect of buspirone may be impaired.
- Low blood sodium may occur when fluoxetine is taken along with diuretics.
- Increased risk of mania and high blood pressure occurs when selegiline is taken along with fluoxetine.
- Rarely, fluoxetine may alter heart rhythm when used with fluticasone/salmeterol (Advair Discus). This effect may be serious and potentially life-threatening. Other drugs may also affect heart rhythms, and so all drugs should be discussed with your physician and pharmacist.

Resources

BOOKS

- Facts & Comparisons. *Drug Facts and Comparisons*. Philadelphia: Wolters Kluwer Health's Clinical Solutions, 2013.
- Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland: New Harbinger, 2013.

PERIODICALS

- Hammad, Tarek A., Thomas Laughren, and Judith Racoosin. "Suicidality in Pediatric Patients Treated with Antidepressant Drugs." *Archives of General Psychiatry* 63, no. 3 (2006): 332–39.
- Handley, A. P., M. Williams. "The Efficacy and Tolerability of SSRI/SNRIs in the Treatment of Vasomotor Symptoms in Menopausal Women: A Systematic Review." *Journal of the American Association of Nurse Practitioners* 27, no. 1 (2015): 54–61.
- Hetrick, S. E., et al. "Newer Generation Antidepressants for Depressive Disorders in Children and Adolescents." *Cochrane Database Systematic Reviews* 11, art. no. CD004851 (2012). <http://dx.doi.org/10.1002/14651858.CD004851.pub3> (accessed February 20, 2015).
- Martenyi, Ferenc, and Victoria Soldatenkova. "Fluoxetine in the Acute Treatment and Relapse Prevention of Combat-Related Post-Traumatic Stress Disorder: Analysis of the Veteran Group of a Placebo-Controlled, Randomized Clinical Trial." *European Neuropsychopharmacology* 16, no. 5 (2006): 340–49.
- Mouti, A., et al. "Fluoxetine for Autistic Behaviors (FAB trial): Study Protocol for a Randomized Controlled Trial in Children and Adolescents with Autism." *Trials* 15, no. 1 (2014): 230.
- Mukerjee, Siddhartha. "Post-Prozac Nation: The Science and History of Treating Depression." *New York Times Magazine*, April 19, 2012.
- Riblet, N., et al. "Reevaluating the Role of Antidepressants in Cancer-Related Depression: A Systematic Review and

Meta-Analysis.” *General Hospital Psychiatry*. 36, no. 5 (2014): 466–73.

Tiihonen, Jari, et al. “Antidepressants and the Risk of Suicide, Attempted Suicide, and Overall Mortality in a Nationwide Cohort.” *Archives of General Psychiatry* 63, no. 12 (2006): 1358–67.

WEBSITES

AHFS Consumer Medication Information. “Fluoxetine.” American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a689006.html> (accessed February 20, 2015).

U.S. Food and Drug Administration. “Fluoxetine (Marketed as Prozac) Information.” <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm109352.htm> (accessed February 20, 2015).

ORGANIZATIONS

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.

National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.

National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

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Fluticasone

Definition

Fluticasone is a type of corticosteroid, or synthetic steroid hormone, that is used to help relieve inflammation, usually from allergies or asthma.

Purpose

Fluticasone propionate is the active ingredient that helps reduce swelling in the nose and airways caused by allergies, often called allergic rhinitis. When a person has seasonal allergies, the pollen or other irritants in the air causes the immune system to react, and mucous membranes in the nose become irritated. Fluticasone helps ease the irritation and inflammation, or swelling. By using the nasal spray as directed, many of the symptoms of seasonal allergies can be prevented or



Fluticasone (nasal). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

controlled. The oral inhaled form of fluticasone reduces swelling and irritation in the airways, making it easier for people who have asthma to breathe. When the skin becomes inflamed and itchy, fluticasone oral can be rubbed on the skin to reduce swelling or itching from allergic reactions or skin conditions such as eczema and psoriasis.

Description

Fluticasone nasal spray does not cure allergies, but when sprayed in each nostril as directed, it can help manage allergy symptoms. Fluticasone is used for people who have seasonal allergies that occur at certain times of year, usually in the spring and fall, or by people who have perennial allergic or nonallergic rhinitis. This means they have sneezing and itching in the nose, along with running or stuffiness. Often, it takes a few days to a week for the fluticasone to begin to work effectively at stopping air irritants. Anyone who uses the spray should be sure to use it regularly each day as directed.

In general, the nasal spray comes in a bottle with a straight spray nozzle. After blowing the nose to clear it as well as possible, the bottle should be shaken slightly, and then placed into the nostril. Pressing down on the sides of the pump nozzle releases a light spray into the nostril. This should be repeated in the other nostril. Usually, fluticasone is used twice per day. The pump may need to be primed before the first use or if it has not been used for some time. The package directions provide further information on how to hold the bottle and use the pump.

Fluticasone also comes as an oral inhaler to help relieve wheezing and other symptoms of asthma. After shaking the canister, the patient holds an applicator to their mouth, closing the mouth around the applicator. A measured dose is released into the mouth as the user breathes in slowly and deeply and then holds the breath for about ten seconds. Some patients use an inhalation aerosol, and some an inhaled powder. Some patients use more than one application at a time.

Topical fluticasone is a cream or ointment to spread on an area of skin that is red, itching, and irritated. After cleaning the area, the patient applies the cream or ointment, rubbing it into the affected area until it soaks into the skin.

U.S. brand names

In the United States, fluticasone nasal spray is sold as Flonase. The spray used to be available only with a doctor's prescription, but in July 2014, the U.S. Food and Drug Administration approved purchase of Flonase Allergy Relief over-the-counter for temporary relief of seasonal allergies. The oral inhalant is sold under the brand name Flovent HFA. Topical fluticasone is sold as Cutivate.

Recommended dosage

Nasal sprays of fluticasone generally are measured to dispense a standard dose when users follow packaging directions. The bottles are designed to dispense 120 sprays of 50 micrograms (mcg) each for adults. This makes up a total maximum dose per day of 200 mcg (one spray in each nostril twice a day, or two sprays in each nostril once per day). Once symptoms are reduced, sprays can be cut to one spray in each nostril once per day for a total dose of 100 mcg per day.

Dosage for oral fluticasone in aerosol containers varies depending on whether patients have been treated before with bronchodilators for asthma. Adult dose for inhalation aerosol varies between 88 mcg and 220 mcg twice a day. For the inhaled powder, the dose varies between 100 mcg and 250 mcg twice a day.

Fluticasone cream or ointment can be applied to the skin of adults and children older than 13 years twice daily in a thin layer over the affected area.

Pediatric

Children 4–11 years old can have one spray in each nostril once day for a dose of 100 mcg and up to two sprays in each nostril once daily (200 mcg) if one spray is not easing their allergic rhinitis symptoms. Once symptoms improve, the child's dose should be lowered again to one spray in each nostril once a day. Children

KEY TERMS

Allergic rhinitis—Symptoms affecting the nose of people who have allergies to pollen or pet dander. Often, these symptoms include itching, running, and stuffiness, or congestion.

Bronchodilator—A medicine that relaxes muscles around the airways to make breathing easier for people with asthma and other chronic breathing problems.

Mucous membrane—Moist, thin tissues that line parts of the body, including the nose and mouth.

age 12 years and older can follow adult dosing, depending on the need to control their allergic rhinitis.

Pediatric dosages of oral fluticasone are lower than the adult doses, at no more than 88 mcg twice a day for aerosol fluticasone, and usually about 50 mcg to 100 mcg twice a day for inhaled fluticasone powder.

Children between 3 months and 12 years old who are using topical fluticasone should be evaluated after four weeks of use. The safety of topical fluticasone has not been determined in children for longer than four months.

Precautions

Anyone using fluticasone should be aware of the drugs, vitamins, supplements, or herbal products that might interact with fluticasone propionate. Because the medicine is available over the counter, it is up to patients to inform their doctors or pharmacists about use of fluticasone and other over-the-counter medicines or supplements, and to be aware of possible interactions. Some people are allergic to fluticasone, and should let their doctor know about any drug allergies.

Corticosteroids can affect one's ability to resist infections, so it is important to be especially cautious while using fluticasone nasal spray and aerosol inhalers. Washing hands often and avoiding people who might have viruses such as measles or chickenpox is recommended for anyone who has not had the diseases or **vaccinations**.

Fluticasone works best when used regularly. Missing a dose might cause a brief return of symptoms, but if a person realizes that a dose of spray or inhaled aerosol was missed, it is best to wait until it is time for the next dose. It is not recommended to double a dose or exceed daily maximum number of sprays.

Topical fluticasone is for external use only, and the cream or ointment should not be used on a person's face, armpits, or groin area. It should only be used for the skin conditions indicated by the doctor when prescribed, only in the area affected, and only until the condition improves. People who have open sores or wounds should avoid putting fluticasone on those areas. It is also advised to avoid having vaccinations while using fluticasone cream or ointment.

Pediatric

Studies have shown that corticosteroid nasal sprays can work better than antihistamines in controlling nasal congestion for children with allergic rhinitis. Fluticasone nasal spray is usually not recommended in children younger than age two. Parents of children two to four years old should consult a physician about the use of Flonase for their child. Because fluticasone is a corticosteroid, parents should discuss possible side effects, particularly on growth rate, with their child's physician. Studies have shown a slight decrease in the growth rate of children who received Flonase nasal spray, but the effects were not significant enough to justify warnings against use of the drug in children. Parents should only place a small amount of topical fluticasone in a baby's diaper area and should only use it for diaper rash if directed to do so by a doctor.

Pregnant or breastfeeding

Use of fluticasone by pregnant women is recommended only when the benefits of the drug's use outweigh the risks. Some corticosteroids are excreted in breast milk, but there are no studies showing that fluticasone appears in breast milk. Still, it is best not to use the drug while breastfeeding without discussing possible risks with a physician.

Other conditions and allergies

People who have had or currently have tuberculosis, cataracts, or glaucoma should talk to their doctors before using fluticasone. Anyone who has sores in the nose or eye or who recently injured their nose or had surgery in the nose may need to delay use of Flonase and should first consult a doctor. It also is important to inform a doctor of any infections or planned surgery, including dental surgery, when on fluticasone.

Side effects

Fluticasone nasal spray can cause several side effects, including:

- nosebleeds or irritation in the nose
- headache
- nausea and vomiting

- coughing
- dizziness
- shortness of breath

Serious side effects may include flu-like symptoms, muscle weakness, and an enlarged face and neck. Anyone using fluticasone nasal spray who has serious or unusual symptoms should stop its use and report the symptoms to a doctor right away.

Fluticasone in aerosol inhaler form may cause:

- headache
- sore throat
- sore, white patches in the throat or mouth
- runny or stuffy nose
- problems speaking or swallowing
- earache

Serious side effects may include new or increased acne, easy bruising, and an enlarged face or neck. Anyone using fluticasone oral aerosol who has serious or unusual symptoms should stop its use and report the symptoms to a doctor right away.

Side effects of fluticasone cream or ointment may include:

- dry skin
- skin breakdown
- hives or welts
- irritated, red, or burning skin
- itching and rash
- numb fingers

Interactions

A number of drugs and supplements have interactions with fluticasone. It is important to read package literature and discuss concerns about interactions with a doctor or pharmacist. Patients should inform their doctors or pharmacists of any other steroids they are using orally, or through their noses or on their skin.

Drugs

Use of fluticasone nasal or oral aerosol sprays along with several antiviral medicines used to treat HIV/AIDS, such as ritonavir and tenofovir, can increase how much fluticasone propionate is absorbed into the bloodstream, which causes more severe side effects from fluticasone. About 30 other medicines cause less serious, but moderate interactions. Among these are several antibiotics, such as **amoxicillin** and **clarithromycin**. The topical form of the drug has about 50 medicines with which it has minor interactions. It is important to discuss

all other medications with a doctor before using fluticasone in any form.

Food and other substances

Grapefruit juice may affect use of fluticasone, and patients taking the drug should inform their doctor or pharmacist if they are drinking or eating grapefruit juice.

Resources

PERIODICALS

Barr, James G., et al. "Allergic Rhinitis in Children." *British Medical Journal* 249 (July 1, 2014). <http://dx.doi.org/10.1136/bmj.g4153> (accessed February 20, 2015).

OTHER

U.S. Food and Drug Administration. *Allergy Relief for Your Child*. September 2013. <http://www.fda.gov/downloads/forconsumers/consumerupdates/ucm273729.pdf> (accessed February 20, 2015).

WEBSITES

"Fluticasone HFA Aerosol Inhaler." Drugs.com. <http://www.drugs.com/cdi/fluticasone-hfa-aerosol-inhaler.html> (accessed January 5, 2015).

"Fluticasone Topical." Drugs.com. <http://www.drugs.com/cdi/fluticasone-cream.html> (accessed January 5, 2015).

GSK. "FDA Approves Flonase Allergy Relief for Sale Over-the-Counter in the United States," July 24, 2014. <http://us.gsk.com/en-us/media/press-releases/2014/fda-approves-flonase-allergy-relief-for-sale-over-the-counter-in-the-united-states/> (accessed February 20, 2015).

MedlinePlus. "Flonase Nasal Spray." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a695002.html> (accessed January 5, 2015).

MedlinePlus. "Fluticasone Oral Inhalation." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601056.html> (accessed January 5, 2015).

ORGANIZATIONS

American Academy of Allergy, Asthma & Immunology, 555 East Wells Street, Suite 1100, Milwaukee, WI 53202, (414) 272-6071, <http://www.aaaai.org>.

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chronic breathing problems. Fluticasone is a corticosteroid, or synthetic steroid. Salmeterol is a long-acting beta-agonist, a drug that helps relax the airways.

Purpose

People who have severe asthma and chronic obstructive pulmonary disease (COPD) have problems breathing and symptoms related to tightening of the airways, or bronchi. These symptoms can include wheezing, coughing, and shortness of breath, in addition to a tight feeling in the chest that makes deep breathing difficult. Fluticasone propionate helps to ease the inflammation or swelling around the airways to make breathing easier, and salmeterol increases the effect by relaxing and opening air passages. The combined drug is designed to help prevent severe asthma attacks and exacerbations, or flare-ups, of COPD.

Description

The combination of fluticasone and salmeterol is sold in the United States as Advair. Advair comes in a canister that can be used as a fast-acting inhaler with metered doses for people who have asthma or as a medication that should be taken regularly twice a day to slowly improve breathing for people who have COPD. The prescribed medication comes in several forms such as an aerosol liquid or powder, or in a disk, depending on the patient's age and whether the drug is used for asthma or COPD.



Advair Diskus (fluticasone propionate/salmeterol).

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Fluticasone/salmeterol

Definition

Fluticasone propionate and salmeterol is a combination of drugs used to prevent severe asthma attacks and

People who have asthma often can control the symptoms with maintenance medications, including bronchodilators that contain only drugs such as **albuterol** or fluticasone. Some people have more severe asthma or occasional attacks that are more severe. Combined fluticasone and salmeterol (Advair) is available for these patients only and when other asthma medications do not work. Patients with asthma may only use Advair until their asthma is in better control. Once it is, they should return to use of a low-dose or medium-dose corticosteroid inhaler or the methods they typically use to control their asthma.

COPD is a chronic respiratory disease that is usually progressive, or gets worse over time. People who have COPD often have emphysema and chronic bronchitis and have obstructed airways. Combined fluticasone and salmeterol may be used as maintenance therapy in these patients, or over longer periods as a regular treatment.

U.S. brand names

In the United States, combined fluticasone propionate and salmeterol is sold under the trade name Advair. The following products are available only with a doctor's prescription:

- Advair HFA, an inhaler for use in asthma for patients 12 and older
- Advair Diskus, a prescription medicine for asthma treatment in children age four and older and adults
- Advair Diskus 250/50, which is used for adults who have COPD

Canadian brand names

In Canada, fluticasone propionate and salmeterol are sold as Advair Inhalation Aerosol.

Recommended dosage

Advair HFA inhalers come in 45, 115, and 230 microgram (mcg) forms. In each case, the larger number refers to the amount of fluticasone propionate. Each form has 21 mcg of salmeterol. The metered dose is delivered by the mouthpiece each time a patient inhales. The dose is chosen by the prescribing physician based on the severity of a patient's asthma. Patients should use Advair exactly as prescribed.

Advair Diskus is dosed by inhaling the fluticasone and salmeterol orally. It comes in strengths of 100, 250, and 500 mcg of fluticasone, each with 50 mcg of salmeterol. Adults and teens who are 12 years or older should inhale the metered drug through their mouths for one inhalation twice a day. They should take the drug 12 hours apart, so doses are usually inhaled once in the

KEY TERMS

Asthma—A lung condition, usually of allergic origin, in which the airways become narrow due to smooth muscle contraction, causing wheezing, coughing, and shortness of breath.

Bronchodilator—A drug that relaxes bronchial muscles, resulting in expansion of the bronchial air passages that lead to and from the lungs.

Chronic obstructive pulmonary disease (COPD)—A term used to describe chronic lung diseases, such as chronic bronchitis, emphysema, and asthma.

morning and once in the evening. The recommended starting dose is based on asthma severity, and the maximum dosage per day is 500 mcg of fluticasone and 50 mcg of salmeterol.

The dosage for Advair Diskus 250/50 to maintain COPD is one inhalation of the powder twice a day 12 hours apart. It is important to keep the doses and intervals between them as regular as possible and not to exceed the maximum daily dose of two inhalations, even if COPD symptoms do not improve. It may take a few weeks for symptoms to begin improving.

Pediatric

Children 4–11 years old receive only one dose of 100 mcg fluticasone/50 mcg salmeterol twice a day.

Precautions

Advair is not intended for quick relief of asthma attacks. Using only salmeterol for asthma is not recommended. Clinical studies showed that patients with asthma who used salmeterol had more severe asthma episodes that required hospital treatment or caused death. Studies have not shown whether use of salmeterol has increased risk of death in patients with COPD. Anyone who used Advair and has breathing problems that get worse after a dose of the medication should seek emergency medical treatment. All patients considering use of fluticasone and salmeterol should discuss potential risks of the drug with their doctors before beginning the medication.

It is important that patients using fluticasone and salmeterol review medication guides that accompany the drug before first use and discuss any questions with a pharmacist or physician. Patients who use Advair again or continue using it for maintenance of COPD should

review the medication guides regularly to check for new or changing warnings and other information.

Pediatric

Children and teens who use fluticasone and salmeterol may have increased risk of hospitalization from asthma attacks, and anyone taking Advair should also have a rescue inhaler with them. No studies have been done to establish a reason to limit use of Advair Diskus in children older than four years. There are no studies establishing safety or effectiveness of fluticasone and salmeterol in children younger than four years old.

Fluticasone and salmeterol can cause slowed growth in children. Parents should discuss these risks with their child's doctor.

Geriatric

Older people who have problems with their heart and blood vessels should use special caution with fluticasone and salmeterol and be sure to discuss potential health risks of the medication with a healthcare provider before beginning its use. There is some increased risk of glaucoma, cataracts, and osteoporosis with use of fluticasone and salmeterol.

Pregnant or breastfeeding

Fluticasone and salmeterol are pregnancy category C. There have been adverse effects on an unborn fetus when the drug is given at high doses in animal studies. There are no studies on the drug's effect in human pregnancies, so women who are pregnant should only use Advair if the benefits outweigh the risks. The drug's maker recommends that nursing mothers discontinue the drug's use while breastfeeding unless doing so poses too much risk to the mother.

Other conditions and allergies

People who have severe hypersensitivity to milk proteins should not take fluticasone and salmeterol. Anyone who has seizures, irregular heartbeat, osteoporosis, high blood pressure, diabetes, glaucoma, liver disease, heart disease, or problems with their immune system should discuss these conditions with their doctor. A patient undergoing surgery, including dental surgery, should inform the doctor or dentist about use of Advair before undergoing the procedure.

Side effects

The most serious side effect of fluticasone and salmeterol is worsened asthma symptoms, such as coughing, chest tightness, and wheezing following use of the inhaled drug. These symptoms, along with hives, a

rash, swelling, or choking, are signs that a person needs immediate medical help. Other possible side effects include:

- runny nose and sneezing
- blurred vision or blindness
- chills
- headache and eye or sinus pain
- difficulty breathing
- sore or irritated throat and difficulty swallowing
- sweating
- uncontrollable shaking
- rapid heartbeat

Other side effects have been reported, and any unusual symptoms that begin after starting the drug should be reported to a doctor.

Interactions

Before beginning use of Advair, patients should reveal all other medications, herbal formulas, and supplements they take so that doctors and pharmacists can check for possible interactions.

Drugs

More than 50 drugs are known to have major interactions with fluticasone and salmeterol. Among these are several antifungal medicines used to treat fungal infections, beta blockers used to treat high blood pressure and other conditions, antibiotics to treat infections, and oral contraceptives (birth control pills). Anyone taking Advair should be sure the doctor prescribing the drug and the pharmacist filling the prescription have a complete list of all other prescription and over-the-counter medicines being used.

Food and other substances

People drinking grapefruit juice or eating grapefruit should talk to their doctors about eating the fruit while using fluticasone and salmeterol.

Resources

PERIODICALS

DiSantostefano, Rachael L., et al. "Patient Comprehension of Medication Guides for Asthma and Chronic Obstructive Pulmonary Disease Medications." *Therapeutic Innovation & Regulatory Science* 48, no. 5 (2014): 574–82.

WEBSITES

"Fluticasone/Salmeterol Inhaler." Drugs.com. <http://www.drugs.com/cdi/fluticasone-salmeterol-inhaler.html> (accessed January 5, 2015).

GlaxoSmithKline. "Advair." Advair.com. <http://www.advair.com/> (accessed January 5, 2015).

MedlinePlus. "Fluticasone and Salmeterol Inhalation." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699063.html> (accessed January 5, 2015).

U.S. National Library of Medicine. "Fluticasone/Salmeterol (By Breathing)." PubMed Health. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0010369/> (accessed February 20, 2015).

ORGANIZATIONS

American Academy of Allergy, Asthma & Immunology, 555 East Wells Street, Suite 1100, Milwaukee, WI 53202-3823, (414) 272-6071, <http://www.aaaai.org/home.aspx>.

American Lung Association, 55 W. Wacker Drive, Suite 1150, Chicago, IL (202) 452-1805, (800) 586-4872, <http://www.lung.org/>.

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Fluvoxamine

Definition

Fluvoxamine is an antidepressant of the type known as selective serotonin reuptake inhibitors (SSRI).



Fluvoxamine, 100 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Fluvoxamine is used to treat obsessive-compulsive disorder (OCD). It was the first SSRI to be approved by the U.S. Food and Drug Administration (FDA) for treating OCD in children, adolescents, and adults.

Off-label use

Fluvoxamine may also be prescribed off-label for treating depression, but it is not approved by the FDA for this purpose.

Description

Serotonin is a brain chemical that carries nerve impulses from one nerve cell to another. Researchers think that depression and certain other mental disorders may be caused, in part, by there not being enough serotonin released and transmitted in the brain. Like the other SSRI antidepressants **fluoxetine** (Prozac), **sertraline** (Zoloft), and paroxetine (Paxil), fluvoxamine increases the level of serotonin (also known as 5-HT) in the brain. Increased serotonin levels may be beneficial in patients with OCD, alcoholism, certain types of headaches, post-traumatic stress disorder (PTSD), premenstrual tension and mood swings, and panic disorder.

Fluvoxamine is available in 25, 50, and 100 milligram (mg) tablets.

U.S. brand names

Fluvoxamine is marketed in the United States under the brand name Luvox.

Origins

Fluvoxamine was approved for use in adults in 1993. In 1997, the FDA approved this medication for the treatment of OCD in children and adolescents.

Recommended dosage

Fluvoxamine therapy in adults is started as a single 50 mg dose taken at bedtime. Based on the patient's response to the medication, the dosage can be increased by 50 mg every four to seven days until maximum benefit is achieved. The maximum dosage is 300 mg per day. Dosages over 100 mg per day should be divided into two equal doses, with one taken in the morning and the other in the afternoon.

Pediatric

Fluvoxamine therapy in children is started as a single 25 mg dose, initially taken at bedtime. Based on the patient's response to the medication, the dosage can be

KEY TERMS

Depression—A mental state characterized by excessive sadness and loss of interest in life; other symptoms may include altered sleep or eating patterns, loss of concentration, agitation, lack of energy, and, in severe cases, attempts at self-harm or suicide.

Obsessive-compulsive disorder—A disorder in which affected individuals have an obsession (such as a fear of contamination, or thoughts they do not like to have and cannot control) and feel compelled to perform certain acts to neutralize the obsession (such as repeated hand washing).

Off-label—The use of a prescription medication to treat conditions outside the indications approved by the Food and Drug Administration (FDA). It is legal for physicians to administer these drugs, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Selective serotonin reuptake inhibitors (SSRIs)—A class of antidepressants that works by blocking the reabsorption of serotonin in brain cells, raising the level of the chemical in the brain.

Serotonin—A brain chemical that carries nerve impulses from one nerve cell to another.

Serotonin syndrome—A condition that results from the combination of SSRI drugs such as fluvoxamine and members of another class of antidepressants known as monoamine oxidase inhibitors (MAOIs).

increased by 25 mg every four to seven days until maximum benefit is achieved. Maximum dosage in children is 200 mg per day. Dosages over 100 mg per day should be given as equally divided morning and afternoon doses.

Precautions

Patients taking fluvoxamine should be monitored closely for the onset of mania, seizures, thoughts of suicide, and skin problems (including itching, hives, and rashes).

A group of serious side effects, called serotonin syndrome, has resulted from the combination of SSRI drugs such as fluvoxamine and members of another class of antidepressants known as monoamine oxidase inhibitors (MAOIs). Serotonin syndrome usually consists of at least three of the following symptoms:

- diarrhea

- fever
- extreme perspiration
- mood or behavior changes
- overactive reflexes
- fast heart rate
- restlessness
- shivering or shaking

Like other selective serotonin reuptake inhibitors, fluvoxamine carries a warning regarding use in children and young people up to 24 years of age, who may be at risk for increased suicidal thoughts and actions during treatment, especially during the first few months. Persons with a personal history or family history of bipolar disorder or who have previously attempted or considered suicide are also at increased risk.

Fluvoxamine treatment should not be abruptly discontinued. Until patients understand the effects that fluvoxamine may have on them, they should avoid driving, operating dangerous machinery, or participating in hazardous activities.

Pregnant or breastfeeding

Physicians and their patients should weigh the risks and benefits of this drug for women who are or wish to become pregnant, as well as for women who are breastfeeding.

Other conditions and allergies

People with impaired liver function, bipolar disorder (manic depression), a history of seizures, or suicidal thoughts or tendencies should take fluvoxamine only under close physician supervision.

Side effects

Common side effects of fluvoxamine therapy include decreased sex drive and diminished sexual performance.

Less common side effects of fluvoxamine therapy are changes in mood, behavior, or thinking; difficulty breathing; difficulty urinating; and twitches or uncontrollable movements of the face or body.

Rare side effects include:

- difficulty moving
- blurred vision
- clumsiness or problems with balance
- seizures
- difficulty moving the eyes
- increased uncontrollable movements of the body or face

- changes in the menstrual period
- redness or irritation of the eyes or skin
- peeling, itching, or burning sensation of the skin
- sore throat
- fever, and/or chills
- easy bruising
- nosebleeds
- in women, abnormal milk production

People may also experience symptoms of serotonin syndrome, which usually consists of at least three of the following:

- restlessness
- overexcitement
- irritability
- confusion
- diarrhea
- fever
- overactive reflexes
- difficulty with coordination
- uncontrollable shivering or shaking
- trembling or twitching

Interactions

Fluvoxamine interacts with a long list of other medications. Individuals who are starting this drug should review the other medications they are taking with their physician and pharmacist for possible interactions. Patients should always inform all their healthcare providers, including dentists, that they are taking fluvoxamine.

Drugs

Because of the risk of serotonin syndrome, fluvoxamine should never be taken in combination with monoamine oxidase inhibitors. People taking any MAOI—for example, phenelzine sulfate (Nardil) or tranylcypromine sulfate (Parnate)—should stop the MAOI inhibitor and wait at least 14 days before starting fluvoxamine or any other antidepressant. The same holds true when discontinuing fluvoxamine before starting an MAOI. The diet pills dexfenfluramine and fenfluramine also may increase the incidence of serotonin syndrome when taken with fluvoxamine.

When taken together with fluvoxamine, the effects of the following drugs may be enhanced:

- benzodiazepines
- beta blockers
- clozapine
- the antiseizure drugs **phenytoin** and **carbamazepine**
- tricyclic antidepressants
- pimozide
- cholesterol-lowering drugs such as **atorvastatin**, **lovastatin**, and **simvastatin**

Other interactions include:

- When **bupirone** is given with fluvoxamine, the therapeutic effect of bupirone may be decreased and the risk of seizures increased.
- Increased risk of mania and high blood pressure occurs with selegiline.
- Fluvoxamine given with **warfarin** (a blood thinner) may increase the possibility of bleeding.

Food and other substances

Individuals should not use alcohol while taking fluvoxamine.

Resources

BOOKS

Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger, 2013.

PERIODICALS

van Balkom, A. J., et al. "Cognitive Therapy versus Fluvoxamine as a Second-Step Treatment in Obsessive-Compulsive Disorder Nonresponsive to First-Step Behavior Therapy." *Psychotherapy and Psychosomatics* 81, no. 6 (2012): 366–74.

OTHER

U.S. Food and Drug Administration. "FDA-Approved Medication Guide (Fluvoxamine)." <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM249169.pdf> (accessed February 24, 2015).

U.S. Food and Drug Administration. "Highlights of Prescribing Information (Fluvoxamine Maleate)." http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021519Orig1s0081bl.pdf (accessed February 24, 2015).

U.S. Food and Drug Administration. "Highlights of Prescribing Information (Luvox CR)." http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022033s0101bl.pdf (accessed February 24, 2015).

WEBSITES

AHFS Consumer Medication Information. "Fluvoxamine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a695004.html> (accessed February 24, 2015).

National Alliance on Mental Illness. "Luvox® (Fluvoxamine)." http://www2.nami.org/Template.cfm?Section=About_Medications&Template=/TaggedPage/TaggedPageDisplay.cfm&TPLID=51&ContentID=20819 (accessed February 24, 2015).

U.S. Food and Drug Administration. "Antidepressant Use in Children, Adolescents, and Adults." <http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm096273.htm> (accessed February 24, 2015).

U.S. Food and Drug Administration. "Fluvoxamine Maleate Information." <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a695004.html> (accessed February 24, 2015).

ORGANIZATIONS

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.

National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.

National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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REVIEWED BY JAMES E. WAUN, MD, RPH

Focalin see **Dexmethylphenidate**

Formoterol/budesonide see **Budesonide/formoterol**

Fosamax see **Alendronate**

Fosinopril

Definition

Fosinopril sodium is a blood pressure medication (an antihypertensive) that belongs to the class of angiotensin-converting enzyme (ACE) inhibitors. It may be given alone or in a fixed combination with **hydrochlorothiazide** (HCT), a diuretic.

Purpose

Fosinopril is used to treat:

- hypertension (high blood pressure) in adults and in children over the age of six years
- congestive heart failure (CHF) in adults
- diabetic nephropathy in hypertensive patients with type 2 diabetes



Fosinopril, 20 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

- Alport syndrome, a rare genetic disorder characterized by scarring of kidney tissue and eventual kidney failure

Fosinopril in fixed combination with hydrochlorothiazide is used to treat patients with hypertension whose blood pressure is not adequately controlled by either an ACE inhibitor or a diuretic used alone (monotherapy).

Fosinopril works by inhibiting the action of the angiotensin-converting enzyme (ACE), an enzyme that converts angiotensin I (a peptide hormone) into angiotensin II, another form of the hormone that causes blood vessels to constrict, thus raising blood pressure. Fosinopril binds to ACE, preventing the enzyme from forming angiotensin II. This inhibition of ACE allows the patient's blood vessels to relax, lowering blood pressure, reducing the workload of the heart, and allowing more blood and oxygen to flow to the heart. It also reduces hypertension in patients with diabetic nephropathy. Fosinopril does not cure CHF or high blood pressure, but it can lower the risk of heart attack and stroke; slow the progress of diabetic nephropathy; and relieve such symptoms of CHF as difficulty breathing, fatigue, and swelling.

Fosinopril is different from other ACE inhibitors, such as **lisinopril** and **captopril**, in that it can be eliminated from the body via metabolic pathways in the liver as well as by pathways in the renal system. This makes fosinopril a safer choice in treating patients with some loss of kidney function, as the drug is less likely to accumulate in the body.

Off-label uses

Fosinopril is used off label to treat kidney problems in patients with scleroderma, a skin disorder that affects the kidneys and other internal organs in its diffuse form.

Description

Fosinopril sodium is a whitish to off-white crystalline powder available in tablet form for oral administration. Fosinopril and fosinopril HCT are dispensed only as tablets. These medications should be stored away from moisture, heat, and light at temperatures between 68°F and 77°F (20°C and 25°C). They should not be stored in the bathroom and should be kept away from children and pets.

U.S. brand names

Fosinopril is sold by Bristol-Myers Squibb under the brand name Monopril. It is sold under the brand name Monopril HCT in its fixed combination form.

Origins

Fosinopril was approved by the FDA in 1991 as a new molecular entity (NME).

Recommended dosage

Fosinopril is dispensed as 10 milligram (mg), 20 mg, or 40 mg tablets. Fosinopril HCT is dispensed as either 10/12.5 mg or 20/12.5 mg tablets.

Patients are advised to take these drugs with a glass of water at the same time each day, with or without meals as they prefer. However, taking the daily dose on an empty stomach an hour before a meal allows more efficient absorption of the drug.

A missed dose should be taken as soon as it is remembered, unless it is almost time for the next dose. Patients should never take a double dose of fosinopril to make up for a missed dose.

Fosinopril dosage for various conditions is as follows:

- Hypertension in adults: The initial dose is 10 mg once daily; the dosage may be increased or decreased according to the drug's effectiveness in controlling blood pressure and the number or severity of side effects.
- Congestive heart failure: The initial dose is 10 mg once daily, with the dose adjusted according to the drug's effectiveness in relieving symptoms and the number and severity of side effects. The maximum recommended dosage is 40 mg per day.

- Diabetic nephropathy: The initial and most common dose is 10 mg once daily.

Fosinopril HCT dosage is as follows:

- Hypertension in adults: The initial dose is 10/12.5 mg once per day. The maximum recommended dosage is 80/50 mg per day.

Pediatric

The recommended dose of fosinopril for children weighing more than 110 pounds (50 kg) is 5–10 mg once per day. A recommended dosage is not available for children weighing less than 110 pounds; however, dosages between 0.1 and 0.6 mg per kg have been found to be effective in children.

The safety and effectiveness of fosinopril HCT in children have not been established.

Precautions

Patients should not take antacids containing aluminum, magnesium, or simethicone within two hours before or two hours after taking fosinopril.

As with all prescription medications, patients prescribed fosinopril or fosinopril HCT for any of its uses should inform their physicians of any other medications they are taking, including over-the-counter medications, nutritional supplements, and herbal preparations as well as other prescription drugs. They should also inform their healthcare providers of any known allergies to foods, preservatives, or dyes.

Pediatric

There are no data related to the safety and efficacy of fosinopril in children younger than 5 years.

Geriatric

Elderly patients with heart or kidney problems may require some adjustment in dosage.

Pregnant or breastfeeding

Fosinopril and fosinopril HCT carry the FDA pregnancy category C during the first trimester of pregnancy and category D during the second and third trimesters. Category C means that the drug has been shown to harm the fetus in animal studies, but that no data from human studies are available. Category D means that there is positive evidence of harm to the fetus based on data from drug trials and marketing studies. In spite of the risks, drugs in both category C and category D may be prescribed for a pregnant

KEY TERMS

Alport syndrome—A genetic disorder characterized by scarring of kidney tissue and eventual end-stage renal disease.

Angioedema—A condition marked by the sudden and rapid swelling of subcutaneous tissues and mucous membranes, often as an allergic reaction to some foods or drugs, including ACE inhibitors.

Angiotensin-converting enzyme (ACE)—An enzyme that converts a hormone known as angiotensin I into another form known as angiotensin II, which constricts blood vessels and contributes to high blood pressure.

Antihypertensive—Any medication given to control high blood pressure.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Congestive heart failure (CHF)—A condition in which the heart cannot pump enough blood to supply the body's tissues with sufficient oxygen and nutrients; back up of blood in vessels and the lungs causes buildup of fluid (congestion) in the tissues.

Diabetic nephropathy—A progressive kidney disease that develops as a complication of diabetes, in which the capillaries supplying the filtering units (glomeruli) of the kidneys lose their ability to filter body fluid. Hypertension is an early symptom of diabetic nephropathy.

Diuretic—Any drug given to increase the body's output of urine.

Hydrochlorothiazide (HCT)—A diuretic drug that acts by inhibiting the kidneys' ability to retain water. It is often given together in fixed combinations with fosinopril and other ACE inhibitors.

Hypertension—High blood pressure.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Scleroderma—A chronic, systemic autoimmune disorder in which the patient's skin thickens and hardens. The diffuse form of scleroderma also affects the internal organs, most often the kidneys, esophagus, and lungs.

woman if the physician determines that the potential benefits outweigh the risks.

Women who are pregnant or intend to become pregnant should tell their physicians before taking fosinopril or fosinopril HCT. The FDA recommends that women taking fosinopril should discontinue the drug if they are or become pregnant, as ACE inhibitors can cause low blood pressure in the mother, severe kidney failure, excess potassium, and even death of the newborn.

Fosinopril and fosinopril HCT should not be used by women who are breastfeeding, as the drugs pass into breast milk.

Other conditions and allergies

Patients with any of the following conditions must notify their doctor before taking fosinopril:

- A history of angioedema, an allergic reaction to food or drugs characterized by the sudden and rapid swelling of subcutaneous tissues and mucous membranes. This is

considered a medical emergency, as airway obstruction can occur, and can be triggered by fosinopril or other ACE inhibitors.

- A history of dehydration, heart failure, severe diarrhea, low blood sodium levels, or kidney disease. These conditions may cause blood pressure to drop too low when taking fosinopril.
- A history of liver disease.
- A known allergy to ACE inhibitors.
- A history of stroke, recent heart attack, or kidney transplant.
- The diagnosis of an autoimmune disease like lupus, rheumatoid arthritis, or scleroderma.

In addition, patients should alert their healthcare provider if they are receiving treatments to lower sensitivity to wasp or bee stings, receiving kidney dialysis, scheduled for surgery or any procedure requiring anesthesia, or presently taking any other medication for hypertension.

Side effects

Fosinopril and fosinopril HCT are generally well tolerated, but may cause the following common side effects in patients with hypertension:

- coughing
- dizziness
- nausea/vomiting

The following side effects are common in patients with CHF:

- dizziness
- coughing
- low blood pressure
- muscle pain
- nausea/vomiting
- chest pain unrelated to the heart
- upper respiratory infections

Less common side effects include:

- low blood potassium levels
- postural hypotension (a sudden drop in blood pressure when rising from a sitting or lying-down position to standing)
- weakness
- diarrhea
- headache
- unusual tiredness
- urinary frequency (in men only)

Side effects that are rarely reported include decreased sex drive, mild weight gain, and dry eyes.

The following side effects should be reported to a doctor immediately:

- sudden swelling of the face, arms, legs, eyes, lips, or tongue, or problems with swallowing or breathing (symptoms of angioedema)
- sudden and severe stomach pain (may indicate a condition called intestinal angioedema)
- light-headedness severe enough to cause fainting
- chills, fever, or other signs of infection (may indicate a drop in the number of white blood cells)
- yellow discoloration of the skin or the whites of the eyes, dark urine, and pale stools (symptoms of jaundice and may indicate liver damage)
- muscle pains or cramps, one-sided weakness, or shortness of breath
- confusion, memory problems, depression, or other changes in mood or mental status
- changes in vision

- sped-up, slowed-down, or irregular heartbeat
- unusual sweating

Other conditions and allergies

Fosinopril is reported to be less effective in African Americans than in members of other racial or ethnic groups. The reason for this difference is not yet known.

Interactions

Fosinopril is known to interact with various drugs, supplements, and foods.

Drugs

Fosinopril and fosinopril HCT are known to interact with the following drugs:

- Diuretics given separately (**furosemide**, other thiazide diuretics) may increase the risk of low blood pressure.
- Everolimus and sirolimus (immunosuppressant drugs) increase the risk of angioedema.
- Potassium-sparing diuretics (**spironolactone**, triamterene), potassium supplements, and trimethoprim increase the risk of overly high blood potassium levels.
- Insulin, as well as **glipizide**, **metformin**, and other oral diabetes medications, may increase the risk of low blood sugar.
- Injectable gold (sodium aurothiomalate) given to treat rheumatoid arthritis may increase the risk of nausea, vomiting, flushing, and low blood pressure.
- Aliskiren (Tekturna) is an antihypertensive drug that belongs to the class of renin inhibitors, drugs that interfere with the formation of angiotensin II at an earlier stage (the formation of angiotensin I from a precursor called angiotensinogen).
- Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, and **celecoxib** may decrease the effectiveness of fosinopril and may increase the risk of kidney problems.
- The side effects of lithium may be increased by fosinopril.

Herbs and supplements

Fosinopril is reported to interact with bitter melon (lowers blood potassium levels). Agrimony and reishi mushrooms increase the effects of fosinopril.

Food and other substances

Alcohol may increase such side effects of fosinopril as light-headedness or fainting.

Patients should also avoid salt substitutes containing potassium, as they may interact with fosinopril to increase the levels of potassium in the blood.

Resources

BOOKS

- Opie, Lionel H., and Bernard J. Gesh. *Drugs for the Heart*. 8th ed. Philadelphia: Elsevier/Saunders, 2013.
- Ramrakha, Punit, and Jonathan Hill. *Oxford Handbook of Cardiology*. 2nd ed. New York: Oxford University Press, 2012.
- Sheps, Sheldon. *Mayo Clinic: 5 Steps to Controlling High Blood Pressure: Your Personal Guide to Preventing and Managing Hypertension*. 2nd ed. Rochester, MN: Mayo Clinic, 2015.

PERIODICALS

- Chitnis, A. S., et al. "Comparative Effectiveness of Different Angiotensin-Converting Enzyme Inhibitors on the Risk of Hospitalization in Patients with Heart Failure." *Journal of Comparative Effectiveness Research* 1 (2012): 195–206.
- Meyers, R. S., and A. Siu. "Pharmacotherapy Review of Chronic Pediatric Hypertension." *Clinical Therapeutics* 33 (2011): 1331–56.
- "Towards Better Patient Care: Drugs to Avoid in 2014." *Prescribe International* 23 (2014): 161–65.

WEBSITES

- American College of Cardiology. "Fosinopril." CardioSmart.org. <https://www.cardiosmart.org/Healthwise/d002/42/d00242> (accessed February 11, 2015).
- American Heart Association. "Types of Blood Pressure Medications: ACE Inhibitors." Heart.org. http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/PreventionTreatmentofHighBloodPressure/Types-of-Blood-Pressure-Medications_UCM_303247_Article.jsp (accessed February 9, 2015).
- Medscape Reference. "Fosinopril/Hydrochlorothiazide (Rx): Dosage and Uses." <http://reference.medscape.com/drug/fosinopril-hydrochlorothiazide-342334#0> (accessed February 9, 2015).
- Micromedex. "Fosinopril (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/fosinopril-oral-route/description/drg-20069186> (accessed February 9, 2015).

ORGANIZATIONS

- American College of Cardiology (ACC), Heart House, 2400 N Street NW, Washington, DC 20037, (202) 375-6000, ext. 5603, Fax: (202) 375-7000, (800) 253-4636, ext. 5603, resource@acc.org, <http://www.cardiosource.org/>.
- American Heart Association (AHA), 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.
- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Fulvicin see **Griseofulvin**

Furosemide

Definition

Furosemide (pronounced fur-OH-seh-mide) is a diuretic medication ("water pill") classified as a cardiovascular agent to manage congestive heart failure and edema (fluid retention) in humans and some other mammals. Furosemide is classified as a loop diuretic because its mechanism of action affects the loop of Henle in the nephrons of the kidneys. Furosemide acts to inhibit the reabsorption of sodium and chloride in this portion of the nephron during the process of urine formation. It is considered a short-acting diuretic because it begins to act within an hour and reaches peak effectiveness within two hours; its effect lasts about six to eight hours.

Purpose

Furosemide is used to manage the following conditions in adults:

- congestive heart failure (CHF)
- ascites
- edema (fluid retention) associated with cirrhosis of the liver and kidney disease
- hypertension resistant to other treatments



Lasix (furosemide), 80 mg. (© Cengage Learning®.)

- acute pulmonary edema/hypertensive crisis
- elevated levels of potassium (hyperkalemia) or magnesium (hypermagnesemia) in the blood
- increased intracranial pressure

It is recommended for the treatment of hypertension in patients who do not respond to thiazide diuretics, and in patients with impaired kidney function who should not take thiazide diuretics. In children, furosemide is used to treat edema and resistant hypertension.

Description

Furosemide is available for oral administration in two forms, tablets and liquid. Furosemide tablets are white and round or oval in shape, and available in 20, 40, and 80 milligram (mg) strengths. Furosemide liquid solution is available only as a generic rather than a brand-name formulation. The 10 mg per milliliter (mL) solution of the drug is flavored orange, and the 40 mg/5 mL solution is flavored pineapple/peach.

Furosemide is also available as an injection in a 10 gram (g) per mL syringe. The injectable form is administered intramuscularly or intravenously only by a physician or nurse in a hospital; patients are prescribed an oral form of furosemide for use at home.

U.S. brand names

Furosemide is marketed in the United States by Sanofi, a French pharmaceutical company, under the brand name Lasix. It is also sold in the United States under the brand name Furocot. The injectable form is sold in the United States under the brand names Lasix and Furomide MD.

Canadian brand names

Furosemide is marketed in Canada under the brand names Apo-Furosemide, Lasix, and Lasix Special.

International brand names

Furosemide is marketed by at least eight different international manufacturers under numerous brand names, including Beronald, Desdemin, Durafurid, Edemid, Fuluvamide, Furosedon, Lasilix, Mirfat, Nicorol, Odemase, Profemin, Rosemide, Salix, Teva-Furosemide, Trofurit, and Urex.

Origins

Furosemide, originally called frusemide, is an older drug, having been first approved by the FDA in 1966. It has been available in generic formulations since the 1970s.

KEY TERMS

Antihypertensive—Any medication given to control high blood pressure.

Ascites—Accumulation of fluid in the peritoneal cavity, often associated with cirrhosis of the liver or congestive heart failure.

Congestive heart failure—A condition in which the heart cannot pump enough blood to supply the body's tissues with sufficient oxygen and nutrients; back up of blood in vessels and the lungs causes buildup of fluid (congestion) in the tissues.

Diuretic—Any drug given to increase the body's output of urine. Diuretics are sometimes called water pills.

Edema—A condition where tissues retain excess fluid.

Loop diuretic—A type of diuretic that acts on the loop of Henle in the nephrons (basic functional units) of the kidney to prevent reabsorption of sodium and chloride.

Loop of Henle—The portion of a nephron that leads from the proximal convoluted tubule to the distal convoluted tubule. It is named for Friedrich Henle (1809–1885), the German anatomist who first identified it.

Nephron—The basic structural unit of the kidney, responsible for regulating the concentration of water and soluble chemicals in the blood by filtering the blood, reabsorbing the compounds needed by the body, and excreting the rest in the urine. Each kidney in humans contains between 800,000 and 1,000,000 nephrons.

Recommended dosage

Furosemide dosages for conditions in adults are as follows:

- congestive heart failure (CHF): 20–80 mg by mouth once daily; may be increased by 20–40 mg every 6 to 8 hours, not to exceed 600 mg/day
- edema (fluid retention) associated with cirrhosis of the liver and kidney disease: 20–80 mg by mouth once daily; may be increased by 20–40 mg every 6 to 8 hours, not to exceed 600 mg/day
- resistant hypertension: 20–80 mg by mouth per day, divided into two doses taken 12 hours apart
- acute pulmonary edema/hypertensive crisis: intravenous furosemide, 0.5–1 mg per kilogram (kg, or 2.2 lb.) of body

weight (or 40 mg total) administered over 1 or 2 minutes; may be increased to 80 mg if patient fails to respond within 1 hour but should not exceed 160–200 mg/dose

- hyperkalemia or hypermagnesemia: intravenous furosemide, 40–80 mg intravenously for hyperkalemia; 20–40 mg intravenously every 3 to 4 hours for hypermagnesemia
- increased intracranial pressure: intravenous furosemide, 0.5–1 mg/kg (or 40 mg) administered over 1 or 2 minutes; may be increased to 80 mg if patient fails to respond within 1 hour but should not exceed 160–200 mg/dose

Patients who take one dose of furosemide per day should take it early in the day to avoid having to rise to urinate during the night; those who must take two or more doses should take the last dose before 6 p.m. whenever possible. Patients should not exceed their prescribed dose, as high doses of furosemide can cause irreversible hearing loss.

Patients who are prescribed the liquid formulation of furosemide should use a marked measuring spoon, an oral syringe, or a medicine cup to measure the dose, as ordinary household tablespoons vary in the amount of liquid they hold and so may not provide an accurate dose. The pharmacist can also supply the patient with a measuring device.

Furosemide tablets should be stored at room temperature away from heat and light. Furosemide solution should be stored tightly closed in a light-resistant container at room temperature, 59°F–86°F (15°C–30°C); the liquid formulation should be used within 60 to 90 days after opening the bottle. Furosemide should not be stored in the bathroom and should be kept out of the reach of children and pets.

Pediatric

To treat edema in infants and children, the initial dose is 2 mg/kg by mouth per day (about 0.9 mg per pound per day), increased by 1–2 mg/kg every 6 to 8 hours; not to exceed 6 mg/kg.

To treat resistant hypertension in children and adolescents between 1 and 17 years of age, the dose is 0.5–2 mg/kg by mouth every 12 or 24 hours; individual doses should not exceed 6 mg/kg/dose.

Geriatric

Elderly patients need more careful monitoring because of the increased risk of dehydration and electrolyte loss. The recommended dosage is an initial dose of 10 mg per day by mouth, gradually adjusted upward.

Precautions

Patients with any of the following conditions should notify their doctor before using furosemide:

- being dehydrated or having low blood plasma volume (hypovolemia)
- low blood levels of calcium, potassium, or sodium
- low blood pressure
- swollen prostate gland, bladder obstruction, or other problems with urination
- history of gout, hearing problems, lupus, diabetes, or anemia
- severe kidney or liver disease
- recent MRI or other imaging test involving injection of a radioactive dye

Pregnant or breastfeeding

Furosemide is a pregnancy category C drug, which means that the drug has been shown to harm the fetus in animal studies but that no data from human studies are available, so risk to the fetus cannot be ruled out. The drug may cause loss of blood plasma volume in the mother and should be used during pregnancy only if the benefit clearly outweighs the risk.

Furosemide is known to pass into breast milk and could potentially harm a nursing baby; therefore, nursing mothers should inform their doctor before taking furosemide. In addition, the drug is known to slow milk production.

Other conditions and allergies

Patients with any of the following conditions should not use furosemide:

- severe electrolyte depletion
- hepatic coma
- severe allergy to sulfa drugs (sulfamethoxazole, sulfasalazine, sulfisoxazole)
- allergy to furosemide itself or to any of the components in the tablets or solution
- inability to urinate (anuria)

Side effects

Common side effects of furosemide include:

- headache
- muscle cramps
- increased sensitivity to sunlight (photosensitivity)
- skin rash
- constipation or diarrhea

- frequent urination
- anemia

Less common side effects include:

- chills or fever
- sore throat
- indigestion
- itchy skin
- unusual bruising or bleeding
- sores or white spots on the lips or in the mouth

Patients should consult their doctor at once if they notice any of the following side effects of furosemide:

- symptoms of angioedema (a severe allergic reaction), which include sudden swelling of the face, arms, legs, eyes, lips, or tongue and problems with swallowing or breathing
- symptoms of jaundice, which include yellow discoloration of the skin or the whites of the eyes, dark urine, and pale stools
- dizziness, fainting spells, or lightheadedness
- signs of dehydration or electrolyte imbalance, which include dry mouth, thirst, weakness, drowsiness, nausea or vomiting, low blood pressure, decreased urination, and a rapid or irregular heartbeat
- ringing in the ears or hearing problems
- high blood sugar levels in patients diagnosed with diabetes
- vertigo (sensation of spinning, or the feeling that objects and surroundings are spinning around the self)
- signs of a furosemide overdose, which include irritability, mood changes, drowsiness, severe muscle cramps, numbness or tingling pains in the hands or feet, rapid breathing, seizures, weak pulse, and tremor

Interactions

The doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Drugs

Furosemide interacts with a number of different OTC and prescription medications:

- ACE inhibitors (medications given to control high blood pressure—e.g., **enalapril**, **fosinopril**, **lisinopril**, **captopril**) may increase the effects on lowering blood pressure.

- Aminoglycoside antibiotics (e.g., kanamycin, streptomycin, gentamicin, tobramycin, neomycin) intensify toxic side effects of furosemide, particularly the risk of hearing loss.
- Barbiturates may reduce diuretic activity of furosemide.
- **Cephalexin** and cephaloridine may increase risk of kidney damage.
- **Cyclosporine** increases risk of gout.
- Fibrates (**fenofibrate**, clofibrate) may increase blood levels of furosemide.
- High doses of **aspirin** and other salicylates increase risk of toxic side effects if used together with furosemide.
- Laxatives (may increase risk of low blood potassium levels).
- Lithium side effects may be increased by furosemide.
- **Metformin** and other antidiabetic drugs may increase risk of low blood sugar if taken with furosemide.
- NSAIDs (e.g., **ibuprofen**, **ketoprofen**, **celecoxib**, **ketorolac**, naproxen) increase the risk of kidney impairment when used with furosemide.
- Sucralfate (drug used to treat duodenal ulcers) may hinder absorption of furosemide.
- Thiazide diuretics increase the diuretic effect of furosemide.

Other drugs that may interact with furosemide include aliskiren (an antihypertensive drug), chloral hydrate (a sedative), **digoxin** (used to treat congestive heart failure), and corticosteroids (e.g., prednisone, hydrocortisone, dexamethasone).

Herbs and supplements

Patients using furosemide should avoid dong quai, ephedra, yohimbe, and ginseng, as these herbs may worsen hypertension. They should also avoid garlic, which may increase the antihypertensive effect of furosemide.

Food and other substances

The patient's blood level of furosemide may be decreased if the drug is taken together with food.

Patients should be warned against eating large amounts of licorice, as licorice interacts with furosemide to lower the level of potassium in the blood.

Resources

BOOKS

Opie, Lionel H., ed. *Drugs for the Heart*. 8th ed. Philadelphia: Elsevier/Saunders, 2013.

Ramrakha, Punit, and Jonathan Hill. *Oxford Handbook of Cardiology*. 2nd ed. New York: Oxford University Press, 2012.

Sheps, Sheldon. *Mayo Clinic: 5 Steps to Controlling High Blood Pressure: Your Personal Guide to Preventing and Managing Hypertension*. 2nd ed. Rochester, MN: Mayo Clinic, 2015.

Wouters, Lars, ed. *Diuretics: Pharmacology, Therapeutic Uses, and Adverse Side Effects*. Hauppauge, NY: Nova Science Publishers, 2013.

PERIODICALS

Pacifici, G. M. "Clinical Pharmacology of Furosemide in Neonates: A Review." *Pharmaceuticals* 6, no. 9 (2013): 1094–129.

Pan, A., et al. "Prehospital Use of Furosemide for the Treatment of Heart Failure." *Emergency Medicine Journal* 32, no. 1 (2015): 36–43.

Roush, G. C., R. Kaur, and M. E. Ernst. "Diuretics: A Review and Update." *Journal of Cardiovascular Pharmacology and Therapeutics* 19, no. 1 (2014): 5–13.

Wu, M. Y., et al. "Loop Diuretic Strategies in Patients with Acute Decompensated Heart Failure: A Meta-Analysis of Randomized Controlled Trials." *Journal of Critical Care* 29, no. 1 (2014): 2–9.

WEBSITES

"Furosemide." Drugs.com. <http://www.drugs.com/furosemide.html> (accessed February 27, 2015).

"Furosemide (Rx)." Medscape.com. <http://reference.medscape.com/drug/lasix-furosemide-342423> (accessed February 27, 2015).

Micromedex. "Furosemide (Injection Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/furosemide-injection-route/description/drg-20071261> (accessed February 27, 2015).

Micromedex. "Furosemide (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/furosemide-oral-route/description/drg-20071281> (accessed February 27, 2015).

ORGANIZATIONS

American College of Cardiology (ACC), Heart House, 2400 N Street NW, Washington, DC 20037, (202) 375-6000, ext. 5603, Fax: (202) 375-7000, (800) 253-4636, ext. 5603, resource@acc.org, <http://www.cardiosource.org/>.

American Heart Association (AHA), 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rebecca J. Frey, PhD

REVIEWED BY GREGORY A. PRATT, RPH

G

Gabapentin

Definition

Gabapentin is an antiseizure medication.

Purpose

Gabapentin is used in combination with other antiseizure (anticonvulsant) drugs to manage partial seizures with or without generalization in individuals over the age of 12. Gabapentin can also be used to treat partial seizures in children between the ages of 3 and 12.

Off-label use

Off-label uses (legal uses not approved by the U.S. Food and Drug Administration [FDA]) include treatment of severe, chronic pain caused by nerve damage, such as occurs in shingles, diabetic neuropathy, multiple sclerosis, or postherpetic neuralgia. Gabapentin was previously studied in the treatment of bipolar disorder but did not show any effectiveness in clinical trials.

Description

Brain cells normally transmit nerve impulses from one cell to another by secreting chemicals known as neurotransmitters. Gabapentin is chemically related to a naturally occurring neurotransmitter called GABA (gamma-aminobutyric acid). The actual mechanism of action by which gabapentin acts in the brain to control seizures and treat pain is not known, although it appears to alter the action of nerve cells.

Gabapentin is available in 100, 300, and 400 milligram (mg) capsules; in 600 and 800 mg tablets; and as a liquid solution containing 250 mg per 5 milliliters (mL).

U.S. brand names

Gabapentin is sold under the trade name Neurontin.

Origins

Gabapentin was approved for use in the United States in 1993. A liquid formulation was approved for use in 2000. Use in children ages 3 to 12 was also approved by the FDA in 2000.

Recommended dosage

For epilepsy, people over the age of 12 can begin with an initial dose of 300 mg three times a day, which can be gradually increased as necessary, usually to no more than 1,800 mg daily.

Pain dosing involves a gradual increase, with an initial dose of 300 mg on the first day, followed by 300 mg twice on the second day, and 300 mg three times on day three. A physician may increase this dose to a maximum daily dose of 1,800 mg.

Pediatric

For children ages 3 to 12, the dose is based on body weight, initially 10–15 mg per kilogram (kg, or 2.2 lb.) per day in three separate doses. The physician may choose to increase this dose as necessary. For a child under the age of 3, the decision about use and dosage will be made by the doctor.

Geriatric

For older adults, the maximum daily dose does not usually exceed 600 mg three times a day.

Precautions

Patients should not suddenly discontinue gabapentin, as this can result in an increased risk of seizures. If the medication needs to be discontinued, the dosage should be reduced gradually over a week.

Until an individual understands the effects that gabapentin may have, he or she should avoid driving, operating dangerous machinery, or participating in hazardous activities.



Gabapentin, 600 mg. (© Cengage Learning®.)

Some patients taking gabapentin have shown changes in their mental health, including the development of suicidal thoughts and behavior. If patients taking gabapentin exhibit any changes in mood or behavior, they (or their caregivers) should contact their physician.

Pregnant or breastfeeding

Women who are or wish to become pregnant or who are breastfeeding should assess the risks and benefits of taking gabapentin with their healthcare provider.

Other conditions and allergies

People with decreased kidney functioning should discuss the risks and benefits of this drug with their physician.

Side effects

Multiple side effects often occur when a patient starts taking gabapentin. While these side effects usually go away on their own, if they last or are particularly troublesome, the patient should consult a doctor. More common side effects that occur when first starting to take gabapentin include:

- blurred or double vision
- muscle weakness or pain

KEY TERMS

Gamma-aminobutyric acid (GABA)—A neurotransmitter that helps to lower or reduce the level of excitement in the nerves, leading to muscle relaxation, calmness, sleep, and the prevention of seizures.

Neurotransmitter—A chemical in the brain that transmits messages between neurons, or nerve cells.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to prescribe these drugs, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Seizure—A sudden attack, spasm, or convulsion.

- swollen hands, feet, or legs
- trembling or shaking
- increased fatigue or weakness
- unsteadiness
- clumsiness
- uncontrollable back-and-forth eye movements or eye rolling

Less common side effects include:

- back pain
- constipation or diarrhea
- decreased sexual drive
- dry mouth and eyes
- frequent urination
- headache
- indigestion
- low blood pressure
- ringing in the ears
- runny nose
- slurred speech
- difficulty thinking and sleeping
- weight gain
- twitching
- nausea and/or vomiting
- weakness
- depression
- irritability
- mood changes or changes in thinking

- decreased memory

Rare side effects include:

- pain in the lower back or side
- difficulty urinating
- fever and/or chills, cough, or hoarseness

Pediatric

Children under age 12 who have the following more common side effects should see a doctor immediately: aggressive behavior, irritability, anxiety, difficulty concentrating and paying attention, crying, depression, mood swings, increased emotionality, hyperactivity, and suspiciousness or distrust.

Interactions

Individuals should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs and supplements.

Drugs

Antacids can decrease gabapentin levels in the blood. They should be taken at least two hours before taking gabapentin.

Food and other substances

Alcohol should be avoided while taking gabapentin.

Resources

BOOKS

Mosby's Drug Reference for Health Professions. 5th ed. St. Louis, MO: Mosby, 2015.

PERIODICALS

Canadian Agency for Drugs and Technologies in Health. "Gabapentin for Adults with Neuropathic Pain: A Review of the Clinical Evidence and Guidelines." *Rapid Response Reports*. Ottawa, Canada: September 26, 2014. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0069865/> (accessed February 24, 2015).

OTHER

U.S. Food and Drug Administration. "Medication Guide (Neurotonin)." <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM229208.pdf> (accessed February 24, 2015).

WEBSITES

AHFS Consumer Medication Information. "Gabapentin." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a694007.html> (accessed February 24, 2015).

Epilepsy Foundation. "Gabapentin." <http://www.epilepsy.com/medications/gabapentin> (accessed February 24, 2015).

Micromedex. "Gabapentin." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/gabapentin-oral-route/description/drg-20064011> (accessed February 24, 2015).

ORGANIZATIONS

Epilepsy Foundation, 8301 Professional Place East, Suite 200, Landover, MD 20785-2353, (800) 332-1000, Contact Us@efa.org, <http://www.epilepsy.com/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Galantamine

Definition

Galantamine belongs to a class of drugs called acetylcholinesterase inhibitors.

Purpose

Galantamine is used to treat the symptoms of Alzheimer's disease (AD).



Galantamine, 16 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

Alzheimer's disease develops when brain cells, called neurons, undergo an early death. Though AD cannot be cured, it is thought that the premature death of these neurons may be prevented or slowed if stimulated by a brain chemical called acetylcholine. Acetylcholine is recycled by an enzyme called acetylcholinesterase. Galantamine works by inhibiting this enzyme. The inhibition of acetylcholinesterase increases the concentration of available acetylcholine.

Galantamine has only been studied and is only used in patients with mild-to-moderate AD, according to the Alzheimer's Disease Assessment Scale. It is not used in patients with severe AD.

Galantamine is available in 4, 8, and 12 milligram (mg) tablets.

U.S. brand names

In the United States, galantamine is sold under the brand name Razadyne (formerly Reminyl).

Recommended dosage

The recommended initial dose of galantamine in adults is 4 mg twice daily. After a minimum of four weeks of treatment with galantamine, the dosage may be increased to 8 mg twice daily. Further increases to 12 mg twice daily should be initiated only after a minimum of four weeks at the previous dose.

Increased side effects associated with higher doses may prevent the increase in dose in some patients.

Other conditions and allergies

Patients with moderate liver or kidney problems should not exceed 16 mg of galantamine daily.

Precautions

Galantamine should not be used in patients with severe liver or kidney problems. Patients who are undergoing anesthesia or bladder or gastrointestinal surgery should take galantamine only after a discussion with their physician. Patients with gastrointestinal problems should be closely monitored if it is decided that they should take galantamine. Galantamine should also be used under close physician supervision in patients who have Parkinson's disease, severe asthma, or chronic obstructive pulmonary disease. Because galantamine may slow down the heart, patients with any heart conditions, and especially patients taking other medications that slow down the heart, should be evaluated before taking galantamine.

KEY TERMS

Acetylcholine—A naturally occurring chemical in the body that transmits nerve impulses from cell to cell. Acetylcholine causes blood vessels to dilate, lowers blood pressure, and slows the heartbeat. Central nervous system well-being is dependent on a balance among the neurotransmitters acetylcholine, dopamine, serotonin, and norepinephrine.

Acetylcholinesterase—The chemical responsible for the breakdown of acetylcholine.

Alzheimer's disease—A progressive, neurodegenerative disease characterized by loss of function and death of nerve cells in several areas of the brain, leading to loss of mental functions, including memory and learning. Alzheimer's disease is the most common cause of dementia.

Parkinson's disease—A disease of the nervous system most common in people over age 60, characterized by a shuffling gait, trembling of the fingers and hands, and muscle stiffness.

Pregnant or breastfeeding

Since there are no well controlled studies for the use of galantamine in pregnancy, galantamine should only be used if the potential benefits justify the potential risks to the fetus.

Side effects

The most common side effects reported with the use of galantamine are nausea, vomiting, diarrhea, loss of appetite, and abdominal pain. These occur most often during dosage escalation. The average duration of nausea is five to seven days. Side effects tend to be less frequent if the patient is taking a total daily dosage of 16 mg. Eleven percent of patients receiving 24 mg daily lose weight, while 6% of patients receiving 16 mg daily experience weight loss.

Other common side effects include dizziness, headache, tremors, fatigue, depression, agitation, irritation, and insomnia. These side effects have a higher incidence and severity if higher doses are used. If side effects become severe, the dosage should be adjusted downward under physician supervision.

Interactions

There is currently little data regarding potential drug interactions with galantamine.

Drugs

Medications that are known to increase levels of galantamine in the body include cimetidine, **erythromycin**, **ketoconazole**, and **paroxetine**.

Resources

PERIODICALS

- Bond, M., et al. "The Effectiveness and Cost-Effectiveness of Donepezil, Galantamine, Rivastigmine, and Memantine for the Treatment of Alzheimer's Disease (Review of Technology Appraisal No. 111): A Systematic Review and Economic Model." *Health Technology Assessment* 16, no. 21 (2012): 1–470.
- Di Santo, S. G., et al. "A Meta-Analysis of the Efficacy of Donepezil, Rivastigmine, Galantamine, and Memantine in Relation to Severity of Alzheimer's Disease." *Journal of Alzheimer's Disease* 35, no. 2 (2013): 349–61.
- Jiang, Deqi, et al. "Efficacy and Safety of Galantamine Treatment for Patients with Alzheimer's Disease: A Meta-Analysis of Randomized Controlled Trials." *Journal of Neural Transmission* (December 30, 2014): e-pub ahead of print. <http://dx.doi.org/10.1007/s00702-014-1358-0> (accessed February 25, 2015).
- Kröger, E., et al. "Treatment with Rivastigmine or Galantamine and Risk of Urinary Incontinence: Results from a Dutch Database Study." *Pharmacoepidemiology and Drug Safety* (February 4, 2015): e-pub ahead of print. <http://dx.doi.org/10.1002/pds.3741> (accessed February 25, 2015).
- Lee, J. H., et al. "The Effects of Galantamine Treatment on Attention and its Relationship with Cognition and Activities of Daily Living in Patients with Mild to Moderate Alzheimer's Disease." *Journal of Clinical Neurology* 11, no. 1 (2015): 66–72.

OTHER

National Institute for Health and Care Excellence. "Donepezil, Galantamine, Rivastigmine, and Memantine for the Treatment of Alzheimer's Disease." UK National Health Service. <http://www.nice.org.uk/guidance/ta217/resources/guidance-donepezil-galantamine-rivastigmine-and-memantine-for-the-treatment-of-alzheimers-disease-pdf> (accessed February 25, 2015).

WEBSITES

- AHFS Consumer Medication Information. "Galantamine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699058.html> (accessed February 25, 2015).
- Alzheimer Scotland. "Reminyl (Galantamine Hydrobromide): Drug Treatment for Alzheimer's." http://www.alzscot.org/information_and_resources/information_sheet/1763_reminyl_galantamine_hydrobromide_drug_treatment_for_alzheimer_s (accessed February 25, 2015).
- Alzheimer's Association. "Current Alzheimer's Treatments." http://www.alz.org/research/science/alzheimers_disease_treatments.asp (accessed February 25, 2015).

ORGANIZATIONS

- Alzheimer's Association, 225 N. Michigan Avenue, Floor 17, Chicago, IL 60601-7633, (312) 335-8700, (800) 272-3900, (866) 699-1246, TTY: (866) 403-3073, info@alz.org, <http://www.alz.org/>.
- Alzheimer's Foundation of America, 322 Eighth Avenue, 7th Floor, New York, NY 10001, (646) 638-1542, (866) 232-8484, Fax: (646) 638-1546, <http://www.alzfdn.org/>.
- Alzheimer's Society, Devon House, 58 St Katharine's Way, London E1W 1LB, England, +44 0300 222 11 22, Enquiries @alzheimers.org.uk, <http://www.alzheimers.org.uk/>.

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Gemfibrozil

Definition

Gemfibrozil belongs to a group of drugs called fibrates. It is an antilipidemic agent, meaning that it helps to reduce the amount of lipids (fats), such as fatty acids and triglycerides, in the blood.

Purpose

Gemfibrozil, when used in conjunction with a diet that limits the intake of fats and cholesterol, can lower



Gemfibrozil, 600 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

high levels of triglycerides in the blood. High triglyceride levels cause a condition called hyperlipidemia, which can lead to inflammation of the pancreas, also known as pancreatitis. Gemfibrozil can also help to prevent heart disease in individuals who have high triglyceride levels and high cholesterol levels if the individual has not responded to other cholesterol-lowering drugs and the benefits of taking gemfibrozil outweigh the drug's potential risks.

Description

Gemfibrozil is taken by mouth as a 600 milligram (mg) tablet. This is the most commonly prescribed form, but it is also available as a 300 mg capsule. The drug works by reducing the amount of very-low-density lipoprotein (VLDL) that the liver produces. Because triglycerides are a fat, they are not soluble in water. They must combine with VLDL to be transported through the blood. By reducing the amount of VLDL available, gemfibrozil reduces the amount of triglycerides in the blood. VLDL also carries some cholesterol molecules through the blood, so individuals taking gemfibrozil may see a small decrease in high-density lipoprotein cholesterol (HDL, or “bad” cholesterol) and a slight increase in low-density lipoprotein cholesterol (LDL, or “good” cholesterol), although reduction of cholesterol levels is not the primary function of gemfibrozil. Gemfibrozil does not cure the overproduction of triglycerides or cholesterol; it only helps to control their concentration in the blood when used with a low-fat, low-cholesterol diet.

U.S. brand names

In the United States, gemfibrozil is sold under the brand name Lopid. Lopid is a 600 mg, elliptical-shaped, white, scored tablet.

International brand names

Gemfibrozil is manufactured by more than a dozen manufacturers. In addition to being sold as a generic drug, it is sold under many different brand names internationally. Some of these include:

- Ausgem (Australia)
- Bisil (Thailand)
- Brozil (Malaysia, Singapore)
- Chang Hen Lin (China)
- Fibrolip (Greece)
- Gemfi-1A Pharma (Germany)
- Panazil (Taiwan)
- Pildar (Spain)
- Zilop (Indonesia)

KEY TERMS

Cholesterol—A waxy substance made by the liver that circulates in the bloodstream; it is also acquired through diet. Cholesterol is essential to the human body, but too much can increase the risk of cardiovascular disease and other conditions.

Fatty acids—Complex molecules produced during the breakdown of fats and oils.

Lipoprotein—A protein present in blood plasma.

Triglycerides—Large molecules found in the blood that consist of three molecules of fatty acid and one molecule of glycerol. High levels of triglycerides can increase the risk of coronary artery disease.

Origins

Gemfibrozil was first approved by the U.S. Food and Drug Administration (FDA) in July 1998.

Recommended dosage

The usual recommended dosage for gemfibrozil is 1,200 mg daily, divided into two doses of 600 mg each. The drug is normally taken in the morning and in the evening, 30 minutes before eating.

A missed dose should be taken as soon as it is remembered unless it is close to the time for the next dose. In this case, the missed dose should be skipped and regular dosing resumed.

Pediatric

This drug is not intended for pediatric use.

Geriatric

No information is available about how increasing age impacts the effectiveness or side effects of this drug.

Precautions

Before beginning gemfibrozil, patients should tell their healthcare provider about all over-the-counter and prescription drugs they take, as well as any medicinal herbs or dietary supplements. It is especially important to mention any cholesterol-lowering drugs or diabetes medicines that are being taken, as their use may be incompatible with the use of gemfibrozil. Patients should also tell their doctor about any allergies to foods or medicines. It is essential to alert the doctor to any present or past liver, kidney, or gallbladder disease, as this drug may worsen or reactivate those conditions.

Pregnant or breastfeeding

Gemfibrozil carries the FDA pregnancy category C. This means that no adequate human studies have been performed during pregnancy, or that adverse fetal effects have been found in animal studies, but no available human data is available. There is no data on how this drug affects breastfeeding infants. The drug should be used by pregnant or breastfeeding women only if there are no alternatives and benefits outweigh risks to mother and child. If a woman becomes pregnant while taking gemfibrozil, she should call her healthcare provider immediately.

Other conditions and allergies

Individuals with liver disease should not use gemfibrozil. Individuals with an underactive thyroid (hypothyroidism) should use this drug with caution. Other medical conditions that may affect the use of this drug or require additional monitoring include diabetes, gallbladder disease, kidney disease, and a history of muscle pain or weakness. This drug may increase the risk of developing gallstones. Any stomach or side pain, nausea, or vomiting should be reported to a doctor immediately.

Side effects

Serious side effects of gemfibrozil that require the prompt attention of a doctor include:

- bladder pain
- bloody, cloudy, or dark-colored urine
- painful or difficult urination
- frequent urge to urinate
- fever and/or chills
- hoarseness, cough, or sore throat
- lower back, side, or stomach pain
- hive-like swellings on the face or body (may be signs of an allergic reaction; treat as a medical emergency)
- muscle pain or tenderness, stiffness, or weakness
- shortness of breath or difficulty breathing (may be signs of an allergic reaction; treat as a medical emergency)
- blurred vision

More common but less serious side effects include:

- stomach upset, sour stomach, heartburn, or belching
- diarrhea
- change in taste or unpleasant aftertaste
- burning, itching, prickling, or tingling sensations

Less common and less serious side effects include:

- constipation
- dizziness or light-headedness

- a sensation of spinning or movement of surroundings
- nausea or vomiting
- skin rash

Some side effects are temporary and will disappear as the body becomes used to the drug. However, any change in health status or unusual problems, sensations, or pains should be reported to a doctor.

Interactions

Gemfibrozil interacts with many drugs. Interactions with herbal medications and dietary supplements are not known. It is important to tell the treating physician and pharmacist about all medications that are being taken.

Drugs

Below is a list of drugs gemfibrozil is known to interact with. This list may not be complete. Individuals should consult their healthcare provider and pharmacist for the latest information on drug interactions.

Individuals taking the following drugs should not take gemfibrozil:

- **simvastatin** (Zocor)
- repaglinide (Prandin, in Prandimet)

Gemfibrozil also interacts with the following types of drugs. The dosage of these drugs may need to be changed or an alternative to gemfibrozil prescribed to prevent serious adverse effects:

- anticoagulant drugs such as **warfarin** (Coumadin)
- cholesterol-lowering drugs called statins, such as atorvastatin (Lipitor), fluvastatin (Lescol), and **lova-statin** (Mevacor)
- **colchicine** (Colcrys)

Resources

BOOKS

Sorrentino, Matthew J., ed. *Hyperlipidemia in Primary Care: A Practical Guide to Risk Reduction*. New York: Springer, 2011.

WEBSITES

- American Heart Association. "Hyperlipidemia." Heart.org. http://www.heart.org/HEARTORG/Conditions/Cholesterol/AboutCholesterol/Hyperlipidemia_UCM_434965_Article.jsp (accessed February 9, 2015).
- "Gemfibrozil." Drugs.com. <http://www.drugs.com/gemfibrozil.html> (accessed February 9, 2015).
- MedlinePlus. "Gemfibrozil." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a686002.html> (accessed February 9, 2015).

Physicians' Desk Reference. "Lopid." PDR Health. <http://www.pdrhealth.com/drugs/lopid> (accessed February 12, 2015).

ORGANIZATIONS

American Heart Association (AHA), 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.

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REVIEWED BY CHRISTY McDONALD LENAHA, DNP, MSN, APRN, FNP-BC

Geodon see **Ziprasidone**

Glatiramer

Definition

Glatiramer (pronounced glah-TEER-ah-mer) acetate is an immunomodulator (a drug that changes or modifies the body's immune response) that is considered a first-line treatment for relapsing-remitting multiple sclerosis. It consists of four amino acids (glutamic acid, lysine, alanine, and tyrosine) that occur in myelin basic protein (MBP), an important protein in the myelination (insulation) of the nerves in the nervous system. Glatiramer acetate is also classified as a disease-modifying treatment (DMT) for multiple sclerosis.

Purpose

Glatiramer is approved by the U.S. Food and Drug Administration (FDA) for treating multiple sclerosis (MS) in adults after the initial episode, for reducing the frequency of relapses, and for treating relapsing-remitting MS. Although it was thought that glatiramer might also slow the progression of MS when the drug was first put on the market in the mid-1990s, several studies conducted in 2004 showed that it is ineffective in preventing the progression of the disease. It is therefore not approved by the FDA for this purpose.

The drug's mechanism of action is not yet clearly understood. Some researchers think that it helps to suppress the inflammatory response that occurs in MS; others hypothesize that glatiramer acts to divert the body's autoimmune destruction of myelin because the drug resembles MBP so closely.

Off-label uses

Glatiramer is used off label as an orphan drug for the treatment of amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's disease).

Description

Glatiramer is available as a liquid for subcutaneous injection, as a powder to be reconstituted for injection, and as a kit containing either a 20 or 40 milligram per milliliter (mg/mL) prefilled syringe. The prefilled syringes are the form most commonly used in the United States because they allow patients to self-inject at home. When properly stored or reconstituted, glatiramer should be a clear liquid without cloudiness or particles floating in it.

U.S. brand names

Glatiramer is sold in the United States under the brand name Copaxone.

Canadian brand names

Glatiramer is sold in Canada under the brand name Copaxone.

International brand names

Glatiramer is sold under the brand name Copaxone in numerous countries and under the brand name Donecept in Ireland.

Origins

Glatiramer was developed in the 1980s by a team of scientists at the Weizmann Institute of Science in Israel.



Copaxone (glatiramer). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Amyotrophic lateral sclerosis (ALS)—A neurodegenerative disorder characterized by the progressive loss of muscle strength, resulting in difficulty swallowing, speaking, and breathing. It is also known as Lou Gehrig's disease.

Axon—The long, slender projection of a nerve cell that conducts electrical impulses away from the body of the nerve cell.

Myelin basic protein (MBP)—A protein that is important in maintaining the structure of myelin, a material that forms an insulating sheath around the axon of a nerve cell.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Orphan drug—A medication that has been developed to treat a rare disease, defined in the United States as a disease or disorder affecting fewer than 200,000 people.

It was tested in three major clinical trials in Israel, the United States, and Italy beginning in the early 1990s. The drug received FDA approval in 1996. A higher-dose, lower-frequency form of glatiramer acetate was approved by the FDA in early 2014.

The drug's patent expired in May 2014. As of early 2015, however, there were no licensed generic versions of glatiramer approved for sale. Patients should avoid any so-called generic forms of the drug that may be offered for sale online.

Recommended dosage

The standard adult dose for treatment of multiple sclerosis is one 20 mg/mL subcutaneous injection once daily, or one 40 mg/mL subcutaneous injection three times a week. If the three-times-per-week schedule is chosen, the doses must be at least 48 hours apart. The higher-dose, lower-frequency form is thought to improve patient compliance.

Pediatric

The safety and effectiveness of glatiramer have not been established in children.

Precautions

Individuals who are known to be allergic to either glatiramer itself or to mannitol (a sugar alcohol, or polyol, used in the manufacture of some pharmaceutical products) should not use glatiramer.

Patients should be instructed about the proper way to inject themselves with glatiramer, to care for their injection devices, and to dispose of used needles:

- If prefilled syringes are used, they should be stored in the refrigerator, but must not be allowed to freeze.
- Patients should inject themselves at the same time on each occasion. Before the injection, the patient must decide which of seven body sites (arms, thighs, hips, or lower abdomen) will be used for the day's injection. The patient should not use any of the sites more than once a week, and may find it helpful to mark each day's site on a calendar.
- The prefilled cartridge should be removed from the refrigerator about 20 minutes before the injection and allowed to come to room temperature. It should not be warmed in hot water or a microwave. The patient should carefully check the appearance of the liquid in the syringe; it should be clear. If it is cloudy, has changed color, or contains visible particles, it should not be used. The patient should call the manufacturer at (800) 887-8100 and ask for advice.
- While the syringe is warming, the patient should wash his or her hands with soap and water and avoid touching his or her face or hair. When the syringe has warmed to room temperature, the patient should cleanse the injection site with an alcohol wipe or swab. After removing the cap from the syringe and taking care not to touch the needle, the patient should take a two-inch fold of skin between the thumb and index finger, and insert the needle into the fold of skin.
- When the needle has been fully inserted, the patient should release the fold of skin and push the plunger at the top of the syringe until the drug has been completely injected. The patient should then remove the needle and cover the injection site with a dry, clean cotton ball. The patient should apply pressure to the injection site but not rub it. The cover should be replaced on the needle, and the syringe and any unused drug inside it should be discarded.
- Glatiramer should never be injected into a vein or muscle or administered intravenously.
- Patients should not stop taking glatiramer without first consulting their healthcare provider.
- Used needles should be stored in a puncture-proof container, kept away from children and pets, and

disposed of in accordance with state or local laws. A pharmacist can provide information about obtaining such containers and disposing of them properly.

Pediatric

Glatiramer is not recommended for use in children younger than 18 years.

Geriatric

No special precautions are required for elderly patients using glatiramer.

Pregnant or breastfeeding

Glatiramer carries the FDA pregnancy category B, which means that no studies of reproduction in animals have indicated harm to the fetus, and there are no adequate, well-controlled studies of glatiramer in pregnant women.

It is not known whether glatiramer passes into breast milk or whether it could harm a nursing infant. Patients who are lactating should tell their healthcare provider before they use glatiramer.

Side effects

Common side effects of glatiramer include:

- redness, pain, or burning at the injection site
- flushing or hot flashes
- nausea
- weakness
- headache
- stuffy or runny nose

Less common side effects include:

- weight gain
- visual disturbances

Patients should check with their healthcare provider if any of the following side effects occur:

- anxiety
- bleeding at the injection site
- chest pain
- fast or irregular heartbeat
- pain in the neck, side, or lower back
- painful or difficult urination
- swollen or tender lymph nodes in the groin, neck, or armpit
- difficulty breathing
- excessive muscle tone
- facial swelling or puffiness

Interactions

Glatiramer has known interactions with various drugs and herbal supplements.

Drugs

Glatiramer interacts with the following classes of drugs:

- Monoclonal antibodies (e.g., natalizumab, **adalimumab**, canakinumab, **infliximab**) interact with glatiramer to increase the patient's risk of infection.
- Glatiramer lowers the effectiveness of vaccines (e.g., diphtheria, anthrax, polio, hepatitis, HPV, influenza, typhoid, yellow fever, rabies, rubella) and may cause severe interactions. Patients taking glatiramer should not be given vaccines unless the benefits outweigh the risks.
- Immunosuppressants (e.g., **tacrolimus**, everolimus, sirolimus, temsirolimus) interact with glatiramer to increase a patient's risk of infection.

Herbs and supplements

Glatiramer is known to interact with astragalus, maitake mushrooms, and echinacea. Patients who use any herbal preparations should tell their doctor before using glatiramer.

Food and other substances

Glatiramer is not known to interact with alcohol or any foods.

Resources

BOOKS

Giesser, Barbara S., ed. *Primer on Multiple Sclerosis*. 2nd ed. New York: Oxford University Press, 2015.

Schapiro, Randall T. *Managing the Symptoms of Multiple Sclerosis*. 6th ed. New York: Demos Medical Publishing, 2014.

Silberstein, Stephen, and Michael Marmura. *Essential Neuropharmacology: The Prescriber's Guide*. Cambridge, UK: Cambridge University Press, 2010.

PERIODICALS

Caporro, M., et al. "Two Decades of Subcutaneous Glatiramer Acetate Injection: Current Role of the Standard Dose, and New High-Dose Low-Frequency Glatiramer Acetate in Relapsing-Remitting Multiple Sclerosis Treatment." *Patient Preference and Adherence* 8 (2014): 1123–34.

Carrithers, M. D. "Update on Disease-Modifying Treatments for Multiple Sclerosis." *Clinical Therapeutics* 36 (2014): 1938–45.

Glanz, B. I., et al. "Treatment Satisfaction in Multiple Sclerosis." *International Journal of MS Care* 16 (2014): 68–75.

WEBSITES

National Multiple Sclerosis Society. "Copaxone." <http://www.nationalmssociety.org/Treating-MS/Medications/Copaxone> (accessed February 12, 2015).

Medscape Reference. "Glatiramer (Rx)." <http://reference.medscape.com/drug/copaxone-glatiramer-343213> (accessed February 10, 2015).

Micromedex. "Glatiramer (Subcutaneous Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/glatiramer-subcutaneous-route/description/drg-20064045> (accessed February 10, 2015).

ORGANIZATIONS

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

Multiple Sclerosis Association of America (MSAA), 706 Haddonfield Road, Cherry Hill, NJ 08002, (856) 488-4500, Fax: (856) 661-9797, (800) 532-7667, MS questions@mysaa.org, <http://www.mysaa.org/>.

National Multiple Sclerosis Society (800) 344-4867, <http://www.nationalmssociety.org/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Gleevec see **Imatinib**

Glimepiride

Definition

Glimepiride (pronounced gly-MEP-ir-ide) is a medium- to long-acting oral antidiabetic drug. It is classified as a second-generation (sometimes a third-generation) sulfonylurea. Sulfonylureas work by stimulating the release of insulin from the beta cells in the pancreas; they are sometimes categorized as secretagogues for this reason.

Purpose

Glimepiride is used to treat patients with type 2 diabetes who have been unsuccessful in controlling their diabetes with diet and exercise. Glimepiride may be used alone, or together with insulin or another oral antidiabetic drug. It does not cure type 2 diabetes but assists in its management, and it is reported to be more effective than DPP-4 inhibitors (another type of antidiabetic drug) in preventing the gradual impairment of insulin secretion



Glimepiride, 1 mg. (U.S. National Library of Medicine, Pillbox)

that characterizes type 2 diabetes. It cannot be used to treat type 1 diabetes.

Description

Glimepiride is formulated as a tablet colored various shades of green, pink, blue, or peach to distinguish the various dosages. Amaryl tablets and some of the generics are scored across the middle to simplify breaking the tablet in half.

U.S. brand names

Glimepiride is sold under the brand name Amaryl in the United States. Generic formulations are also available as glimepiride tablets.

International brand names

Glimepiride is sold under a range of different international brand names, including Acotril (Philippines), Adinsulin (Greece), Adiuvan (Argentina), AMDM (South Korea), Amarel (France), Amaride (Taiwan), Amarylle (Belgium), Apo-Glim (Poland), Aylide (Australia), Diamel (Italy), and Glimedoc (Germany).

Origins

Glimepiride was developed in Europe by Sanofi (formerly Sanofi-Aventis), a pharmaceutical company headquartered in Paris. It was approved by the FDA in 1995 as a new molecular entity (NME). Glimepiride went off patent in 2005 and as of 2015 was manufactured by at least 10 companies, including Ranbaxy, Teva Pharmaceuticals, and Mylan Laboratories.

KEY TERMS

Dipeptidyl peptidase-4 (DPP-4) inhibitors—A group of oral antidiabetic drugs that work by inhibiting an enzyme that slows down the lowering of blood glucose levels. DPP-4 inhibitors are also known as gliptins.

Hypoglycemia—Abnormally low blood sugar, usually defined as blood glucose levels below 3.3 or 3.9 millimoles per liter (mmol/L) or 60 or 70 milligrams per deciliter (mg/dL). It is a common complication of treating diabetes with insulin or oral diabetes medications.

Monotherapy—The use of a single medication or therapy to treat a disease or condition.

Secretagogue—Any substance that causes another substance to be secreted. Glimepiride is an insulin secretagogue.

Type 2 diabetes—Formerly called adult-onset diabetes; this disease prevents the body from properly using glucose (sugar) but can often be controlled with diet and exercise.

Recommended dosage

Glimepiride tablets sold under the brand name Amaryl are dispensed as 1, 2, or 4 milligram (mg) tablets. Generic glimepiride tablets are dispensed as 1 mg, 2 mg, 3 mg, 4 mg, 6 mg, and 8 mg tablets.

The recommended initial dosage of glimepiride for the treatment of type 2 diabetes in adults is 1–2 mg by mouth every morning, after breakfast or with the first meal. The dose may be increased by 1–2 mg every one or two weeks, but it must not exceed 8 mg per day.

Glimepiride may be used alone (monotherapy) or with **metformin** or insulin if the patient's blood sugar level does not respond to the maximum dose of glimepiride. Several studies conducted in 2014 indicated that patients whose diabetes was not adequately controlled with the maximum dose of glimepiride responded well to lower doses of glimepiride taken together with **sitagliptin**, an oral antidiabetic drug classified as a DPP-4 inhibitor.

Pediatric

The safety and effectiveness of glimepiride have not been established in children.

Other conditions and allergies

The recommended dose for patients with renal (kidney) impairment is 1 mg by mouth once per day, with the dosage adjusted according to the patient's fasting blood glucose levels.

Glimepiride is not recommended for patients with severe liver disorders; however, in milder cases, the patient may be given 1 mg by mouth once per day, with adjustments made according to the results of blood tests of liver function.

Precautions

As with all prescription medications, patients prescribed glimepiride should inform their healthcare providers of any other medications they are taking, including over-the-counter medications, nutritional supplements, and herbal preparations, as well as other prescription drugs. They should also inform their healthcare providers of any known allergies to foods, preservatives, or dyes.

Pediatric

Glimepiride is not recommended for use in children.

Geriatric

There are no indications that the safety and effectiveness of glimepiride are affected by age alone in the geriatric population. Older adults with kidney or liver disorders should consult their healthcare providers before taking glimepiride.

Pregnant or breastfeeding

Glimepiride carries the FDA pregnancy category C, which means that the drug has been shown to harm the fetus in animal studies but that no data from human studies are available. There were no studies as of 2015 that had determined risk to the infants of lactating mothers. Women who are pregnant or breastfeeding should consult their healthcare providers before taking glimepiride.

Other conditions and allergies

Patients with a history of impaired kidney or liver function should consult their healthcare providers before taking glimepiride.

Side effects

The most common side effects reported for glimepiride are as follows:

- hypoglycemia
- dizziness

- weakness
- headaches
- nausea

Rare side effects of glimepiride include:

- diarrhea
- low levels of sodium in the blood
- vomiting
- stomach pain
- anemia
- changes in vision
- a severe adverse reaction after drinking alcohol

Patients who experience any of the following side effects should consult their healthcare provider at once:

- symptoms of high blood sugar (increased thirst and appetite, increased urination, fatigue, nausea and vomiting, shortness of breath)
- symptoms of hypoglycemia (sweating, tremor, mood changes, irritability, extreme hunger, dizziness, cold sweats, seizures, blurred vision, loss of coordination, mental confusion, difficulty speaking); can also be caused by an overdose of glimepiride
- symptoms of impaired liver function (jaundice, darkened urine, pain in the upper right quadrant of the abdomen)
- symptoms of angioedema (itching, hives, sudden unexplained swelling of the lips and mucous membranes, difficulty breathing)
- fever, chills, or sore throat
- chest pain, irregular heartbeat, rapid heartbeat, shortness of breath

Interactions

Glimepiride is known to interact with many medications and with alcohol.

Drugs

Glimepiride is known to interact with a large number of medications, including:

- antifungal medications (**fluconazole**, miconazole, **ketoconazole**)
- some decongestants (phenylephrine, pseudoephedrine)
- diuretics (amiloride, bumetanide, metolazone, ethacrynic acid, **furosemide**, **hydrochlorothiazide**, **torsemide**, triamterene)
- sulfonamide antibiotics (e.g., sulfadiazine, sulfadoxine, sulfamethoxazole)

- monoamine oxidase inhibitors (MAOIs; e.g., phenelzine, selegiline, isocarboxazid)
- antiseizure medications (**carbamazepine**, **phenytoin**, and fosphenytoin)
- beta-blockers (e.g., **sotalol**, **timolol**, **propranolol**, **atenolol**)
- salicylates (**aspirin**, diflunisal)
- **rifampin**
- nonsteroidal anti-inflammatory drugs (NSAIDs; naproxen, ibuprofen, **diclofenac**, **celecoxib**, **indomethacin**, **ketoprofen**, **ketorolac**, **nabumetone**)
- corticosteroids (cortisone, dexamethasone, hydrocortisone, fludrocortisone, **methylprednisolone**, **prednisone**, prednisolone, **triamcinolone**)
- fluoroquinolone antibiotics (e.g., **ciprofloxacin**, gemifloxacin, **levofloxacin**, gatifloxacin, ofloxacin)
- chloramphenicol
- **warfarin** (blood thinner)
- estrogens and **oral contraceptives**
- **fluoxetine** (a selective serotonin reuptake inhibitor [SSRI] antidepressant)
- isoniazid
- thyroid medications (**levothyroxine**, liothyronine, thyroid extract)

Food and other substances

Patients taking glimepiride should not drink alcoholic beverages because a serious or life-threatening reaction may result. Some patients experience a reaction similar to that caused by disulfiram (Antabuse) if they drink alcohol while using glimepiride, with effects including nausea, vomiting, throbbing headache, flushing, visual disturbances, and rapid heart rate.

Resources

BOOKS

- Hillson, Rowan. *Diabetes Care: A Practical Manual*. New York: Oxford University Press, 2015.
- Saudek, Christopher G., Richard R. Rubin, and Thomas W. Donner. *The Johns Hopkins Guide to Diabetes: For Patients and Families*. 2nd ed. Baltimore, MD: Johns Hopkins University Press, 2014.

PERIODICALS

- Gudipaty, L., et al. "Effect of Exenatide, Sitagliptin, or Glimepiride on Beta-cell Secretory Capacity in Early Type 2 Diabetes." *Diabetes Care* 37, no. 9 (2014): 2451–58.
- Umayahara, R., et al. "Low-dose Glimepiride with Sitagliptin Improves Glycemic Control without Dose-Dependency in Patients with Type 2 Diabetes Inadequately Controlled on High-Dose Glimepiride." *Endocrine Journal* 61, no. 12 (2014) 1163–70.

WEBSITES

"Amaryl." <http://www.drugs.com/amaryl.html> (accessed February 10, 2015).

Medscape Reference. "Glimepiride (Rx)." <http://reference.medscape.com/drug/amaryl-glimepiride-342707> (accessed February 10, 2015).

Micromedex. "Glimepiride (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/glimepiride-oral-route/description/drg-20072155> (accessed February 10, 2015).

National Health Service (NHS). "Glimepiride." <http://www.nhs.uk/medicine-guides/pages/MedicineOverview.aspx?condition=Diabetes&medicine=glimepiride&preparationGlimepiride%201mg%20tablets> (accessed February 10, 2015).

ORGANIZATIONS

American Diabetes Association (ADA), 1701 North Beauregard Street, Alexandria, VA 22311, (800) DIABETES (342-2383), <http://www.diabetes.org/>.

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Glipizide

Definition

Glipizide and its extended-release form glipizide XL are oral drugs for controlling blood sugar levels in individuals with type 2 diabetes mellitus. Glipizide is in the sulfonylurea class of oral antidiabetic agents.

Purpose

Type 2 diabetes usually develops in adults who gradually become insulin resistant, which means that they lose the ability to respond to the hormone insulin for controlling their blood sugar (glucose) levels. It is often associated with lifestyle factors, such as being overweight or obese. Unlike type 1 diabetes, an autoimmune disorder that usually develops during childhood in which the body's immune system destroys insulin-producing beta cells in the pancreas, individuals with type 2 diabetes usually continue to produce insulin but fail to respond to it adequately. Regardless of type, the results of uncontrolled diabetes are the same—too much blood glucose (hyperglycemia) over time can lead to serious



Glipizide XL, 10 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

medical problems, including heart disease, stroke, kidney and nerve damage, blindness, and premature death.

Although some individuals with type 2 diabetes can control their blood sugar with dietary changes, exercise, and weight loss, most individuals eventually require oral diabetes drugs such as glipizide. Glipizide helps control blood sugar levels but does not cure diabetes. It cannot treat type 1 diabetes or diabetic ketoacidosis that occurs with untreated high blood sugar. Glipizide is sometimes prescribed for other purposes.

Description

Glipizide is a second-generation sulfonylurea drug that stimulates beta cells to release more insulin. Glipizide binds to and partially blocks potassium channels on beta cell membranes. This depolarizes the cell membrane, which opens calcium channels and increases insulin release.

Glipizide also helps improve insulin utilization. Sulfonylurea drugs may increase the sensitivity of insulin receptors and decrease glucose production by the liver, thereby helping to lower blood glucose. Second-generation sulfonylureas, such as glipizide, are more potent for a shorter time than first-generation sulfonylureas. Glipizide takes effect in 30 minutes, with maximum effects in 2 to 3 hours. Its bioavailability (the amount of drug utilized by the body) is essentially 100%. Glipizide lowers glycated hemoglobin (HbA1c), the average blood sugar concentration over the preceding two to three months, by about one point. Unlike some other

KEY TERMS

Cholesterol—A fat-soluble steroid alcohol (sterol) found in animal fats and oils and produced in the body from saturated fats; high blood levels of low-density lipoprotein (LDL) or “bad” cholesterol increase the risk of heart disease.

Glomerular filtration rate (GFR)—A blood test that assesses kidney function. The GFR measures the amount of blood that passes through the glomeruli, which are tiny blood vessels in the kidneys that remove waste products from the blood.

Glucose—The form of sugar that the body assimilates and utilizes.

Hemoglobin A1c (HbA1c)—Glycated hemoglobin; a stable binding of glucose to hemoglobin A in the blood, which can be used to determine the average blood glucose level for the previous two to three months.

Hyperglycemia—Abnormally high blood glucose.

Hypoglycemia—Abnormally low blood glucose.

Insulin—A protein hormone synthesized in the pancreas and secreted by beta cells of the islets of Langerhans. Insulin is required for the metabolism of carbohydrates, lipids, and proteins and regulates

blood sugar levels by facilitating the uptake of glucose into tissues, converting sugars to glycogen, fatty acids, and triglycerides and preventing release of glucose from the liver.

Insulin resistance—Reduced sensitivity to insulin by insulin-dependent processes, such as glucose uptake, resulting in lower activity of these processes and/or increased insulin production; typically occurring with prediabetes or type 2 diabetes.

Ketoacidosis—An increase in ketone bodies and reduced alkalinity of the blood and tissues, resulting in sickly sweet breath, headache, nausea, vomiting, and visual disturbances due to uncontrolled diabetes.

Sulfonylurea—A hypoglycemic compound, such as glipizide, used for oral treatment of type 2 diabetes.

Type 2 diabetes—Also known as adult-onset or non-insulin-dependent diabetes; the most common form of diabetes, most often developing in obese adults and characterized by high blood sugar (hyperglycemia) due to impaired insulin utilization, often coupled with an inability to increase insulin production.

antidiabetic agents, glipizide does not raise blood pressure or LDL (“bad”) cholesterol.

There is a variety of newer antidiabetic drugs available, but many of these do not lower blood glucose as well as older, generic drugs such as glipizide and **metformin**, and they are far more expensive. Through some pharmacy programs, a three-month supply of glipizide may cost as little as \$10. Additionally, the newer drugs may not be any safer than glipizide.

Glucotrol is available as 5 and 10 milligram (mg) oral tablets. Glucotrol XL is available as 2.5 mg, 5 mg, and 10 mg long-acting tablets. Most generic glipizides are 5 mg and 10 mg extended-release tablets. Regular tablets are generally taken one or more times per day, 30 minutes before breakfast or meals. Extended-release tablets are usually taken once a day with breakfast. The medication should be stored in the tightly closed container it came in, at room temperature, and away from excess heat and moisture (not in the bathroom).

U.S. brand names

Glipizide and glipizide XL are available in the United States in various generic formulations, as well as under the brand names Glucotrol and Glucotrol XL.

International brand names

There are many international brand names for glipizide and glipizide XL. Minidiab is the most common brand name; others include:

- Glibenese
- Glizide
- Glix
- Glucotrol and Glucotrol XL
- Melizide

Origins

Sulfonylureas have been used to treat type 2 diabetes since the 1950s, although chlorpropamide is the only first-generation sulfonylurea that is still in use. Glipizide first became available in 1984. Glipizide and other second-generation sulfonylureas (**glyburide** and **glimepiride**) require smaller doses than the first-generation drugs. Although all sulfonylureas have similar effects on blood sugar levels, they differ in their frequency of use, side effects, and interactions with other drugs.

Recommended dosage

Glipizide is usually initiated at a low dose and gradually increased if needed. After some time, glipizide may become less effective, and dosages may require adjustment. Daily doses above 15 mg are divided into two doses every 12 hours. Additional dosing recommendations include:

- The dosage for immediate-release (regular) tablets is started at 5 mg once daily, increased by 2.5–5 mg every several days based on blood glucose measurements. The maintenance range is 2.5–20 mg once daily or every 12 hours, for a maximum dose of 40 mg per day.
- The dosage for extended-release tablets is started at 5 mg once daily with breakfast, with adjustments based on blood glucose no more often than every seven days. The maintenance range is 5–10 mg once daily, with a maximum of 20 mg per day.
- When switching from regular to extended-release tablets, the nearest daily-dose equivalent or 5 mg is taken once daily, with adjustments as needed.
- When switching to glipizide from long half-life (long-lasting) sulfonylurea, careful observation is needed for one to two weeks because of the potential for hypoglycemia.
- When switching to glipizide from insulin therapy, the recommended dose is substituted for fewer than 20 units of insulin. For greater than 20 units of insulin, the recommended glipizide dose is initiated along with 50% of the insulin dose, with a gradual decrease in insulin depending on response.

Extended-release tablets must be swallowed whole, not chewed, divided, or crushed. Doctors should provide specific instructions for a missed dose, but in general, the dose should be taken as soon as possible unless it is almost time for the next dose. In this case, the missed dose should be skipped, and the regular dosing schedule resumed.

Geriatric

Elderly patients should be started at 2.5 mg once daily, with an increase of 2.5–5 mg per day every one to two weeks, depending on blood glucose responses measured every few days. Patients may be switched to once-daily extended-release tablets at the closest total daily-dose equivalent or lower end of the recommended range, for a maximum of 20 mg per day. Elderly patients are particularly susceptible to hypoglycemia from glucose-lowering drugs, and recognizing hypoglycemia in the elderly can be difficult; thus, initial and maintenance dosing should be conservative. Monitoring for cardiovascular disease indicators, such as blood

pressure and cholesterol levels, may be more important than tight glycemic control.

Other conditions and allergies

Patients with liver impairment should be started at 2.5 mg of immediate-release tablets once daily, since extended-release glipizide has not been studied with hepatic impairment.

Glipizide has not been studied with kidney impairment, but a dosage decrease of 50% has been suggested for patients with a glomerular filtration rate of less than 50 milliliters (mL) per minute.

Extended-release glipizide should not be used by patients with severe gastrointestinal narrowing causing esophageal dysmotility.

Precautions

Patients should discuss glipizide risks with their physician. Precautions include:

- Blood and urine sugar levels should be checked regularly to monitor responses to glipizide. Other lab tests, including HbA1c, may be ordered.
- Glipizide can cause sun sensitivity. Patients should avoid unnecessary or prolonged sun exposure and wear protective clothing, sunglasses, and sunscreen.
- Patients should consult their doctor if they become ill or injured, develop an infection or fever, or experience unusual stress. These conditions can affect blood sugar and required glipizide dosages and may put patients at risk of severe hypoglycemia.
- The empty tablet shell from extended-release tablets may be visible in stool; this does not indicate that the drug was not absorbed.
- Patients should tell their doctors and dentists that they take glipizide before undergoing any type of surgical procedure.
- Patients should not stop taking glipizide without consulting their doctor.
- Symptoms of glipizide overdose can include hypoglycemia, seizures, and loss of consciousness.
- Patients should always wear a diabetic identification bracelet in case of emergency.

Pediatric

The safety and effectiveness of glipizide have not been established in pediatric patients.

Geriatric

Elderly patients taking glipizide may be at risk for severe hypoglycemia.

Pregnant or breastfeeding

Glipizide carries the FDA pregnancy category C, which means that the drug has been shown to harm the fetus in animal studies but that no data from human studies are available. It should be used with caution in pregnant women only if benefits outweigh potential risks. Although it is not known whether glipizide passes into breast milk, breastfeeding is not recommended while taking this drug.

Other conditions and allergies

Patients should tell their doctor and pharmacist if they are allergic to glipizide, any glipizide ingredients, or any other medications. Individuals allergic to other sulfonamide derivatives or sulfa drugs may have an allergic reaction to glipizide. In addition:

- Patients with type 1 diabetes or diabetic ketoacidosis with or without coma should not take glipizide.
- Patients who are debilitated, malnourished, or with adrenal or pituitary insufficiency are at risk for severe hypoglycemia from glipizide.
- Hypoglycemia may be difficult to recognize in patients with autonomic neuropathy.
- Patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency (an inherited condition that causes premature destruction of red blood cells) are at risk for hemolytic anemia when treated with sulfonylurea agents.
- Patients should tell their doctor if they have or have ever had hormone disorders of the adrenal, pituitary, or thyroid glands or heart, kidney, or liver disease.
- Patients taking extended-release glipizide should tell their doctor if they have short bowel syndrome due to surgery, disease, or a congenital disorder; intestinal narrowing or blockage; or ongoing diarrhea.

Side effects

All oral diabetes drugs carry side effects that include hypoglycemia, weight gain, nausea, and swelling of the legs and ankles (edema). There is a higher risk of hypoglycemia with glipizide than with some other diabetes drugs. Sulfonylureas generally cause a weight gain of 5–10 lb. (2–5 kg). Patients should notify their doctor if any of the following symptoms are severe or persistent:

- diarrhea
- gas
- jitters
- dizziness
- uncontrollable shaking of a body part

- red or itchy skin
- rash
- hives
- blisters

The doctor should be contacted immediately in case of any of the following symptoms:

- yellowing of the skin or eyes
- light-colored stools
- dark urine
- pain in the upper-right stomach
- unusual bruising or bleeding
- fever
- sore throat

Interactions

It is very important that the doctor and pharmacist be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used or planning to be used by the patient, as well as any medications that the patient stops using while taking glipizide. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

Drugs that may interact with glipizide include:

- anticoagulants such as **warfarin**
- **aspirin** and other nonsteroidal anti-inflammatory medications (NSAIDs) such as **ibuprofen** and naproxen
- beta-blockers such as **atenolol**, labetalol, **metoprolol**, nadolol, and **propranolol**
- calcium channel blockers such as **amlodipine**, **diltiazem**, felodipine, isradipine, nicardipine, **nifedipine**, nimodipine, nisoldipine, and verapamil
- chloramphenicol
- cimetidine
- diuretics
- **fluconazole**
- hormone replacement therapy and hormonal contraceptives including birth control pills, patches, rings, implants, and injections
- insulin or other medications to treat high blood sugar or diabetes
- isoniazid
- monoamine oxidase inhibitors (MAOIs) such as isocarboxazid, phenelzine, selegiline, and tranylcypromine
- asthma and cold medications

- medications for mental illness and nausea
- miconazole
- oral steroids such as dexamethasone, **methylprednisolone**, and **prednisone**
- **phenytoin**
- probenecid
- salicylate pain relievers such as choline magnesium trisalicylate, choline salicylate, diflunisal, magnesium salicylate, and salsalate
- sulfa antibiotics such as co-trimoxazole
- **sulfasalazine**
- thyroid medications

Herbs and supplements

Glipizide may interact with niacin.

Food and other substances

Patients should talk to their doctor about the safe use of alcohol while taking glipizide. Alcohol may worsen glipizide side effects and, rarely, cause symptoms such as flushing, headache, nausea, vomiting, chest pain, weakness, blurred vision, mental confusion, sweating, choking, breathing difficulty, and anxiety.

Resources

PERIODICALS

- Boyko, Edward J. "Observational Research—Opportunities and Limitations." *Journal of Diabetes and its Complications* 27, no. 6 (2013): 642–48.
- Parekh, Trisha M., et al. "Hypoglycemia after Antimicrobial Drug Prescription for Older Patients Using Sulfonylureas." *Archives of Internal Medicine* 174, no. 10 (2014): 1605–12.
- Pratley, Richard E., Simon R. Heller, and Mary Alice Miller. "Treatment of Type 2 Diabetes Mellitus in the Older Adult: A Review." *Endocrine Practice* 20, no. 7 (2014): 722–36.
- Zhang, Yifei, et al. "Lipid Profiling Reveals Different Therapeutic Effects of Metformin and Glipizide in Patients with Type 2 Diabetes and Coronary Artery Disease." *Diabetes Care* 37, no. 10 (2014): 2804–12.

WEBSITES

- American Diabetes Association. "What Are My Options?" Diabetes.org. <http://www.diabetes.org/living-with-diabetes/treatment-and-care/medication/oral-medications/what-are-my-options.html> (accessed February 10, 2015).
- "Choosing Drugs: Oral Diabetes Drugs." *Consumer Reports*. <http://www.consumerreports.org/health/resources/pdf/best-buy-drugs/Diabetes-2pager-March2009.pdf> (accessed February 10, 2015).
- Humphries, Andrea, et al. "Medicines for Type 2 Diabetes: A Review of the Research for Adults." Effective Health Care

Program, Agency for Healthcare Research and Quality. <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=721> (accessed February 10, 2015).

MedlinePlus. "Glipizide." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a684060.html> (accessed February 10, 2015).

Medscape Reference. "Glipizide (Rx)." <http://reference.medscape.com/drug/glucotrol-glipizide-342708> (accessed February 10, 2015).

U.S. Food and Drug Administration. "Women and Diabetes—Diabetes Medicines." FDA.gov. <http://www.fda.gov/ForConsumers/ByAudience/ForWomen/WomensHealthTopics/ucm216110.htm> (accessed February 10, 2015).

ORGANIZATIONS

Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, (301) 427-1364, <http://www.ahrq.gov/>.

American Diabetes Association, 1701 North Beauregard Street, Alexandria, VA 22311, (800) DIABETES (342-2383), <http://www.diabetes.org/>.

National Institute of Diabetes and Digestive and Kidney Diseases, 9000 Rockville Pike, Bethesda, MD 20892-2560, (301) 496-3583, <http://www.niddk.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Glucophage see **Metformin**

Glucotrol see **Glipizide**

Glyburide

Definition

Glyburide is a prescription drug that helps lower blood sugar (glucose) levels in individuals with type 2 diabetes. It is a white, crystalline compound that belongs to a class of antidiabetic drugs called sulfonylureas.

Purpose

Glyburide is used to treat type 2 diabetes. It is never used to treat type 1 diabetes. Glyburide works by increasing the amount of insulin that the pancreas produces and helping insulin-resistant cells use glucose more effectively. This drug is most effective in conjunction with lifestyle changes such as controlling diet,



Glyburide, 5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

engaging in regular exercise, and quitting smoking. Sometimes it is taken with other diabetes-regulating drugs, such as **metformin** (Glucophage).

Glyburide does not cure diabetes, but if taken correctly, it can help reduce the level of glucose circulating in the blood. High blood glucose levels can be life-threatening. Complications from too much blood glucose include an increased risk of heart disease, stroke, kidney damage, nerve damage to the limbs, vision loss, reduced sexual performance, and gum disease.

Description

Glyburide tablets are available in strengths of 1.25, 2.5, and 5 milligrams (mg). Glynase PresTab contains micronized particles of the drug. The particles have a diameter in nanometers, which changes the way they dissolve in the body. Available strengths of micronized tablets are 1.5 mg, 3 mg, and 6 mg.

U.S. brand names

Glyburide is sold in the United States under the brand names Micronase and DiaBeta, and it is also available as a generic drug.

Canadian brand names

Glyburide is sold in Canada under the brand names Apo-Glyburide, Diabeta, Gen-Glybe, Novo-Glyburide, Nu-Glyburide, PMS-Glyburide, ratio-Glyburide, and Sandoz Glyburide. It is also sold as a generic drug.

International brand names

Internationally, glyburide is produced by many pharmaceutical manufacturers. In addition to being sold as a generic drug, it is sold under more than two dozen different brand names. Some of these include Glibenclamide (United Kingdom, France, Japan, Italy), Antiglucon and Diabitin (Taiwan), Benclamid and Broi (Argentina), Benglycom and Diabitor (Philippines), Daonil (many countries), and Gilbenclamid (Germany and many other countries).

Glyburide is also sold in pill form in combination with metformin, another diabetes drug, under a variety of names.

Origins

Glyburide was approved by the U.S. Food and Drug Administration (FDA) in May 1984.

Recommended dosage

When starting glyburide, the usual recommended dosage is 2.5–5 mg of regular tablets or 1.5–3 mg of micronized tablets taken at breakfast. The maintenance dose is between 1.25 mg and 20 mg of regular tablets or 0.75 to 12 mg of micronized tablets. Maintenance doses are taken either once daily or at 12-hour intervals depending on the individual's dosage, lifestyle, and response to medication. The maximum allowable dose is 20 mg of regular tablets or 12 mg of micronized tablets daily.

Pediatric

No data is available about safe and appropriate dosages for children.

Geriatric

The elderly are particularly susceptible to developing hypoglycemia and should be dosed conservatively.

Precautions

In a well-controlled study of glucose-lowering drugs, patients who took another drug in the sulfonylurea class (tolbutamide) for five to eight years were 2.5 times more likely to die from cardiovascular complications than individuals who were treated with dietary changes alone or dietary changes plus insulin. Although glyburide was not specifically studied, a warning regarding this risk has been issued for all antidiabetic drugs in this class.

Additional precautions include:

- Glyburide should not be used to treat individuals with type 1 diabetes.

KEY TERMS

Hypoglycemia—An abnormally low level of glucose (sugar) in the blood.

Insulin—A hormone made by the pancreas that controls blood glucose (sugar) levels by moving excess glucose into muscle, liver, and other cells for storage.

Insulin resistance—A condition in which the cells of the body do not respond to insulin to the degree they normally should. This creates a condition in which more and more insulin must be used to control glucose levels in the blood.

Type 1 diabetes—A chronic immune system disorder in which the pancreas does not produce sufficient amounts of insulin, a hormone that enables cells to use glucose for energy. Also called juvenile diabetes, it must be treated with insulin injections.

Type 2 diabetes—In this form of diabetes, the pancreas either does not make enough insulin or cells become insulin resistant and do not use insulin efficiently. Formerly called adult-onset diabetes.

- Individuals switching between regular and micronized tablets will need to have their blood glucose levels retested, as these forms of the drug act differently in the body.
- Response to glyburide can diminish over time, so dosage adjustments may be necessary.
- Glyburide can make individuals more susceptible to sunburn. People taking this drug should keep their bodies covered when possible and use sunscreen with an SPF of 30 or greater.

Geriatric

This drug can cause hypoglycemia in any individual, but elderly, malnourished, or debilitated individuals are at especially high risk.

Pregnant or breastfeeding

Glyburide carries the FDA pregnancy category B. This means that animal studies indicate no fetal risk, but there is not enough human data. It has been studied to see if it is safe to use during pregnancy to treat gestational diabetes, but additional research is needed. It is not known whether glyburide passes into breast milk. However, other drugs in the sulfonylurea class do pass

into breast milk and have been shown to cause prolonged low blood sugar (hypoglycemia) in nursing infants, so this drug should be used with extreme caution while breastfeeding. Women who become pregnant while taking glyburide should call their healthcare provider immediately to discuss their options.

Other conditions and allergies

It is particularly important to tell the healthcare provider about any allergy to sulfa or sulfa drugs before starting this drug.

Individuals with pituitary or adrenal insufficiency are at higher-than-average risk for developing hypoglycemia.

Individuals with glucose 6-phosphate dehydrogenase (G6PD) deficiency may develop hemolytic anemia when treated with glyburide or any other drug in this class.

Individuals with liver or kidney impairment are at higher risk of developing hypoglycemia, as the drug is not cleared from their body as rapidly as with normal functioning. In addition, response to glyburide may change in individuals who develop a fever or who are highly stressed.

Side effects

An allergic reaction to glyburide is a medical emergency. Signs of an allergic reaction include hives or swelling on the face or body and difficulty breathing. Get immediate medical help if these signs develop.

Individuals who experience any of the following side effects should stop taking glyburide and call their healthcare provider promptly:

- excessive bleeding or unusual bruising
- yellowing of the skin or eyes (jaundice)
- clay-colored stools
- dark-colored urine
- upper stomach pain
- confusion, slurred speech, or lack of coordination
- vomiting or diarrhea
- severe weakness

Common but less serious side effects include:

- nausea, upset stomach
- muscle or joint pain
- blurred vision
- light skin rash or redness

Some side effects are temporary and will disappear as the body becomes used to the drug. However, any

change in health status or unusual problems, sensations, or pains should be reported to a healthcare provider.

Interactions

Glyburide is known to interact with various drugs and with alcohol. Before beginning treatment with glyburide, patients should tell their healthcare provider about all over-the-counter and prescription drugs they take, as well as any medicinal herbs or dietary supplements.

Drugs

Glyburide interacts with bosentan (Tracleer) in a way that decreases the effectiveness of both drugs and increases the chance for liver damage. Bosentan should not be taken by individuals taking glyburide.

Glyburide interacts with gatifloxacin (Tequin) and can result in either hypoglycemia or hyperglycemia. Gatifloxacin should not be taken by individuals taking glyburide.

Glyburide is reported to interact with more than 875 drugs. This makes it especially important for patients to review all of their medications, including nonprescription drugs, with their physician and pharmacist before starting this drug. Classes of drugs that interact with glyburide include:

- angiotensin-converting enzyme (ACE) inhibitors
- cold and allergy medicines containing pseudoephedrine
- **aspirin** and nonsteroidal anti-inflammatory medications (NSAIDs) such as **ibuprofen** (Advil, Motrin) and naproxen (Aleve)
- beta-blockers
- calcium channel blockers
- steroid drugs
- anticoagulant drugs such as **warfarin** (Coumadin)
- diuretics
- hormonal birth control (pills, patches, implants)
- monoamine oxidase inhibitors (MAOIs)
- some drugs used to treat mental disorders
- quinolone and fluoroquinolone antibiotics
- sulfa antibiotics

This is not a complete list. Because so many drugs interact with glyburide, it is essential to check with a pharmacist for the most complete and up-to-date information before starting to take this drug.

Food and other substances

Glyburide interacts with alcohol. Drinking alcohol while taking this drug can result in increased side effects.

Resources

BOOKS

Mazze, Roger S., et al. *Staged Diabetes Management*. 3rd ed. Hoboken, NJ: John Wiley, 2012.

PERIODICALS

Zeng, Y. C., et al. "The Use of Glyburide in the Management of Gestational Diabetes Mellitus: A Meta-Analysis." *Advances in Medical Science* 59, no. 1 (2014): 95–101.

WEBSITES

"Glyburide." Drugs.com. <http://www.drugs.com/glyburide.html> (accessed February 11, 2015).

Healthwise. "Glyburide." University of Michigan Health System. <http://www.uofmhealth.org/health-library/d00248a1> (accessed February 11, 2015).

MedlinePlus. "Glyburide." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a684058.html> (accessed February 11, 2015).

ORGANIZATIONS

American Diabetes Association, 1701 North Beauregard Street, Alexandria, VA 22311, (800) DIABETES (342-2383), askADA@diabetes.org, <http://www.diabetes.org/>.

International Diabetes Federation, 166 Chaussee de La Hulpe, B-1170 Brussels, Belgium, +32 2 538 55 11, Fax: +32 2 538 51 14, info@idf.org, <http://www.idf.org/>.

National Diabetes Education Program, One Diabetes Way, Bethesda, MD 20814-9692, (301) 496-3583, <http://www.ndep.nih.gov/>.

National Diabetes Information Clearinghouse (NDIC), 1 Information Way, Bethesda, MD 20892-3560, Fax: (703) 738-4929, (800) 860-8747, ndic@info.niddk.nih.gov, <http://diabetes.niddk.nih.gov/>.

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Grifulvin V see **Griseofulvin**

Griseofulvin

Definition

Griseofulvin is an oral, systemic antifungal agent used to treat tinea infections—collectively called ringworm—that affect the skin, hair and beard, scalp, or nails. Griseofulvin is in a drug class called miscellaneous antifungal agents.



Griseofulvin (Gris-PEG), 250 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Griseofulvin is a safe, effective, and low-cost drug used for treating skin infections. It is the drug of choice for treating tinea capitis, a contagious scalp infection caused by fungi in the genera *Trichophyton* and *Microsporum* that causes scaly patches penetrated by a few dry brittle hairs. Tinea capitis requires systemic (body-wide) treatment, because the drug must penetrate the hair follicles. Griseofulvin is also the drug of choice for onychomycosis (tinea unguium), a fungal infection of the fingernail or toenail bed. Onychomycosis often follows a fungal infection of the foot and cannot usually be effectively treated with over-the-counter (nonprescription) creams and ointments. Griseofulvin is also used to treat:

- tinea barbae or “barber’s itch,” which is ringworm of the face and neck
- tinea corporis, a fungal skin infection that causes red, scaly rashes
- tinea cruris or “jock itch,” a fungal skin infection of the groin or buttocks
- tinea pedis or “athlete’s foot,” a fungal infection of the skin on the feet and between the toes
- other dermatophytoses or parasitic fungi infections of the skin, nails, or hair

Griseofulvin sometimes may be prescribed for other purposes.

Description

Griseofulvin is a fungistatic agent that inhibits the growth of fungi that live on dead tissues of the hair, nails, and outer layers of skin and that grow in warm, moist areas of the body. The drug is deposited preferentially in infected skin, where it binds tightly to newly formed keratin—proteins of the hair and nails that are produced by cells called keratinocytes. The binding of griseofulvin to keratin makes the keratinocytes highly resistant to fungal invasion. Eventually the infected cells are sloughed off and replaced by healthy cells.

U.S. brand names

The U.S. brand names for griseofulvin are Grifulvin V, Gris-PEG, and Fulvicin. There are also various generic forms of griseofulvin.

Canadian brand names

Canadian brand names for griseofulvin include Fulvicin U/V.

International brand names

There are many international brand names for griseofulvin. Fulcin and Grisovin are among the common brand names. Griseofulvin may not be approved for human use in all countries.

Origins

Gris-PEG ultramicrosize 125 and 250 milligram (mg) oral tablets were approved by the U.S. Food and Drug Administration (FDA) in 1975. Various generic griseofulvin microsize and ultramicrosize tablets have received FDA approval since then, including 500 mg microsize oral tablets and capsules and 125 mg/mL oral suspensions.

Recommended dosage

Griseofulvin is available as microsize and ultramicrosize oral tablets. These are not interchangeable, because the ultramicrosize dosages are smaller than the microsize dosages. Liquid suspensions should be well shaken before each use to mix them evenly. Griseofulvin should be kept tightly closed in its original container, away from excess heat and moisture (not in the bathroom). The liquid suspension should be protected from light.

Griseofulvin is taken by mouth, usually once per day, although it may be taken two to four times per day. Recommended adult dosages for tinea capitis, tinea corporis, and tinea cruris are 500 mg per day of microsize griseofulvin or 375 mg per day of the ultramicrosize. An

KEY TERMS

Dermatophytoses—Diseases of the skin, hair, or nails caused by parasitic fungi.

Jaundice—Yellowing of the eyes and skin due to the accumulation in the blood of a heme breakdown product; an indication of liver dysfunction.

Keratin—Fibrous proteins that form the basis of tissues such as hair and nails.

Onychomycosis—Tinea unguium; a fungal disease of the fingernails or toenails.

Ringworm—Any of several contagious fungal diseases of the skin, hair, or nails characterized by ring-shaped patches.

Tinea barbae—Ringworm of the face and neck, also known as “barber’s itch.”

Tinea capitis—A contagious fungal infection (ringworm) of the scalp.

Tinea corporis—A fungal infection (ringworm) of the skin.

Tinea cruris—A fungal infection of the groin and perineum; also known as “jock itch.”

Tinea pedis—Ringworm of the feet; also known as “athlete’s foot.”

alternate dose for the ultramicrosize is 20 mg per kilogram (kg, or 2.2 lb.) of body weight once per day. For tinea pedis and onychomycosis, the recommended dosages are 1,000 mg per day as a single dose or 500 mg every 12 hours of the microsize, or 250 mg every 8 hours of the ultramicrosize.

Treatment duration depends on the site of infection:

- skin infections (tinea corporis): 2–4 weeks
- hair and scalp infections (tinea capitis): typically 4–6 weeks, possibly up to 12
- foot infections (tinea pedis): 4–8 weeks
- fingernail infections: 3–4 months
- toenail infections: 6 months

A missed dose should be taken as soon as possible unless it is almost time for the next dose. In this case, the missed dose should be skipped and the regular dosing schedule resumed.

Pediatric

Recommended microsize dosages for tinea infections in children over two years of age are:

- 11 mg/kg/day as a single dose or divided into half doses every 12 hours
- 125–250 mg per day for children weighing 13.6–22.7 kg (30–50 lb.)
- 250–500 mg per day for children weighing more than 22.7 kg (50 lb.)

Recommended ultramicrosize dosages are:

- 7.3 mg/kg/day
- 82.5–165 mg per day for children weighing 13.6–22.7 kg (30–50 lb.)
- 165–330 mg per day for children weighing more than 22.7 kg (50 lb.)

Precautions

Once patients start taking griseofulvin, symptoms often begin to improve very rapidly; however, it is important to continue taking the medication for as long as prescribed to ensure that the infection is completely cleared. Patients should call their doctor if they continue to have symptoms after the griseofulvin course is completed. Lab tests will be ordered to determine the patient’s response to griseofulvin.

Griseofulvin may make the skin sensitive to sunlight. It is important to avoid unnecessary and prolonged sun exposure, wear protective clothing and sunglasses, and use sunscreen. Severe skin reactions and skin diseases have been reported with griseofulvin use. Some of these reactions have resulted in hospitalizations or death. The drug should be stopped immediately if severe skin reactions occur.

Liver function problems used to be associated with griseofulvin use, but recent findings have suggested that they are apparently not as significant as once thought. Nevertheless, patients should tell their doctor if they drink alcohol and should undergo liver function tests if treatment lasts more than one month. The drug should be discontinued if jaundice (yellowing of the skin and eyes) occurs, as this could indicate liver problems.

Pediatric

The safety and effectiveness of griseofulvin have not been established in children younger than two years.

Pregnant or breastfeeding

Griseofulvin is in the FDA pregnancy category C, which means it should be avoided during pregnancy unless the benefits outweigh the risks. Although there have been no adequate studies in pregnant women, animal studies have shown griseofulvin to be toxic to embryos and to cause birth defects in laboratory animals.

Although it is not known whether griseofulvin is excreted in human milk, it should not be used by nursing mothers because it has a potential for causing tumors.

Other conditions and allergies

Patients should tell their doctor and pharmacist if they are allergic to griseofulvin or any other medications. Patients should tell their doctor if they have a history of alcohol abuse or have ever had liver disease or lupus (an autoimmune disease). Patients with liver failure or porphyria (a usually hereditary abnormality of porphyrin metabolism) should not take griseofulvin.

Side effects

The most common side effects of griseofulvin are rash and hives (urticaria). Other possible side effects include:

- headache
- fatigue
- dizziness
- insomnia
- mental confusion
- light sensitivity
- nausea
- vomiting
- stomach discomfort
- diarrhea
- gastrointestinal bleeding
- low white blood cell count (leukopenia)
- liver toxicity
- excess protein in the urine
- nephrosis (kidney disease)
- oral thrush (a yeast infection of the mouth)

Rare side effects of griseofulvin include:

- allergic skin disease (angioedema)
- lupus-like syndrome
- menstrual irregularities
- tingling, prickling, or creeping sensation of the skin (paresthesia)

The healthcare provider should be consulted if any of the following symptoms are severe or persistent:

- headache
- upset stomach
- vomiting
- diarrhea or loose stools
- thirst
- fatigue

- dizziness
- faintness

If any of the following symptoms occur, the healthcare provider should be called immediately:

- fever
- sore throat
- skin rash
- mouth soreness or irritation

Interactions

To avoid drug interactions, the doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

Patients should be sure to tell their doctor and pharmacist if they are taking **oral contraceptives**, **cyclosporine**, phenobarbital, or anticoagulants ("blood thinners") such as **warfarin** (Coumadin). Serious or life-threatening drug interactions that require using alternative medications may occur with:

- astemizole
- cisapride
- dihydroergotamine
- dihydroergotamine intranasal
- dronedarone
- ergotamine
- **erythromycin**
- erythromycin ethylsuccinate
- erythromycin lactobionate
- erythromycin stearate
- ethinyl estradiol
- everolimus
- ivabradine
- **lovastatin**
- ranolazine
- sertindole
- silodosin
- **simvastatin**
- sirolimus
- terfenadine
- tolvaptan
- ulipristal

Griseofulvin has significant interactions that require close monitoring if taken in combination with more than 100 other drugs, so patients should be sure to consult with their healthcare provider and pharmacist regarding all other medications they are taking.

Herbs and supplements

Griseofulvin may interact with vitamin supplements. Patients should tell the treating physician if they are taking any herbal or dietary supplements, including vitamins.

Food and other substances

Griseofulvin absorption is increased if taken with high-fat meals; this is recommended for optimal effectiveness.

Resources

PERIODICALS

Feinberg, Arthur N., et al. "Pediatric Dermatologic Disorders." *Journal of Alternative Medicine Research* 6, no. 2 (2014): 95–137.

WEBSITES

A.D.A.M., Inc. "Fungal Nail Infection." MedlinePlus. <http://www.nlm.nih.gov/medlineplus/ency/article/001330.htm> (accessed January 24, 2015).

A.D.A.M., Inc. "Tinea Capitis." MedlinePlus. <http://www.nlm.nih.gov/medlineplus/ency/article/000878.htm> (accessed January 24, 2015).

AHFS Consumer Medication Information. "Griseofulvin." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682295.html> (accessed January 24, 2015).

Micromedex. "Griseofulvin (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/griseofulvin-oral-route/description/drg-20064116> (accessed January 24, 2015).

ORGANIZATIONS

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, 888-INFO-FDA (463-6332), <http://www.fda.gov/>.

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brain function and has an effect on blood pressure, mood, concentration, and impulse control. Guanfacine helps regulate norepinephrine levels in the body and is used in treating high blood pressure, attention deficit hyperactivity disorder (ADHD), and anxiety.

Purpose

Guanfacine is used to treat some of the symptoms of ADHD and anxiety, although it is not one of the main drugs used to treat anxiety. It works by regulating actions of the sympathetic nervous system, resulting in decreased blood pressure, reduced anxiety, improved concentration, and control of impulsive behavior and other stressful emotions present with both anxiety and ADHD.

Description

Guanfacine affects the natural body chemical norepinephrine. Norepinephrine is a type of neurotransmitter in the nervous system, a chemical necessary for normal brain and body functioning. Neurotransmitters bind to chemical receptors on the surface of neurons (brain cells) and blood vessels. Once bound to a receptor, they affect physiological processes. Neurotransmitter signaling pathways are responsible for many regulatory processes, including blood pressure and neuronal signaling that affects mood, concentration, and impulse control. Drugs such as guanfacine block the receptors for norepinephrine, resulting in more of the chemical left in the brain. This affects areas of the brain involving



Guanfacine, 1 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Guanfacine

Definition

Guanfacine is a medication that inhibits the neurological signaling chemical norepinephrine. Norepinephrine is a type of neurotransmitter involved in normal

judgment, response to external stimuli, emotional responses, mental focus, sleep, and impulse control.

U.S. brand names

Guanfacine is sold under the brand name Tenex for treating high blood pressure and Intuniv for treating ADHD.

Recommended dosage

Guanfacine is given in pill form, and doses are taken at bedtime. The dose chosen depends on the disorder being treated, the patient's age, individual patient response to the medication regarding its effectiveness, and individual patient response to the medication regarding side effects. The dose of guanfacine in adults for treating high blood pressure or anxiety is 1–3 milligrams (mg) taken once per day (as needed) to control symptoms. Patients are dosed at the lowest possible effective dose to avoid the development of adverse side effects. Slowly increasing the dose over time helps with minimizing side effects.

Pediatric

Guanfacine used in children for ADHD is dosed based on weight, and the dose is gradually increased over time. For example, children who weigh between 60 and 90 lb. (27–40.5 kg) are usually started at a dose of 0.5 mg at bedtime. The dose is increased by 0.5 mg per week, up to 1.5 mg per day if needed. If higher doses are required for improvement, after two weeks at the 1.5 mg-per-day dosing, the dose is increased to 2 mg per day. Doses are lowered if side effects become intolerable.

Precautions

When a patient discontinues the use of guanfacine, the dose needs to be tapered down slowly. If guanfacine is abruptly discontinued, there may be side effects such as rebound high blood pressure and anxiety. Rare but serious side effects of guanfacine may include sudden loss of consciousness or abnormally low heart rate. Kidney and liver function as well as blood pressure may be monitored while taking guanfacine.

Geriatric

Guanfacine should be used with caution in elderly patients, who are more likely to have coexisting health conditions.

Pregnant or breastfeeding

Guanfacine is classified as category B for pregnancy. This means that either the drug has not been

studied in humans but animal studies have found no evidence of fetal risk, or adverse effects to a fetus have occurred in animal studies but not in well-controlled human studies. The safety of guanfacine use during breastfeeding is unknown, and so its use is not recommended.

Other conditions and allergies

Guanfacine may not be appropriate for use or may require caution in patients with kidney or liver dysfunction, some types of heart disease, or recent heart attack.

Side effects

Sensitivity to guanfacine varies among patients, and some patients may find that lower doses are more than their body system can tolerate. Common side effects of guanfacine are dry mouth, drowsiness, dizziness, constipation, fatigue, weakness, headache, and sexual dysfunction. Side effects of abrupt discontinuation of guanfacine include anxiety, restlessness, and increased blood pressure.

Interactions

Patients should make their doctor aware of all medications and supplements they are taking before using guanfacine.

Drugs

Drugs that affect the liver, including the antidepressant mirtazapine, may affect the metabolism of guanfacine, resulting in too much or too little of the drug in the body. This could lead to increased side effects or even toxic doses. Likewise, guanfacine may affect the metabolism of other drugs, leading to greater or lower doses than therapeutically desired.

Guanfacine should not be used at the same time as antidepressants called monoamine oxidase inhibitors (MAOIs). Use of these medications in the same time period may cause a high blood pressure crisis, which can be severe and life-threatening. Switching between drug treatment with an MAOI to guanfacine may require a waiting period of up to several weeks between drugs. Other drugs that cannot be combined with guanfacine due to risk of high blood pressure include the antibiotic **linezolid**.

Some medications interact with guanfacine to cause additive adverse effects of abnormally low blood pressure, such as the muscle relaxant **tizanidine**. Sedative drugs also should not be used with guanfacine due to additive effects.

KEY TERMS

Attention deficit hyperactivity disorder (ADHD)—A condition characterized by lack of concentration, impulsive or inappropriate behavior (relative to age level), and hyperactivity.

Monoamine oxidase inhibitors (MAOIs)—A group of antidepressant drugs that decrease the activity of monoamine oxidase, a neurotransmitter found in the brain that affects mood.

Neurotransmitter—A chemical messenger that travels through the body and acts in the nervous system. Neurotransmitter signaling is responsible for a wide range of bodily processes and is often the target of medications involving the brain and cardiovascular system.

Neurotransmitter receptor—A physical recipient for chemicals called neurotransmitters. Receptors sit on the surface of cells that make up body tissues, and once bound to the neurotransmitter, they initiate the chemical signaling pathway associated with neurotransmitters.

Norepinephrine—A type of neurotransmitter involved in regulation of concentration, impulse control, judgment, mood, attention span, psychostimulation, and disease states such as ADHD and depression.

Sympathetic nervous system—Part of the nervous system that increases heart rate and blood pressure, sweating, pupil dilation, and mental stress arousal.

Blood pressure medications such as **atenolol** have antagonistic, or opposing, effects with guanfacine and should not be used in the same time period.

Herbs and supplements

Guanfacine should not be used with the herbal supplement yohimbe, as the combination may decrease the efficacy of guanfacine.

Food and other substances

Using alcohol while taking guanfacine may create toxic reactions in the body and should be avoided.

Resources

BOOKS

Brunton, Laurence, et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill Medical, 2011.

Zorumski, Charles F., and Eugene H. Rubin. *Psychiatry and Clinical Neuroscience: A Primer*. New York: Oxford University Press, 2011.

PERIODICALS

Bernknopf, Allison. "Guanfacine (Intuniv) for Attention-Deficit/Hyperactivity Disorder." *American Family Physician* 15, no. 83 (2011): 468–75.

Connor, D. F., et al. "Effects of Guanfacine Extended Release on Oppositional Symptoms in Children Aged 6–12 Years with Attention-Deficit Hyperactivity Disorder and Oppositional Symptoms: A Randomized, Double-Blind, Placebo-Controlled Trial." *CNS Drugs* 24, no. 9 (2010): 755–68.

OTHER

Children's Hospital of Minnesota. "Guanfacine (Tenex® Intuniv®)." <http://www.childrensmn.org/Manuals/PFS/Med/018876.pdf> (accessed February 25, 2015).

WEBSITES

Micromedex. "Guanfacine (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/guanfacine-oral-route/description/drg-20064131> (accessed February 25, 2015).

Stanford School of Medicine. "Guanfacine." <http://whatmeds.stanford.edu/medications/guanfacine.html> (accessed February 25, 2015).

ORGANIZATIONS

American Academy of Child and Adolescent Psychiatry, 3615 Wisconsin Avenue NW, Washington, DC 20016-3007, (202) 966-7300, Fax: (202) 966-2891, <http://aacap.org/>.

Children and Adults with Attention-Deficit/Hyperactivity Disorder, 4601 Presidents Drive, Suite 300, Lanham, MD 20706, (301) 306-7070, (800) 233-4050, Fax: (301) 306-7090, <http://www.chadd.org/>.

Mental Health America, 2000 N. Beauregard Street, 6th Floor, Alexandria, VA 22311, (703) 684-7722, (800) 969-6642, Fax: (703) 684-5968, <http://www1.nmha.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Maria Eve Basile, PhD

REVIEWED BY JAMES E. WAUN, MD, RPH



Halcion see **Triazolam**

Haldol see **Haloperidol**

Haloperidol

Definition

Haloperidol is a major tranquilizer. It is used to treat psychoses, symptoms of dementia, Tourette syndrome, and certain serious behavioral disorders in children.

Purpose

Haloperidol is used in the management of symptoms in people requiring long-term antipsychotic therapy. It is also used for controlling tics and inappropriate vocalizations associated with Tourette syndrome in children and adults.

In children, haloperidol is occasionally used to treat severe behavior problems such as combativeness and extreme outbursts that occur without immediate provocation. It is also occasionally used for short-term treatment of children who display excessive motor activity with accompanying difficulty in attention, aggression, impulse control, mood changes, and coping with frustration. Haloperidol is used only after psychotherapy and other medications have been tried and are found to be unsuccessful.

Description

Haloperidol is a major tranquilizer. It is used to control symptoms of psychotic disorders. It can be administered as a pill or by intramuscular injection (a shot).

A 2011 study published in *The Lancet* found that haloperidol and two other antipsychotic drugs, **risperidone** and **olanzapine**, better treated the mania

associated with bipolar disorder than traditional mood stabilizers. The study included 16,000 participants over a 30-year period. Haloperidol treated manic episodes more successfully than ten other drugs, but it was not effective in managing depression, a key component of bipolar disorder.

U.S. brand names

In the United States, haloperidol is sold under the brand name Haldol.

Recommended dosage

For adults, the recommended initial dosage of haloperidol is 0.5–5 milligrams (mg) taken two or three times each day. The initial dosage depends on the severity of the symptoms in the person being treated. All people taking haloperidol must be carefully monitored to establish an individualized dosage. Physicians have found a great variability in the amount of haloperidol required to control symptoms.

Pediatric

Children require smaller dosages of haloperidol than adults. The recommended initial dosage of haloperidol for controlling psychotic symptoms in children is 0.5–2 mg taken two or three times each day. The recommended dosage for controlling symptoms of Tourette syndrome and other nonpsychotic disorders is between 0.075 mg and 0.05 mg per 1 kilogram (2.2 pounds) of body weight. The total amount is usually divided into two or three doses per day. The goal of therapy is to use the smallest amount of haloperidol that will control symptoms. Children under age three should not be given this drug.

Precautions

Haloperidol may cause hypotension (low blood pressure). Haloperidol carries a risk of causing fatal heart arrhythmias and increases the possibility of having seizures.



Haloperidol, 0.5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Haloperidol may also decrease the time required to change from mania to depression among people with bipolar (manic-depressive) disorder.

Like other antipsychotic medications, haloperidol carries a warning regarding use in elderly people with dementia, who suffer from an increased risk of death during treatment with these agents. The drug is not approved by the U.S. Food and Drug Administration (FDA) for use in treating behavior problems related to senile dementia.

Pregnant or breastfeeding

Women who are pregnant, wanting to become pregnant, or breastfeeding should consult with their doctor before taking haloperidol. Haloperidol may cause extrapyramidal symptoms (EPS) and signs of withdrawal in newborns, especially if the drug was taken during the last trimester of the mother's pregnancy. The primary symptoms of EPS are involuntary movements, such as tremor, contractions, and other motions. Signs of withdrawal include increased agitation, respiratory problems, and trouble feeding. Haloperidol also travels through the breast milk of lactating mothers.

Other conditions and allergies

Individuals with heart or blood pressure problems should be closely monitored while taking haloperidol. People with a history of seizures or who are taking anticonvulsants (medication to control seizures) should

take lower dosages of haloperidol and be closely monitored by a physician until a safe dosage is established.

Side effects

Haloperidol has the potential to produce a serious side effect called tardive dyskinesia. This syndrome consists of involuntary, uncoordinated movements that may not disappear or may only partially improve after the drug is stopped. Tardive dyskinesia involves involuntary movements of the tongue, jaw, mouth, face, or other groups of skeletal muscles. These side effects may appear after people have stopped taking haloperidol. The chance of developing tardive dyskinesia increases with increasing age and dosage of haloperidol. Women are at greater risk than men for developing tardive dyskinesia. There is no known effective treatment for tardive dyskinesia, although gradual (but rarely complete) improvement may occur over a long period.

Haloperidol use may lead to the development of symptoms that resemble Parkinson's disease, but that are not caused by Parkinson's. These symptoms may include a taut or mask-like expression on the face, drooling, tremors, pill-rolling motions in the hands, cogwheel rigidity (abnormal rigidity in muscles characterized by jerky movements when the muscle is passively stretched), and a shuffling gait. Taking the antiparkinson drugs **benztropine** mesylate or trihexyphenidyl hydrochloride along with haloperidol helps to control these symptoms. Medication to control parkinsonian symptoms may have to be continued after haloperidol is stopped, because the drugs are eliminated at different rates from the body.

Other side effects of haloperidol include:

- anxiety
- restlessness
- agitation
- insomnia
- headache
- euphoria
- drowsiness
- depression
- confusion
- dizziness
- seizures

Interactions

Patients should inform their healthcare provider of all medications they are currently taking, including over-the-counter drugs and supplements, before taking haloperidol.

KEY TERMS

Bipolar disorder—A mood disorder marked by alternating episodes of extremely low mood (depression) and exuberant highs (mania), also known as manic-depressive disorder.

Extrapyramidal symptoms (EPS)—A group of side effects associated with antipsychotic medications. EPS includes Parkinson-like symptoms, akathisia (restless legs syndrome), dystonia, and tardive dyskinesia.

Parkinson's disease—A disease of the nervous system most common in people over age 60, characterized by a shuffling gait, muscle stiffness, and tremors.

Tardive dyskinesia—A disorder characterized by involuntary and repetitive body movements that sometimes develops after long-term use of antipsychotic medications.

Tourette syndrome—A neurological disorder characterized by involuntary motor or vocal tics.

Drugs

The simultaneous use of haloperidol and lithium, a common treatment for bipolar (manic-depressive) disorder, has been associated with encephalopathic syndrome. People with this syndrome have symptoms of weakness, lethargy, fever, confusion, and high levels of white blood cells.

Haloperidol may increase the effect of central nervous system depressants such as anesthetics and opiates (some pain killers and sleeping pills). Haloperidol also interferes with the action of the anticoagulant (blood thinning) drug phenindione.

Food and other substances

Haloperidol enhances the depressant effects of alcohol. Use of alcohol should be avoided while taking haloperidol.

Resources

BOOKS

- Martino, Davide, and James F. Leckman, eds. *Tourette Syndrome*. New York: Oxford University Press, 2013.
- Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger Publications, 2013.

PERIODICALS

- Cipriani, Andrea. "Comparative Efficacy and Acceptability of Antimanic Drugs in Acute Mania: A Multiple-Treatments Meta-Analysis." *The Lancet* 378, no. 9799 (2011): 1306–15.
- Hudson, C. J., P. Seeman, and M. V. Seeman. "Parkinson's Disease: Low-Dose Haloperidol Increases Dopamine Receptor Sensitivity and Clinical Response." *Parkinson's Disease* (November 20, 2014): e-pub ahead of print. <http://dx.doi.org/10.1155/2014/684973> (accessed February 25, 2015).
- Morrens, Manuel, et al. "Psychomotor and Memory Effects of Haloperidol, Olanzapine, and Paroxetine in Healthy Subjects after Short-Term Administration." *Journal of Clinical Psychopharmacology* 27, no. 1 (February 2007): 15–21.
- Woodward, Neil D., et al. "A Meta-Analysis of Cognitive Change with Haloperidol in Clinical Trials of Atypical Antipsychotics: Dose Effects and Comparison to Practice Effects." *Schizophrenia Research* 89, nos. 1–3 (January 2007): 211–24.

WEBSITES

- AHFS Consumer Medication Information. "Haloperidol." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682180.html> (accessed February 25, 2015).
- Henry Spink Foundation. "Tourette Syndrome." http://www.henryspink.org/tourette_syndrome.htm (accessed February 25, 2015).
- UK National Health Service (NHS). "Medicines A-Z—Haloperidol." <http://www.nhs.uk/medicine-guides/pages/selectorshow.aspx?medicine=haloperidol> (accessed February 25, 2015).
- U.S. Food and Drug Administration. "Haloperidol (Marketed as Haldol, Haldol Decanoate, and Haldol Lactate) Information." <http://www.fda.gov/Drugs/DrugSafety/Postmarket-DrugSafetyInformationforPatientsandProviders/ucm216907.htm> (accessed February 25, 2015).

ORGANIZATIONS

- American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.
- National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.
- National Tourette Syndrome Association, 42-40 Bell Boulevard, Bayside, NY 11361, (718) 224-2999, Fax: (718) 279-9596, <http://www.tsa-usa.org/>.

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Revised by Ruth A. Wienclaw, PhD

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Humalog see **Insulin lispro**

Humira see **Adalimumab**

Hydrochlorothiazide

Definition

Hydrochlorothiazide is a diuretic, sometimes called a “water pill,” that helps the body rid itself of excess water and salt.

Purpose

Hydrochlorothiazide is generally prescribed either to help lower blood pressure or because the body is retaining excess water due to a medical condition or as a side effect of another medication. It is a diuretic, which means that it helps the body rid itself of excess water and salt by causing the kidneys to increase urine production.

Maintaining a blood pressure in the normal range is important for good health. Elevated blood pressure puts excess strain on the heart, veins, and arteries. Untreated, high blood pressure can lead to an increased risk of serious and even fatal health problems, including heart attack and stroke.

Off-label uses

In some cases, hydrochlorothiazide is used to treat patients with heart failure.

Description

The kidneys are the organs in the human body responsible for filtering the blood and removing waste



Hydrochlorothiazide, 25 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

products. Each kidney contains about one million nephrons, the basic filtering unit within the kidney. As fluid passes through the nephrons, it is filtered, and some substances are reabsorbed into the bloodstream. What is not reabsorbed is excreted from the body as urine. Hydrochlorothiazide works by stopping a portion of the nephron from reabsorbing sodium (a component of salt). The drug reduces sodium reabsorption into the body by about 5%. The sodium that is not reabsorbed is then removed from the body in urine. Because sodium levels in the body are a major factor in determining water retention, additional water is excreted from the body as the level of sodium drops. Thus, both the level of sodium and water in the body are reduced.

Hydrochlorothiazide is prescribed to help lower high blood pressure because it reduces the amount of water in the body, and therefore reduces the volume of blood the heart has to pump. This puts less pressure on the walls of arteries and veins, and makes the heart work less hard.

Hydrochlorothiazide is prescribed for edema and a variety of other situations in which excess fluid is retained because it causes the body to eliminate more sodium, which reduces the amount of water stored in the body.

Hydrochlorothiazide is available as tablets, capsules, or as a liquid.

U.S. brand names

Hydrochlorothiazide is sold under a wide variety of brand names in the United States, including Microzide, Hydro, HCTZ, Oretic, Aquazide H, Zide, and Esidrix. It was previously sold as HydroDiuril, Hydro-Par, and Ezide, but those brands have been discontinued. It is also sold as a combination tablet with a variety of other drugs, including with **metoprolol** as Lopressor HCT and Dutoprol, with bisoprolol as Ziac, with hydralazine as Hydra-Zide, and with **propranolol** as Inderide.

International brand names

Hydrochlorothiazide is manufactured by many different international manufacturers in many strengths and combinations.

Origins

Hydrochlorothiazide was first approved by the U.S. Food and Drug Administration (FDA) in 1959.

Recommended dosage

The dosage of hydrochlorothiazide depends on the condition being treated, its severity, and how well the patient responds to the medication. For treating high blood pressure, the recommended dose is between 12.5

KEY TERMS

Corticosteroid drug—A medication that acts like a type of hormone (cortisol) produced by the adrenal gland of the body. Corticosteroids produced by the body stimulate specific types of functional activity. As a drug, a corticosteroid (sometimes just called a steroid) helps treat inflammation, infection, or trauma to the body.

Diabetes—A disease in which insufficient insulin is made by the body (type 1 diabetes) to metabolize sugars or the cells of the body do not respond adequately to insulin circulating in the blood (type 2 diabetes).

Diuretic—A substance that removes water from the body by increasing urine production.

Edema—Swelling of a body tissue due to the collection of fluids.

Electrolyte—Salts and minerals that ionize in body fluids. The major human electrolytes are sodium (Na⁺), potassium (K⁺), calcium (Ca²⁺), magnesium (Mg²⁺), chloride (Cl⁻), phosphate (HPO₄²⁻), bicarbonate (HCO₃⁻), and sulfate (SO₄²⁻). Electrolytes control the fluid balance of the body and are important in muscle contraction, energy generation, and almost all major biochemical reactions in the body.

Gout—A disease in which uric acid, a waste product that normally passes out of the body in urine, collects in the joints and the kidneys.

Nephron—The basic structural unit of the kidney, responsible for regulating the concentration of water and soluble chemicals in the blood by filtering the blood, reabsorbing the compounds needed by the body, and excreting the rest in the urine.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Stroke—Irreversible damage to the brain caused by insufficient blood flow to the brain as the result of a blocked artery. Damage can include loss of speech or vision, paralysis, cognitive impairment, and death.

Systemic lupus erythematosus (SLE)—A chronic, inflammatory, autoimmune disorder in which the individual's immune system attacks, injures, and destroys the body's own organs and tissues. It may affect many organ systems, including the skin, joints, lungs, heart, and kidneys.

and 50 milligrams (mg), taken once daily. For patients with edema, the recommended dosage is between 25 and 100 mg taken once daily or divided into two daily doses. For edema patients, the total daily dose should not be greater than 200 mg.

When hydrochlorothiazide is used to treat heart failure, the recommended dosage for this off-label use is 25 mg once daily or divided into two daily doses, not to exceed a total dose of 200 mg per day.

In most cases, dosing will be started conservatively with the minimum recommended dosage, and then slowly increased as it becomes clear how the patient responds, how well blood pressure or fluid retention is controlled, and whether the patient experiences any side effects or adverse reactions.

Pediatric

Hydrochlorothiazide may be prescribed for either pediatric hypertension or edema. For treating these conditions in children younger than 6 months of age, the recommended dose is 1–3 mg per kilogram (kg, or 2.2 lb.) of body weight each day, divided into two doses. The total

amount should not exceed 37.5 mg daily. For children ages 6 months to 2 years, the recommended dose is 1–2 mg/kg/day for hypertension, and 1–2 mg/kg/day for edema. For both conditions, the medication is taken once or twice daily, and should not exceed a total dose of 37.5 mg per day. For children ages 2 through 12, the dose is 1–3 mg/kg/day, not to exceed a total dose of 100 mg daily.

Geriatric

Seniors may be more likely to experience serious negative side effects from taking hydrochlorothiazide, especially problems with fluid and electrolyte balance. The generally recommended starting dosage for seniors is 12.5–25 mg per day, which can be increased in increments of 12.5 mg per day over time if the desired result has not been achieved. In seniors, the total dose should not exceed 50 mg per day because of the high risk of serious side effects.

Precautions

Hydrochlorothiazide may cause some people's skin to become more sensitive to sunlight, making it burn

more easily. Individuals taking hydrochlorothiazide should be aware of this and take steps to protect their skin, especially in sensitive areas such as the face, from being in direct sunlight.

Pediatric

Few studies have been done to establish the safety of hydrochlorothiazide in children; however, no studies have found specific dangers to children from the drug. Dosing guidelines exist for children from birth through adulthood. Children should be dosed conservatively, especially if it is expected that they will continue to use the drug for long periods, as the long-term effects of hydrochlorothiazide use in children have not been established.

Geriatric

Seniors are more likely to be at risk for certain side effects associated with hydrochlorothiazide use, especially hypotension (low blood pressure). There is also an increased chance of fluid and electrolyte imbalances in seniors who take this drug. Hydrochlorothiazide may cause dizziness that can lead to falls, so seniors should be especially cautious until they know how the drug affects them.

Pregnant or breastfeeding

Hydrochlorothiazide is a pregnancy class B drug, meaning that there is either evidence from human studies that there is no risk to the fetus, or animal studies have shown no risk, but no studies have yet been done on the risk in humans. While all medications should be used cautiously during pregnancy, class B drugs are believed to pose little or no risk to the fetus. Hydrochlorothiazide is known to be passed to the baby in breast milk; however, it poses little risk to the infant.

Other conditions and allergies

Individuals who have diabetes may not be good candidates for hydrochlorothiazide because it can alter blood sugar levels. Individuals who have gout, systemic lupus erythematosus, liver disease or impairment, kidney (renal) disease or impairment, or problems with fluid and electrolyte balance should only take this medication cautiously and under the careful supervision of an experienced medical professional.

Individuals who have shown an allergy to sulfonamide antibiotics, penicillin, or who have previously experienced an allergic reaction to hydrochlorothiazide should not take this medication.

Side effects

In rare cases, individuals have experienced severe, life-threatening allergic reactions to hydrochlorothiazide. Anyone who experiences swelling of the lips, throat, mouth, tongue, or face; difficulty breathing; rash or hives; or severe dizziness should seek emergency medical attention immediately.

Individuals who experience any of the following side effects should stop taking hydrochlorothiazide and call their doctor promptly:

- any new eye problems, including blurry vision, eye pain, or decreased vision
- decrease in amount of urine produced or frequency of urination
- heart palpitations or an unusually fast or slow heartbeat
- extremely dry mouth
- excessive or unusual thirst
- serious muscle cramps
- weakened muscles

Common but less serious side effects include:

- mild dizziness, especially just after standing
- headache
- lightheadedness
- nausea
- unusual change in weight
- fatigue
- difficulty maintaining an erection
- stomach cramping
- loss of sexual desire
- increased sensitivity to sunlight
- constipation

Interactions

Hydrochlorothiazide may interact with other substances. Patients should be sure to tell their doctor and pharmacist about any prescription medications, over-the-counter medications, supplements, vitamins, and herbs that they are taking. The doctor or pharmacist can check the most complete, up-to-date list of known interactions to ensure that the patient is taking hydrochlorothiazide as safely as possible.

Drugs

Hydrochlorothiazide may interact with a wide variety of medications. These include other drugs for high blood pressure, some antibiotics such as **amoxicillin**, nonsteroidal anti-inflammatory drugs (NSAIDs) such as **ibuprofen**, lithium, and corticosteroids.

Patients taking colestipol or cholestyramine should not take those medications at the same time of day as taking hydrochlorothiazide, but instead should take them at least one hour before or four hours after taking the hydrochlorothiazide.

Resources

BOOKS

- Blush, Joel A. *Integrative Treatment of Hypertension: A Clinical and Mechanistic Approach*. Boca Raton, FL: CRC Press, 2014.
- Wouters, Lars, ed. *Diuretics: Pharmacology, Therapeutic Uses, and Adverse Side Effects*. Hauppauge, NY: Nova Science, 2013.

PERIODICALS

- Calhoun, David A., et al. "Effects of Demographics on the Antihypertensive Efficacy of Triple Therapy with Amlodipine, Valsartan, and Hydrochlorothiazide for Moderate to Severe Hypertension." *Current Medical Research & Opinion* 29, no. 8 (2013): 901–910.

WEBSITES

- American Heart Association. "Types of Blood Pressure Medications." http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/PreventionTreatmentofHighBloodPressure/Types-of-Blood-Pressure-Medications_UC-M_303247_Article.jsp? (accessed February 27, 2015).
- MedlinePlus. "Hydrochlorothiazide." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682571.html> (accessed February 27, 2015).
- Micromedex. "Hydrochlorothiazide (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/hydrochlorothiazide-oral-route/description/drg-20071841> (accessed February 27, 2015).
- University of Maryland Baltimore Washington Medical Center. "Hydrochlorothiazide." <http://www.mybwmc.org/library/41/062500> (accessed February 27, 2015).

ORGANIZATIONS

- American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.
- National Heart, Lung, and Blood Institute (NHLBI), PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbinfo@nhlbi.org, <http://www.nhlbi.nih.gov/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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REVIEWED BY GREGORY A. PRATT, RPh

Hydrochlorothiazide/benazepril see

Benazepril/hydrochlorothiazide

Hydrochlorothiazide/losartan see **Losartan/hydrochlorothiazide**

Hydrochlorothiazide/valsartan see
Valsartan/hydrochlorothiazide

Hydrocodone/acetaminophen

Definition

Hydrocodone is a semisynthetic narcotic with actions and uses similar to those of **morphine**. The primary use of hydrocodone is as an analgesic (pain reliever), but it may also be used as a cough suppressant. It is often combined with acetaminophen, another analgesic.

Purpose

Hydrocodone/acetaminophen is used to treat moderate to severe pain.

Description

Hydrocodone with acetaminophen is available as fixed-combination solutions and tablets. The most common combinations contain 300–325 milligrams (mg) of acetaminophen and 2.5, 5, 7.5, or 10 mg of hydrocodone.



Hydrocodone/acetaminophen (7.5 mg/750 mg). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Due to the presence of hydrocodone, hydrocodone/acetaminophen combinations are classified by the U.S. Drug Enforcement Administration (DEA) as Schedule II drugs. This means that although this drug has an accepted medical use, it carries a high potential for abuse.

U.S. brand names

Hydrocodone/acetaminophen is sold under many brand names in the United States, including Vicodin and Norco.

Recommended dosage

A typical dosing schedule might be one to two tablets every four to six hours, with a maximum daily dose of 60 mg of hydrocodone and 4 grams (g) of acetaminophen.

Dosing may also be adjusted depending on the severity of pain and the patient's age and health status, including liver and respiratory function. Patients should also follow the dosing instructions of their healthcare provider, and dosing may be different when switching from a different narcotic analgesic to hydrocodone or from a short-acting analgesic to sustained-action hydrocodone.

Precautions

Hydrocodone has a high potential for misuse, abuse, and addiction, any of which can result in overdose and death. Risk of addiction should be considered when prescribing hydrocodone, and patients should be monitored for signs of abuse. However, patients should not fear using hydrocodone/acetaminophen for its approved use when prescribed. Once a patient no longer needs hydrocodone/acetaminophen, gradually decreasing the medication will help reduce the likeliness of withdrawal symptoms.

Respiratory depression—very low breathing rate—may occur with hydrocodone use. Patients should be monitored for signs of respiratory depression, especially when starting treatment or after an increase in dosage.

Acetaminophen is associated with liver failure, most often when taken in doses that exceed 4,000 mg (4 g) per day. Acetaminophen is often combined with other drugs, so excessive intakes can occur if individuals are taking more than one medication that contains acetaminophen, including over-the-counter drugs.

Pediatric

Accidental ingestion of hydrocodone could result in a fatal overdose, especially in children.

KEY TERMS

Acetaminophen—A drug for relieving pain and fever. Tylenol is the most common example.

Analgesic—A drug that relieves pain.

Drug schedule—A system of classifying drugs, including narcotics, sedatives, hallucinogens, and other drugs, that are restricted under federal and state laws in the United States. Schedule I substances have no approved medical use, while Schedules II, III, and IV have approved uses. The higher the schedule, the lower the degree of restriction.

Narcotic—A drug that reduces pain and induces sleep. The term is usually applied to opium derivatives, but in modern use has been expanded to include other controlled substances such as cocaine and marijuana.

Respiratory depression—Very low breathing rate, characterized as 12 or fewer breaths per minute; also known as hypoventilation.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

Pregnant or breastfeeding

Infants born to mothers who took opioid narcotics during pregnancy may experience neonatal opioid withdrawal syndrome (also known as neonatal abstinence syndrome). The fetus becomes dependent on the drug while in the womb and experiences symptoms of withdrawal after birth.

Side effects

The following adverse effects have been associated with hydrocodone:

- constipation
- nausea
- vomiting
- somnolence
- urinary tract infections
- headache
- fatigue
- back pain
- dry mouth
- itching
- tremor

PATIENT PROFILE

A 64-year-old woman had undergone total hysterectomy due to uterine prolapse and associated cystocele. After the surgery she experienced pain in her lower abdomen and at her navel, where incisions had been made to insert a laparoscope. She also complained of severe headache, which her gynecologist thought was a reaction to the anesthesia. When the doctor suggested prescribing pain medication, the patient explained that she had been taking methotrexate for fifteen years for rheumatoid arthritis and that her rheumatologist had advised that only acetaminophen could be used as pain medication, since many other analgesics reduced the desired immunosuppressive action of methotrexate. The patient also expressed that she lived alone and did not want to be home alone feeling dizzy and unable to manage daily activities due to unwanted effects of the pain medication. Therefore, to help relieve the patient's pain and to consider both interaction with methotrexate and the patient's preferences, her doctor prescribed hydrocodone bitartrate 5 mg combined in a single tablet with acetaminophen 500 mg (Vicodin). The patient was advised to take one or two tablets every four to six hours as needed. She was also advised that if one tablet of the pain medication was too strong or if she wished to taper the analgesic effects gradually, the tablet was scored and she could take half of one tablet if necessary. The patient was given her first two-tablet dose of the medication almost immediately while in the recovery room.

Hydrocodone is a narcotic, an opioid analgesic that works by blocking receptors on the nerve cells in the brain that produce pain sensations. Acetaminophen works by altering the threshold to pain, meaning that greater nerve stimulation is needed to have the sensation

of pain. Together, as a narcotic/analgesic combination drug, the medication relieves moderate to severe pain effectively without causing marked dizziness or sedation. Common side effects of the combination drug include dizziness, nausea, vomiting, and sleepiness or sedation. Older adults may be more sensitive to the side effects than younger adults.

Although the patient was scheduled to be discharged the same day as her surgery after several hours of recovery, she spent the entire night in the hospital because of vomiting. The nursing staff urged her to eat and to begin walking, but she was unable to take food or to get out of bed without vomiting. It was not known whether this was caused by the anesthesia or from the use of hydrocodone/acetaminophen, which had been given twice since the surgery. Nevertheless, the nausea and vomiting had subsided by the following morning and she was discharged in the care of her daughter. On arriving home and after having broth and tea, she took one hydrocodone/acetaminophen tablet and went to bed. She awoke four hours later and, on arising, found that she felt dizzy and nauseous, followed by more vomiting. Although she avoided taking another dose of pain medication, vomiting occurred again after taking soup in the evening. She reported the nausea and vomiting to her doctor by phone and was instructed to discontinue the hydrocodone/acetaminophen and to just take her usual dose of acetaminophen alone as needed for pain. She was urged to consume plenty of water, soup, and tea to help restore hydration and nutrition. The patient's pain was managed effectively for the next few days using acetaminophen 500 mg alone, and the nausea and vomiting did not recur.

- dizziness
- swelling of the legs
- upper respiratory infection
- muscle spasms

Interactions

Patients should consult with their healthcare provider regarding potential drug interactions with hydrocodone/acetaminophen, including interactions with over-the-counter drugs or supplements.

Drugs

Hydrocodone has a very large number of interactions with other drugs. The following list covers only drug/drug interactions with hydrocodone in which it is

recommended that one or the other drug be switched for something else:

- alvimopan
- artemether/lumefantrine
- buprenorphine
- butorphanol
- cimetidine
- isocarboxazid
- **linezolid**
- lumefantrine
- nalbuphine
- naltrexone
- **paroxetine**
- pentazocine

- phenelzine
- procarbazine
- quinidine
- rasagiline
- selegiline transdermal
- sodium oxybate
- **tramadol**
- tranylcypromine

Hydrocodone/acetaminophen may also interact with monoamine oxidase inhibitors (MAOIs) and other drugs used to treat depression.

Food and other substances

Patients taking hydrocodone should not consume alcoholic beverages or use any products that contain alcohol. The combination of alcohol and hydrocodone may increase the level of the drug in the body, resulting in a potentially fatal overdose.

Resources

BOOKS

Mancano, Michael A., and Jason Gallagher. *Frequently Prescribed Medications: Drugs You Need to Know*. Sudbury, MA: Jones & Bartlett Learning, 2012.

PERIODICALS

Atluri, S., Sudarshan G, et al. "Assessment of the Trends in Medical Use and Misuse of Opioid Analgesics from 2004 to 2011." *Pain Physician* 17, no. 2 (2014): E119–28.

WEBSITES

Andrews, Michelle. "DEA Makes Vicodin, Some Other Pain Meds Harder to Get." *Kaiser Health News*, September 26, 2014. <http://www.medpagetoday.com/PainManagement/PainManagement/47841> (accessed February 24, 2015).

Micromedex. "Hydrocodone and Acetaminophen (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/hydrocodone-and-acetaminophen-oral-route/description/drg-20074089> (accessed February 24, 2015).

U.S. Food and Drug Administration. "Acetaminophen Information." <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm165107.htm> (accessed February 24, 2015).

U.S. Food and Drug Administration. "FDA Approves Extended-Release, Single-Entity Hydrocodone Product with Abuse-Deterrent Properties." November 20, 2014. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm423977.htm> (accessed November 21, 2014).

U.S. National Library of Medicine. "Hydrocodone/Acetaminophen (By Mouth)." PubMed Health. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0010590/> (accessed February 24, 2015).

ORGANIZATIONS

American Academy of Pain Management, 975 Morning Star Drive, Suite A, Sonoma, CA 95370, (209) 533-9744, info@aapainmanage.org, <http://www.aapainmanage.org/>.

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Hydrocodone/ibuprofen

Definition

Hydrocodone/ibuprofen is a prescription-only medication that combines **ibuprofen**, a nonprescription painkiller (analgesic) that belongs to the family of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs), and hydrocodone, an opioid analgesic.

Purpose

Hydrocodone/ibuprofen is used to treat acute pain. It is intended to be used for no more than ten days.

Description

Hydrocodone/ibuprofen tablets are available in a variety of combinations, including:



Hydrocodone/ibuprofen, 7.5 mg/200 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

- 2.5 milligrams (mg) of hydrocodone combined with 200 mg of ibuprofen
- 5 mg of hydrocodone combined with 200 mg of ibuprofen
- 7.5 mg of hydrocodone combined with 200 mg of ibuprofen
- 10 mg of hydrocodone combined with 200 mg of ibuprofen

Due to the presence of hydrocodone, hydrocodone/ibuprofen combinations are all classified by the U.S. Drug Enforcement Administration (DEA) as Schedule II drugs. This means that these medications:

- are medically accepted as a therapeutic agent
- carry a high potential for abuse (although less so than Schedule I drugs)
- carry a high potential of initiating severe psychological or physical dependence
- possess a side effect profile that is potentially dangerous

U.S. brand names

In the United States, hydrocodone/ibuprofen is sold under the brand name Vicoprofen.

Canadian brand names

In Canada, hydrocodone/ibuprofen is sold under the brand names Ibudone, Reprexain, and Vicoprofen.

International brand names

Hydrocodone-containing preparations are no longer available in many countries around the world due to their substantial potential for abuse.

Recommended dosage

For adults and children over 16 years of age, the recommended dose is one tablet taken every 4 to 6 hours. The maximum daily dosage is five tablets in 24 hours. The total duration of treatment should not exceed ten days.

Geriatric

Elderly individuals can receive the same dose as adults, but care should be taken to monitor closely for side effects and lessen the dose if needed.

Precautions

Several precautions are associated with hydrocodone/ibuprofen:

- Hydrocodone/ibuprofen use carries an increased risk of life-threatening heart attack or stroke. Risk elevates over time and in the setting of other cardiovascular risk factors or conditions.

KEY TERMS

Analgesic—A drug used to control pain.

Narcotic—A class of chemical that contains opium or opium-derivatives. These drugs decrease pain, often cause drowsiness, may induce a sense of euphoria or well-being, and have profound side effects that include respiratory depression in overdoses and addictive potential.

Opioid—A substance that resembles opium and binds to the same types of receptors in the body, producing similar effects in pain relief, pleasure, and addictiveness. Does not actually contain opium, but is synthetically produced to mimic its therapeutic benefits.

Tolerance—A decrease in tolerance to a drug so that an individual must take more and more of the drug to achieve the same effect.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

- Ibuprofen use carries an increased risk of life-threatening gastrointestinal irritation, inflammation, ulceration, bleeding, or perforation. People with a history of these problems—especially the elderly, smokers, heavy alcohol drinkers, or those using aspirin, blood thinners, or steroid medications—should use particular caution or take an alternate drug.
- Hydrocodone/ibuprofen increases bleeding time. Patients with clotting disorders or who are taking other medications, such as blood thinners or **aspirin**, should use particular caution and have regular monitoring for the development of anemia. Individuals who are scheduled to have dental or surgical procedures should avoid the use of ibuprofen in the week prior to the procedure.
- Hydrocodone/ibuprofen can cause an increased blood level of potassium, especially in older people, patients with kidney disease or diabetes, and individuals taking other drugs that can increase potassium.
- Hydrocodone/ibuprofen can cause low blood pressure, especially in individuals who are dehydrated or have cardiovascular conditions.
- Hydrocodone/ibuprofen should not be used in patients who are acutely intoxicated with ethanol, hypnotics, centrally acting analgesics, opioids, or psychotropic drugs.
- Because of hydrocodone/ibuprofen's addictive potential, sudden discontinuation after long-term use of the drug can lead to symptoms of withdrawal, including nausea,

vomiting, diarrhea, teary eyes, runny nose, severe sweating, itchy skin, twitchy muscles, and uncontrollable yawning.

- Post-anesthesia patients with slowed bowel motility may be at particular risk for complications from the constipating effects of hydrocodone/ibuprofen.

Gastrointestinal risks may be decreased when the drug is taken with food.

Geriatric

The elderly are at particular risk of complications from hydrocodone/ibuprofen use, especially gastrointestinal irritation with bleeding, heart attack, stroke, confusion, agitation, and kidney impairment. Hydrocodone/ibuprofen should be used with extreme caution and close monitoring in this population.

Pregnant or breastfeeding

Hydrocodone/ibuprofen carries the FDA pregnancy category C, which means that risk cannot be ruled out in pregnant individuals. If possible, use of this drug should be avoided. Babies who have been exposed to hydrocodone/ibuprofen acutely before birth may be born with decreased respiratory drive and a weak suck. Babies who have been exposed to hydrocodone/ibuprofen chronically before birth may experience withdrawal syndrome (neonatal abstinence syndrome) after birth when they no longer receive hydrocodone/ibuprofen through the placenta. These babies may require treatment to avoid severe symptoms of withdrawal.

Hydrocodone/ibuprofen is known to pass into breast milk. It should be avoided by breastfeeding women.

Other conditions and allergies

Hydrocodone/ibuprofen should not be given to individuals with known sensitivity to hydrocodone, hydrocodone/ibuprofen, opiate or opioid drugs, or other ingredients within a specific delivery formulation. This drug should be used with caution in individuals who have had previous reactions to opiates or opioids and should not be taken by individuals who are hypersensitive to ibuprofen or nonsteroidal anti-inflammatory medications or who have the following cluster of three factors: bronchial asthma, aspirin intolerance, and rhinitis. Individuals who have had bronchospasm, asthma, rhinitis, or hives while taking aspirin or other NSAIDs should not take hydrocodone/ibuprofen.

Hydrocodone/ibuprofen should also be avoided in people with:

- systemic lupus erythematosus (hydrocodone/ibuprofen use may increase the risk of a form of non-infectious meningitis)

- asthma or other respiratory problems (hydrocodone/ibuprofen use may cause severe bronchospasm and wheezing)
- recent coronary artery bypass graft (CABG) surgery
- liver disorders (hydrocodone/ibuprofen use may cause hepatitis or liver failure)
- high blood pressure (hydrocodone/ibuprofen use may prompt the onset of high blood pressure or the worsening of preexisting high blood pressure)
- kidney impairment (hydrocodone/ibuprofen use may worsen preexisting kidney problems or prompt the onset of kidney problems in the elderly or individuals who are dehydrated, have heart or liver failure, or are taking diuretic medications or ACE inhibitors)
- history of substance abuse or alcoholism
- gall bladder problems (hydrocodone/ibuprofen can cause spasms in one of the gall bladder valves, resulting in severe pain)
- head injury (hydrocodone/ibuprofen and other opioid drugs may complicate assessment and course of traumatic brain injuries and other causes of brain swelling; respiratory status may also be severely affected when used in the setting of head injury or coma)
- alcohol use
- morbid obesity
- prostate disease
- psychoses
- seizure disorders
- narrowing in the gastrointestinal tract or bowel obstruction
- liver or kidney disease
- suicidality

Side effects

Hydrocodone/ibuprofen has been associated with severe skin reactions, including pustules, blistering, and peeling. The presence of a rash should prompt discontinuation of the drug.

Hydrocodone/ibuprofen can cause severe constipation, which is particularly problematic for individuals with unstable angina or recent heart attack.

The most common side effects of hydrocodone/ibuprofen treatment include:

- flushing
- headache, drowsiness, confusion, unclear thinking, depression
- sweating, itching
- dehydration
- constipation

- swelling
- dry mouth
- urinary retention
- weak muscles
- shortness of breath, respiratory depression
- euphoria
- agitation, hallucinations
- upset stomach, nausea, vomiting
- blurred vision, ringing in the ears
- laboratory evidence of liver damage

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

The following may increase the side effects associated with the hydrocodone element of the formulation:

- alpha- and beta-agonists
- opioid analgesics
- amphetamines
- anticholinergic agents
- antiemetics
- **aripiprazole**
- antipsychotic agents
- cannabis
- crizotinib
- droperidol
- hydrocodone
- **hydroxyzine**
- magnesium sulfate
- methotrimeprazine
- mifepristone
- **zolpidem**

Drugs that are classified as CYP3A4 inhibitors have a profound effect on the hydrocodone element of this formulation and may greatly increase the risk of potentially fatal side effects. There are many drugs in this group, including:

- amiodarone
- anastrozole

- **azithromycin**
- cannabinoids
- cimetidine
- **clarithromycin**
- clotrimazole
- **cyclosporine**
- danazol
- delavirdine
- dexamethasone
- diethyldithiocarbamate
- **diltiazem**
- disulfiram
- entacapone
- **erythromycin**
- ethinyl estradiol
- **fluconazole**
- **fluoxetine**
- **fluvoxamine**
- gestodene
- indinavir
- isoniazid
- **ketoconazole**
- **metronidazole**
- mibefradil
- miconazole
- nefazodone
- nelfinavir
- nevirapine
- norfloxacin
- norfluoxetine
- **omeprazole**
- oxiconazole
- **paroxetine**
- propoxyphene
- quinidine
- quinine
- **ranitidine**
- ritonavir
- saquinavir
- sertindole
- **sertraline**
- troglitazone
- troleandomycin
- **valproic acid**

The hydrocodone element of this formulation may increase the side effects of the following:

- opioid analgesics
- antiemetics
- antipsychotic agents
- beta-blockers
- buprenorphine
- calcium channel blockers
- desmopressin
- diuretics
- hydrocodone
- hydroxyzine
- MAO inhibitors
- methotrimeprazine
- **metoclopramide**

The concomitant (simultaneous) use of the ibuprofen element in the drug may increase potential toxic effects of the following drugs:

- 5-ASA derivatives
- antiplatelet drugs
- aminoglycoside antibiotics
- anticoagulants
- bisphosphonate derivatives
- collagenase
- cyclosporine
- desmopressin
- **digoxin**
- **haloperidol**
- lithium
- **methotrexate**
- salicylates
- **tacrolimus**
- tenofovir
- vancomycin

The risk of potential adverse effects from the ibuprofen element of the drug may be increased with concomitant use of the following drugs:

- ACE inhibitors
- angiotensin II receptor blockers
- tricyclic antidepressants
- corticosteroids
- dextropropofol
- **diclofenac**
- floctafenine
- **ketorolac**
- probenecid
- selective serotonin reuptake inhibitors
- serotonin/norepinephrine reuptake inhibitors
- treprostinil

The ibuprofen element of the drug may hamper the effectiveness of the following drugs:

- aliskiren
- beta-blockers
- eplerenone
- hydralazine
- loop diuretics
- potassium-sparing diuretics
- thiazide diuretics

Bile-acid sequestrants may hamper the effectiveness of the ibuprofen element of the drug.

Herbs and supplements

Kava kava may increase the side effects of the hydrocodone element of this formulation.

The hydrocodone element of this formulation may increase the side effects of cannabis and kava kava.

Food and other substances

The hydrocodone element of this formulation may increase the side effects of alcohol.

Resources

BOOKS

- Aronson, J. K. *Meyler's Side Effects of Analgesics and Anti-inflammatory Drugs*. Oxford: Elsevier, 2010.
- Benzon, Honorio T. *Essentials of Pain Medicine*. 3rd ed. Philadelphia: Saunders, 2011.
- Smith, Howard S. *Current Therapy in Pain*. Philadelphia: Saunders, 2009.
- Waldman, Steven D. *Pain Management*. 2nd ed. Philadelphia: Saunders, 2011.

WEBSITES

- "Hydrocodone." Drugs.com. <http://www.drugs.com/mtm/hydrocodone.html> (accessed February 14, 2015).
- "Ibuprofen." Drugs.com. <http://www.drugs.com/ibuprofen.html> (accessed February 14, 2015).
- MedlinePlus. "Hydrocodone." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a614045.html> (accessed February 14, 2015).
- MedlinePlus. "Ibuprofen." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682159.html> (accessed February 14, 2015).
- U.S. National Library of Medicine. "LactMed: Hydrocodone." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+359> (accessed February 14, 2015).

ORGANIZATIONS

American Chronic Pain Association, PO Box 850, Rocklin, CA 95677, (800) 533-3231, APAC@theacpa.org, <http://www.theacpa.org/>.

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

National Pain Foundation, 14828 W 6 Avenue, Suite 16-B, Room 1, Golden, CO 80401-5000, (720) 541-6808, Fax: (720) 541-6809, <http://www.thenationalpainfoundation.org/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rosalyn S. Carson-Dewitt, MD

REVIEWED BY KEVIN GLAZA, RPh

Hydromorphone

Definition

Hydromorphone is a prescription-only painkiller (analgesic) that belongs to the family of drugs called opioid analgesics. Hydromorphone is a type of synthetic narcotic drug.



Hydromorphone, 4 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Hydromorphone is used to treat moderate to severe pain.

Description

Hydromorphone is classified by the U.S. Drug Enforcement Administration (DEA) as a Schedule II drug. This means that hydromorphone:

- is medically accepted as a therapeutic agent
- carries a high potential for abuse (although less so than Schedule I drugs)
- carries a high potential of initiating severe psychological or physical dependence
- possesses a side effect profile that is potentially dangerous

Hydromorphone is available in a variety of formulations, allowing for varied delivery, including oral (both tablets and liquid), rectal suppository, and injectable forms.

- Oral tablets are available in 2, 4, or 8 milligram (mg) strengths and are scored for easy splitting.
- Extended-release tablets are available in 8 mg, 12 mg, 16 mg, and 32 mg strengths; this is considered an “abuse-deterrent” formulation because it is difficult to crush and extract the pure form of the drug for illicit use.
- Liquid dilaudid contains 1 mg of active drug per milliliter (mL) of solution.
- Rectal suppositories contain 3 mg of active drug.
- Injectable solutions can be administered intravenously, subcutaneously, or intramuscularly, and are available in a variety of concentrations, including 1 mg/mL, 2 mg/mL, 4 mg/mL, and 10 mg/mL.

U.S. brand names

Hydromorphone is sold in the United States under the brand names Dilaudid, Dilaudid-HP, and Exalgo.

Canadian brand names

Hydromorphone is sold in Canada under the brand names Apo-Hydromorphone, Dilaudid, Dilaudid-HP, Hydromorph Contin, Hydromorphone HP, Hydromorphone HP 10, Hydromorphone HP 20, Hydromorphone HP 50, Hydromorphone HP Forte, Hydromorphone Hydrochloride Injection USP, Jurnista, PMS-Hydromorphone, and Teva-Hydromorphone.

International brand names

Hydromorphone is sold under several hundred brand names internationally, including Jurnista (Philippines), Dilid (South Korea), Hydal (Austria), Liberaxim

KEY TERMS

Analgesic—A drug used to control pain.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Drug schedule—A method of classification for drugs including narcotics, sedatives, hallucinogens, and other drugs restricted under federal and state laws in the United States. Schedule I substances have no approved medical use, while Schedules II, III, and IV have approved uses. The higher the schedule, the lower the degree of restriction.

Narcotic—A class of chemical that contains opium or opium-derivatives. These drugs decrease pain, often cause drowsiness, may induce a sense of euphoria or well-being, and have profound side effects that include respiratory depression in overdoses and addictive potential.

Opioid—A substance that resembles opium and binds to the same types of receptors in the body, producing similar effects in pain relief, pleasure, and addictiveness. Does not actually contain opium, but is synthetically produced to mimic its therapeutic benefits.

Tolerance—A decrease in tolerance to a drug so that an individual must take more and more of the drug to achieve the same effect.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

(Mexico), Palladon (Germany, Switzerland, Finland, Sweden, Denmark), and Sophidone (France). In some countries, hydromorphone is only one component of the medication, and there are other medications included in the formulation.

Recommended dosage

Dosing of hydromorphone depends on the specific formulation/delivery system to be used, the patient's previous experience with narcotic drugs, the patient's current tolerance to narcotic medications, and the patient's current narcotic medication regimen. The dosage formats below are examples of possible dosing, but do not completely cover the full range of possibilities for safe dosing.

In adults, for relief of moderate to severe pain:

- oral: 2 to 4 mg every four to six hours; severe pain may require a first dose of 4 to 8 mg
- intravenous: 0.2 to 1 mg every two to three hours, or continuous infusion ranging from 0.5 to 3 mg per hour
- intramuscular or subcutaneous injection: 0.8 to 1 mg every three to four hours
- rectal suppository: 3 mg every six to eight hours

Higher doses may be needed by patients who have a longer history with opioid analgesic use.

Pediatric

Dosing schedules are the same for children who weigh more than 110 lb. (50 kg). Patients or caregivers should follow the healthcare provider's instructions for dosing children who weigh less than 110 lb.

Geriatric

For hydromorphone taken orally, lower doses may be needed in elderly or debilitated patients.

Other conditions and allergies

For patients with renal (kidney) or liver impairment, dosage should be decreased by a quarter to a half of the usual initial dose, and extra care should be taken in monitoring for respiratory or central nervous system depression. The extended-release form should not be used in individuals with severe liver impairment.

Precautions

Boxed warnings are included with this product that cover the following topics:

- Hydromorphone has the potential to cause life-threatening respiratory depression. Particular care should be taken in patients who have demonstrated previous intolerance to opioid pain medications. Additionally, using more than one type of medication that has the potential to cause respiratory depression can greatly increase the threat of respiratory failure.
- Hydromorphone carries serious risk for medication errors. Blood levels achieved by various delivery systems are different, and substitutions between delivery formulations cannot be made without recomputing the appropriate dose of active drug for an individual patient.
- Use of hydromorphone carries increased risk for misuse, abuse, addiction, and overdose.
- Use of hydromorphone presents the life-threatening dangers of accidental exposure to the drug (especially by children).

Hydromorphone injection should not be used in patients who are not habituated (tolerant) to opioid medications.

Because of hydromorphone's addictive potential, sudden discontinuation of the drug can lead to symptoms of withdrawal, including nausea, vomiting, diarrhea, teary eyes, runny nose, severe sweating, itchy skin, twitchy muscles, and uncontrollable yawning.

Hydromorphone can cause drowsiness and can impair physical abilities as well as mental processing and alertness.

Hydromorphone can cause low blood pressure.

Geriatric

Elderly and debilitated patients are at particular risk of complications from hydromorphone use, especially effects on the central nervous system, respiratory system, and constipating effects. Hydromorphone should be used with extreme caution and close monitoring in this population.

Hydromorphone's potential for life-threatening respiratory depression is increased in the elderly, debilitated patients, and individuals with preexisting respiratory conditions. Using more than one type of medication that has the potential for respiratory depression can greatly increase the threat of respiratory failure.

Pregnant or breastfeeding

Hydromorphone carries the FDA pregnancy category C, which means that risk cannot be ruled out in pregnant individuals. If possible, use of this drug should be avoided. Babies who have been exposed to hydromorphone acutely before birth may be born with decreased respiratory drive and a weak suck. There is a boxed warning regarding babies who have been exposed to hydromorphone chronically before birth; they may experience withdrawal syndrome (neonatal abstinence syndrome) after birth when no longer receiving hydromorphone through the placenta. These babies may require treatment to avoid severe symptoms of withdrawal.

Hydromorphone tablets and liquid should not be used for treatment of pain during labor and delivery.

Hydromorphone is known to pass into breast milk. It should be avoided by breastfeeding women.

Other conditions and allergies

Hydromorphone should be avoided or carefully monitored in people with specific conditions, including:

- adrenal problems—hydromorphone may exacerbate these conditions, leading to symptoms such as sexual

problems, problems with fertility, mood issues, and weak bones

- gall bladder problems—hydromorphone can cause spasms in one of the gall bladder valves, resulting in severe pain
- severe respiratory problems, including asthma
- thyroid disease
- morbid obesity
- prostate disease
- psychoses
- narrowing in the gastrointestinal tract
- functional bowel obstruction
- slow heart rates (bradycardia) or other heart conditions—hydromorphone may further slow the heart rate
- history of substance abuse or alcoholism
- head injury—hydromorphone and other opioid drugs may complicate assessment and course of traumatic brain injuries and other causes of brain swelling or may affect respiratory status when used in patients with head injury or coma

Hydromorphone should not be given to individuals with known sensitivity to hydromorphone or other ingredients within a specific delivery formulation. Hydromorphone should also be used with caution in individuals who have had previous reactions to codeine, hydrocodone, levorphanol, **oxycodone**, or oxymorphone.

Hydromorphone rectal suppositories should not be used in patients with increased pressure in the skull (intracranial pressure) or when the patient already has respiratory depression (as with chronic obstructive pulmonary disease, emphysema, a severe spinal abnormality or an enlarged heart that puts pressure on the lungs, or severe states of asthma).

Side effects

The most common side effects of hydromorphone treatment include:

- slow heart rate
- headache, drowsiness, confusion, unclear thinking, depression
- sweating, itching
- dehydration
- constipation
- swelling
- dry mouth
- urinary retention
- weak muscles
- shortness of breath, respiratory depression
- euphoria

- agitation, hallucinations
- upset stomach, nausea, vomiting
- blurred vision, ringing in the ears

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

The following may increase hydromorphone's side effects:

- alpha- and beta-agonists
- opioid analgesics
- amphetamines
- anticholinergic agents
- antiemetics
- **aripiprazole**
- antipsychotic agents
- cannabis
- crizotinib
- droperidol
- hydrocodone
- **hydroxyzine**
- magnesium sulfate
- methotrimeprazine
- mifepristone
- **zolpidem**
- dexmethasone
- diethyldithiocarbamate
- **diltiazem**
- disulfiram
- entacapone
- **erythromycin**
- ethinyl estradiol
- **fluconazole**
- **fluoxetine**
- **fluvoxamine**
- gestodene
- indinavir
- isoniazid
- **ketoconazole**
- **metronidazole**
- mibefradil
- miconazole
- nefazodone
- nelfinavir
- nevirapine
- norfloxacin
- norfluoxetine
- **omeprazole**
- oxiconazole
- **paroxetine**
- propoxyphene
- quinidine
- quinine
- **ranitidine**
- ritonavir
- saquinavir
- sertindole
- **sertraline**
- troglitazone
- troleandomycin
- **valproic acid**

Drugs classified as CYP3A4 inhibitors have a profound effect on hydromorphone, and may greatly increase the risk of potentially fatal side effects. There are many drugs in this group, including:

- amiodarone
- anastrozole
- **azithromycin**
- cannabinoids
- cimetidine
- **clarithromycin**
- clotrimazole
- **cyclosporine**
- danazol
- delavirdine

Hydromorphone may increase the side effects of the following:

- opioid analgesics
- antiemetics
- antipsychotic agents
- beta-blockers
- buprenorphine
- calcium channel blockers
- desmopressin
- diuretics

- hydrocodone
- hydroxyzine
- monoamine oxidase inhibitors (MAOIs)
- methotrimeprazine
- metoclopramide

Herbs and supplements

Kava kava may increase the side effects of hydromorphone.

Hydromorphone may increase the side effects of cannabis and kava kava.

Food and other substances

The hydromorphone element of this formulation may increase the side effects of alcohol.

Resources

BOOKS

- Aronson, J. K. *Meyler's Side Effects of Analgesics and Anti-inflammatory Drugs*. Oxford: Elsevier, 2010.
- Benzon, Honorio T. *Essentials of Pain Medicine*. 3rd ed. Philadelphia: Saunders, 2011.
- Smith, Howard S. *Current Therapy in Pain*. Philadelphia: Saunders, 2009.
- Waldman, Steven D. *Pain Management*. 2nd ed. Philadelphia: Saunders, 2011.

WEBSITES

- "Hydromorphone." Drugs.com. <http://www.drugs.com/mtm/hydromorphone.html> (accessed February 15, 2015).
- MedlinePlus. "Hydromorphone." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682013.html> (accessed February 15, 2015).
- U.S. National Library of Medicine. "LactMed: Hydromorphone." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+3341> (accessed February 15, 2015).

ORGANIZATIONS

- American Chronic Pain Association, PO Box 850, Rocklin, CA 95677, (800) 533-3231, APAC@theacpa.org, <http://www.theacpa.org/>.
- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- National Pain Foundation, 14828 W 6 Avenue, Suite 16-B, Room 1, Golden, CO 80401-5000, (720) 541-6808, Fax: (720) 541-6809, <http://www.thenationalpainfoundation.org/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Hydroxychloroquine

Definition

Hydroxychloroquine sulfate is a drug that fights the parasitic infection that causes malaria. It also combats autoimmune diseases such as arthritis and lupus.

Purpose

Patients may take hydroxychloroquine sulfate to treat:

- malaria, which is a disease caused by a parasite known as *Plasmodium* that is transmitted by bites from infected mosquitoes
- discoid and systemic lupus erythematosus, which are a group of diseases in which the immune system attacks healthy tissue
- rheumatoid arthritis, a chronic inflammatory disease that typically affects joints in the hands and feet

Hydroxychloroquine sulfate has also been used to treat Sjögren's syndrome, but a study in 2014 suggested that it may not be effective for this use. It is also sometimes used to treat arthritis arising from Lyme disease. In this case, it is believed that hydroxychloroquine sulfate is not only useful in treating the inflammation associated with the disease, but also it may attack the infecting bacteria (in the genus *Borrelia*) that cause Lyme disease.



Hydroxychloroquine sulfate, 200 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

Hydroxychloroquine sulfate is one of numerous drugs classified as antiprotozoals. Antiprotozoals fight infections caused by minuscule, one-celled organisms called protozoa. The parasites that cause malaria are parasitic protozoans in the genus *Plasmodium*. When a mosquito bites a person who has malaria, it picks up the protozoa. If it then bites another person, it can transmit the protozoa to another person, thereby spreading the disease. Hydroxychloroquine sulfate is used to fight the protozoa that cause malaria. Scientists are still trying to understand exactly how it works, but it is believed that hydroxychloroquine may allow the accumulation of certain molecules that are toxic to the protozoa. Although hydroxychloroquine sulfate is effective against many malarial protozoa, some organisms are resistant and unaffected by the drug, so alternate measures may need to be taken.

Hydroxychloroquine sulfate is also classified as a disease-modifying anti-rheumatic drug (DMARD). Drugs in this group alleviate some of the symptoms of arthritis, such as joint pain and swelling, and may prevent joint damage that can permanently affect movement. In diseases like rheumatoid arthritis and lupus, the patient's immune system becomes overactive and attacks healthy tissue. Hydroxychloroquine sulfate works by dampening that overactivity, therefore reducing the inflammation associated with these diseases. Lowered inflammation leads to a reduction in symptoms, including the skin rash common to patients with lupus. Scientists are unsure how this drug affects the immune system, but it is believed it may work by interfering with the action of certain immune-system cells, including interleukins and macrophages, that are involved in the attack on healthy tissue.

Prescription hydroxychloroquine sulfate is sold as 200-milligram (mg) tablets, which are taken by mouth.

U.S. brand names

Hydroxychloroquine sulfate is available in the United States under the brand name of Plaquenil.

Canadian brand names

Hydroxychloroquine sulfate is sold in Canada under the names of Apo-Hydroxyquine and Gen-Hydroxychloroquine.

International brand names

Hydroxychloroquine sulfate is also available internationally as Plaquenil, and under a variety of brand names, including:

- Axokine
- Be-easy

- Chloguin
- Dolquine
- Fen Le
- Hydrocad
- Hydroquin
- Ilinol
- Immard
- Oxiklorin
- Planil
- Plaquinol
- Polirreumin
- Quensyl
- Quinoric
- Wilflam
- Zy-Q

Origins

Hydroxychloroquine sulfate received approval from the U.S. Food and Drug Administration in April 1955. It was originally used to prevent and to treat malaria. The drug was a staple in the medical arsenal during World War II when soldiers were fighting in hot, humid conditions in the South Pacific, where malaria was quite common. Some of the patients who were taking the drug for malaria reported that they were also feeling some relief from their arthritis symptoms, such as muscle and joint pain. Hydroxychloroquine sulfate has also been found to alleviate lupus-associated symptoms, including skin rashes, and inflammations of the pericardium and pleura (the lining of the heart and lungs, respectively). Today, the drug is prescribed for all of these health conditions.

Recommended dosage

The typical adult dosages for hydroxychloroquine sulfate are:

- Malaria treatment: An initial dosage of 800 mg, followed by 400 mg in 6–8 hours, 400 mg after 24 hours, and another 400 mg after 48 hours.
- Malaria prevention: A dose of 400 mg per week (on the same day each week), beginning one to two weeks prior to arrival in an area with high risk for exposure and continuing until eight weeks after leaving the area.
- Rheumatoid arthritis: An initial dose of 400–600 mg daily for one to three months, with a maintenance dosage of 200–400 mg daily.
- Systemic lupus erythematosus: An initial dosage of 400 mg once or twice daily for a period of weeks to months, depending on patient response, with a maintenance dosage of 200–400 mg daily.

It is recommended that hydroxychloroquine sulfate be taken with food or milk. The specific dosing instructions accompanying the prescription package should be followed.

Pediatric

Hydroxychloroquine sulfate is used for the treatment and prevention of malaria in children who are at least one year old. It is also prescribed for juvenile dermatomyositis, a rare inflammatory disease that causes muscle weakness and skin rash in children who are between 18 months and 15 years old. Pediatric dosages are calculated in “base” (one 200 mg tablet of hydroxychloroquine sulfate is equivalent to 155 mg base). Typical dosages are:

- **Malaria treatment:** An initial dosage of 10 mg base per kilogram (kg, or 2.2 lb.) of the child’s weight (not to exceed 620 mg base), followed by 5 mg base/kg (not to exceed 310 mg base) at six hours after the first dose, 18 hours after the second dose, and 24 hours after the third dose.
- **Malaria prevention:** A dose of 5 mg base/kg (not to exceed 310 mg base) per week (on the same day each week), beginning two weeks prior to arrival in an area with high risk for exposure and continuing until eight weeks after leaving the area.
- **Juvenile dermatomyositis:** A dose of 7 mg/kg per day.

It is recommended that hydroxychloroquine sulfate be taken with food or milk.

Geriatric

Dosage recommendations are the same for older adults as they are for younger adults.

Precautions

Individuals who are taking this drug should be monitored for issues with knee and ankle reflexes or with muscle weakness. If these problems occur, the patient should stop taking the drug. Patients who take hydroxychloroquine sulfate for a lengthy period of time should have their blood-cell counts monitored periodically. Those patients who experience severe blood disorders that are not attributable to another disease should discontinue use of the drug.

Some patients have experienced damage to their eyes after taking this drug for a long period of time or at high dosage, so doctors will typically have the patients undergo periodic ophthalmologic examinations to check for potential problems. If any are noted, the patient should stop taking hydroxychloroquine sulfate immediately and continue to undergo ophthalmologic exams as recommended. Visual, retinal, and corneal changes can progress even after the patient stops taking the drug.

KEY TERMS

Antiprotozoals—Drugs that fight infections caused by small, one-celled animals called protozoa.

Autoimmune disease—A disorder in which the body’s antibodies mistake the body’s own tissues for foreign invaders. The immune system then attacks and causes damage to these tissues.

Lupus—A group of diseases in which the patient’s immune system attacks healthy tissue.

Lyme disease—A tick-transmitted disease with symptoms that include a rash (often described as a bull’s-eye shape) and flu-like symptoms. Left untreated, Lyme disease can cause joint, heart, and central-nervous-system issues.

Malaria—A mosquito-transmitted disease that causes fever, headache, and vomiting, and can be fatal if left untreated.

Rheumatoid arthritis—A chronic inflammatory disease that typically affects joints in the hands and feet.

Sjögren’s syndrome—A chronic autoimmune disease with common symptoms of dry eyes and dry mouth.

Pediatric

Adults should be especially vigilant in keeping this drug out of the reach of children, as accidental ingestion of this medication by young children has reportedly resulted in fatalities.

Pregnant or breastfeeding

The U.S. Food and Drug Administration has not formally assigned this drug to a pregnancy category, however, use of this drug in pregnant women should be avoided. Animal studies have shown that this drug passes readily from mother to fetus. Nonetheless, doctors may determine that the use of this drug in pregnant women is warranted for the suppression or treatment of malaria. Research suggests that the use of hydroxychloroquine sulfate is compatible with breastfeeding, but patients may still wish to discuss this practice with their healthcare provider.

Other conditions and allergies

Doctors should be cautious in prescribing hydroxychloroquine sulfate to patients with liver (hepatic) disease, with alcoholism, or with the genetic disorder

known as glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Doctors typically do not prescribe hydroxychloroquine sulfate to patients who have the chronic skin disease psoriasis or the rare group of disorders known collectively as porphyria (which mainly affect the skin or nervous system), because the drug may exacerbate symptoms. In some cases, however, doctors may deem that the benefits of hydroxychloroquine sulfate outweigh the risks, prescribe the drug, and then carefully monitor the patient for side effects.

Side effects

Side effects associated with the use of hydroxychloroquine sulfate include:

- headache
- dizziness
- diarrhea
- stomach pain, nausea, and/or vomiting
- loss of appetite
- skin rash

Interactions

Doctors should be cautious in prescribing hydroxychloroquine sulfate to patients who are also taking drugs that may be injurious to the liver. This includes such common medications as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), as well as many other drugs. For this reason, patients should tell their healthcare providers about all prescription and over-the-counter drugs that they use.

Drugs

Interactions may occur with several drugs, including:

- the arthritis drugs auranofin, gold sodium thiomalate, leflunomide
- deferiprone, which is used to treat an inherited blood disorder called thalassaemia major
- **digoxin**, used to treat cardiac arrhythmia (irregular heartbeat)
- teriflunomide, a medication used to treat multiple sclerosis
- thioridazine, which is used to treat the symptoms of schizophrenia
- vigabatrin, an anticonvulsant drug

Herbs and supplements

No specific interactions are noted, but patients should still inform their doctors about any herbs or supplements they are taking, including vitamins.

Foods and other substances

Patients should discuss their level of alcohol consumption with their doctors, as excessive alcohol use is a cause for concern with the use of this drug.

Resources

BOOKS

- Browning, David J. *Hydroxychloroquine and Chloroquine Retinopathy*. New York: Springer, 2014.
- Lebwohl, Mark G., et al. *Treatment of Skin Disease: Comprehensive Therapeutic Strategies*. 4th ed. Philadelphia: Elsevier Saunders, 2013.
- O'Dell, James R., John B. Imboden, and Lester D. Miller. "Rheumatoid Arthritis." In *Current Diagnosis & Treatment in Rheumatology*, edited by John B. Imboden, David B. Hellman, and John H. Stone. 3rd ed. New York: McGraw-Hill, 2013.

PERIODICALS

- Gottenberg, Jacques-Eric, et al. "Effects of Hydroxychloroquine on Symptomatic Improvement in Primary Sjögren Syndrome." *Journal of the American Medical Association (JAMA)* 312, no. 3 (2014): 249–58.
- Phillips, Brandon N., and Dal W. Chun. "Hydroxychloroquine Retinopathy after Short-Term Therapy." *Retinal Cases & Brief Reports* 8, no. 1 (2014): 67–69.
- Sammaritano, Lisa R., and Bonnie L. Bermas. "Rheumatoid Arthritis Medications and Lactation." *Current Opinion in Rheumatology* 26, no. 3 (2014): 354–60.

WEBSITES

- AHFS Consumer Medication Information. "Hydroxychloroquine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601240.html> (accessed February 10, 2015).
- Cannon, Michael. "Hydroxychloroquine (Plaquenil)." American College of Rheumatology. https://www.rheumatology.org/Practice/Clinical/Patients/Medications/Hydroxychloroquine_%28Plaquenil%29/ (accessed February 10, 2015).
- Drugs.com. "Hydroxychloroquine." <http://www.drugs.com/ppa/hydroxychloroquine-sulfate.html> (accessed February 10, 2015).
- Johns Hopkins Lupus Center. "Anti-Malarial Drugs: Hydroxychloroquine (Plaquenil), Chloroquine (Aralen), Quinacrine (Atabrine)." <http://www.hopkinslupus.org/lupus-treatment/lupus-medications/antimalarial-drugs/> (accessed February 20, 2015).
- Micromedex. "Hydroxychloroquine (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/hydroxychloroquine-oral-route/description/drg-20064216> (accessed February 10, 2015).
- NHS. "Hydroxychloroquine Sulphate (Hydroxychloroquine 200mg tablets)." UK Department of Health. <http://www.nhs.uk/medicine-guides/pages/MedicineSideEffects.aspx?condition=Lupus&medicine=hydroxychloroquine%20sulphate> (accessed February 20, 2015).
- U.S. National Library of Medicine. "Hydroxychloroquine Sulfate—Hydroxychloroquine Sulfate Tablet, Film-

Coated.” DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=22d4d993-b86d-478e-ac6d-7bcd217e9906> (accessed February 10, 2015).

ORGANIZATIONS

Arthritis Foundation, 1330 W. Peachtree Street, Suite 100, Atlanta, GA 30309, (404) 872-7100, <http://www.arthritis.org/>.

National Institute of Arthritis and Musculoskeletal and Skin Diseases, 1 AMS Circle, Bethesda, MD 20892-3675, (877) 22-NIAMS (226-4267), (301) 495-4484, Fax: (301) 718-6366, <http://www.niams.nih.gov/>.

Lupus Foundation of America, 2000 L Street NW, Suite 410, Washington, DC 20036, (202) 349-1155, Fax: (202) 349-1156, info@lupus.org, <http://www.lupus.org/>.

Leslie A Mertz, PhD

REVIEWED BY JAMES E. WAUN, MD, RPh

Hydroxyzine

Definition

Hydroxyzine is a medication used to relieve itching and other conditions. It is in a class of drugs called antihistamines and is among the first generation of this type of drug, or among the first developed in its class.



Hydroxyzine hydrochloride, 10 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

When a person who has allergies comes in contact with an allergic trigger (called an allergen), it can cause the release of chemicals called histamines and lead to itching and other symptoms. Antihistamines such as hydroxyzine have substances in them that either reduce or block histamines. Hydroxyzine blocks histamines and reduces activity in the body's central nervous system (CNS).

Hydroxyzine is used to relieve itching caused by hives and rashes brought on by allergies, and the drug's effects on the CNS also help relieve nausea that is brought on by motion sickness or other conditions. Hydroxyzine is sometimes used to help relieve anxiety or sedate people, such as before they have surgery.

Description

Most people who use hydroxyzine take capsules or a syrup by mouth, as directed by their physician and pharmacist. Hydroxyzine also comes in an oral suspension, which consists of tiny particles that dissolve in liquids and can be taken by mouth, and as a solution that can be injected into a muscle by a healthcare professional. Often, the medicine is started with an intramuscular injection, and then the patient takes later doses by mouth. Hydroxyzine is available only by prescription.

U.S. brand names

In the United States, hydroxyzine is sold under the brand name Vistaril. Other brands of the medication are no longer on the market, but pharmacies may carry generic versions of hydroxyzine.

Canadian brand names

In Canada, hydroxyzine is sold under the brand name Apo-Hydroxyzine.

International brand names

Hydroxyzine is sold under a large variety of other brand names in other countries.

Recommended dosage

Dosage of hydroxyzine depends on the type of solution prescribed and the purpose for taking the medication.

- To relieve itching caused by allergic reactions and conditions such as eczema, doctors usually recommend that adults take 25 milligrams (mg) of hydroxyzine three times a day by mouth or three to four times a day by injection into a muscle.
- The usual adult dose of hydroxyzine for relief of anxiety and tension is 50 to 100 mg by mouth or by

KEY TERMS

Antihistamines—Medicines that block the action of histamines, chemicals in the body that trigger allergic reactions.

Central nervous system—The processing area for the body's nerves, consisting mostly of the brain and spinal cord.

Dermatitis—Also called eczema, dermatitis is a skin rash with itching, redness, and swelling that can be chronic or caused by an allergic reaction.

Urticaria—Hives, or patches of raised, red welts on the skin that itch.

injection four times a day. To sedate a patient for an operation, doctors recommend 50 to 100 mg by mouth or injection, and 25 to 100 mg for pain.

- Adults who take hydroxyzine for nausea or vomiting usually have 25 to 100 mg injected into their muscle.

Pediatric

Hydroxyzine should only be given to children with a doctor's prescription. The following are recommended dosages for most uses in children:

- To relieve itching caused by allergic reactions and conditions such as eczema, doctors usually recommend that children younger than age 6 take no more than 50 mg of hydroxyzine per day by mouth or injection in divided doses. Children older than age 6 can take between 50 and 100 mg per day in divided doses.
- The usual dose of hydroxyzine for relief of anxiety with specific causes is 50 mg by mouth per day in divided doses for children younger than age 6. Children older than age 6 can have between 50 and 100 mg per day in divided doses. If used for sedation in children, the dosage is based on the child's weight.
- Children who take hydroxyzine for nausea or vomiting usually receive 25 to 100 mg of the drug by intramuscular injection.

Precautions

Hydroxyzine causes drowsiness, and anyone who takes it should not drive or operate dangerous equipment until they know how the medicine affects them. Taking other medications that depress the CNS, such as narcotics, at the same time or drinking alcohol while taking hydroxyzine can make drowsiness worse.

Pediatric

Adults should not give hydroxyzine to children unless a doctor prescribes the drug for the child.

Geriatric

Studies have shown no real difference in how hydroxyzine affects older adults compared with younger adults, but as people age, their liver, kidneys, and heart may not handle drugs such as hydroxyzine as well. Doctors usually begin older patients at lower doses to monitor the effects of the drug.

Pregnant or breastfeeding

The FDA has not formally assigned hydroxyzine a pregnancy category. No studies have been conducted on the effects hydroxyzine might have on the development of a fetus early in pregnancy, but animal studies show possible harm. Doctors recommend that women who are pregnant or might be pregnant avoid taking hydroxyzine. It is not known whether the drug is passed from mother to infant through breast milk, so a woman who wants to breastfeed her child should not use hydroxyzine.

Other conditions and allergies

Some people are allergic to hydroxyzine and similar drugs.

Side effects

Hydroxyzine can cause side effects, including:

- drowsiness
- dizziness
- headache
- stomach upset
- dryness in the mouth, throat, and nose
- chest congestion
- red skin

Some side effects of hydroxyzine are more severe and should be reported to a doctor immediately, including:

- problems breathing
- increasing anxiety
- weak muscles

Pediatric

In addition to many adult side effects, children can show restlessness, nervousness, tremors, and sleeplessness while on hydroxyzine.

Interactions

Hydroxyzine can interact with other drugs. It is important to tell the doctor about all medications, herbal remedies, and supplements being taken when beginning hydroxyzine.

Drugs

Taking other medications that depress the CNS at the same time as hydroxyzine can increase drowsiness and other side effects. Examples of these drugs are other antihistamines, narcotics, narcotic analgesics such as meperidine (Demerol), and some anticonvulsant drugs such as topiramate (Topamax).

Food and other substances

Anyone taking hydroxyzine should avoid alcohol while taking the medication.

Resources

PERIODICALS

Baldwin, David S., et al. "Evidence-Based Pharmacological Treatment of Anxiety Disorders, Post-Traumatic Stress Disorder and Obsessive-Compulsive Disorder: A Revision of the 2005 Guidelines for the British Association of Psychopharmacology." *Journal of Psychopharmacology* 28, no. 5 (2014): 403–39.

Fitzsimons, Roisin, et al. "Antihistamine Use in Children." *Archives of Disease in Childhood Education and Practice Edition* (2014): e-pub ahead of print. <http://dx.doi.org/10.1136/archdischild-2013-304446> (accessed February 15, 2015).

Honey, Brooke L., Katherine S. O'Neal, and Kim Crosby. "Antihistamines." *Journal of Asthma and Allergy Educators* 4, no. 4 (2013): 191–93.

OTHER

Pfizer Labs. "Vistaril." Pfizer.com. https://www.pfizer.com/files/products/uspi_vistaril.pdf (accessed February 15, 2015).

WEBSITES

"Hydroxyzine." Drugs.com. <http://www.drugs.com/hydroxyzine.html> (accessed February 15, 2015).

MedlinePlus. "Hydroxyzine." U.S. National Library, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682866.html> (accessed February 15, 2015).

ORGANIZATIONS

American Academy of Allergy, Asthma & Immunology, 555 E. Wells Street, Suite 1100, Milwaukee, WI 53202-3823, (414) 272-6071, <http://www.aaaai.org/home.aspx>.

National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, MSC 9806, Bethesda, MD 20892-9806,

(301) 496-5717, Fax: (301) 402-3573, (866) 284-4107, TTY: (800) 877-8339, <http://www.niaid.nih.gov/>.

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Hyoscyamine sulfate

Definition

Hyoscyamine sulfate, often referred to simply as hyoscyamine or hyoscine, is a medication used most often to control problems associated with the gastrointestinal (GI) tract, and sometimes to treat other problems related to certain nerves and muscles within the body. Hyoscyamine is in a class of drugs called antispasmodics/anticholinergics.

Purpose

Many functions and movements in the body happen involuntarily. For example, certain nerves in the body help to regulate heart rate or help the eye's pupils respond to light. Many nerves and smooth muscles also work together to control the activity in the stomach for



Hyoscyamine sulfate SL, 0.125 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

digesting food and eliminating waste in the form of urine and stool. Although individuals control some of these movements, others occur without notice, through a complex network of signals from nerves that instruct body function, such as telling the stomach to release fluids such as acid.

Anticholinergic medications block impulses from parasympathetic nerves, and antispasmodic medications can decrease or prevent spasms in smooth muscles, such as the ones that line the bowel wall. Because hyoscyamine has both of these agents, the drug can help manage ulcers, spasms in the stomach, irritable bowel syndrome, colic in babies, and other problems with the GI system. In addition, the drug helps to control problems with the bladder, movements related to Parkinson's disease, and poisoning from anticholinesterase agents.

Description

Hyoscyamine comes in a tablet or liquid to swallow and in the form of an extended-release, or long-lasting, tablet. Doctors prescribed that patients take the drug exactly as prescribed and to continue its use until directed to stop. Hyoscyamine does not cure any disorders, but it does relieve the symptoms of several conditions and diseases. The U.S. Food and Drug Administration (FDA) has not approved labeling of the drug's safety or effectiveness.

U.S. brand names

Hyoscyamine brand names include:

- Cystospaz
- ED-Spaz
- Hyomax
- Hyophen
- Hyosyne
- Levsin
- Oscimin

Recommended dosage

Dosage of hyoscyamine varies depending on the condition being treated and the severity of symptoms. In general, adults and children ages 12 and older may take a 0.125 milligram (mg) tablet by mouth every 4 hours as needed, as long as they do not take more than 12 tablets in a 24-hour period.

Pediatric

Children between 6 and 12 years old can take one half or one whole 0.125 mg tablet every 4 hours as

KEY TERMS

Anticholinesterase agents—Drugs that promote or augment action in the parasympathetic nervous system. They are used mostly in the treatment of Alzheimer's disease and sometimes to treat gastrointestinal problems such as obstructions.

Gastrointestinal (GI)—Describes any condition or system associated with the stomach and intestine.

Irritable bowel syndrome—A condition affecting the large intestine that causes bloating, cramping, and changes in bowel habits.

needed, as long as they do not take more than six tablets in a 24-hour period.

Precautions

There is no evidence supporting the use of hyoscyamine and similar antispasmodics in the treatment of conditions such as irritable bowel syndrome, although the drugs are prescribed for this condition.

Geriatric

Studies have not shown differences in how elderly adults react to the drug compared with younger adults, but doses may need adjusting for seniors. Older patients are more likely to experience toxic effects from hyoscyamine because of age-related reductions in kidney function.

Pregnant or breastfeeding

Hyoscyamine is a pregnancy category C drug. It is unknown whether the medication can harm an unborn child, so the drug should only be given to a pregnant woman if clearly necessary. There is evidence of hyoscyamine being passed from a mother through breast milk, so doctors and nursing mothers should use caution if the mother is taking hyoscyamine and chooses to breastfeed her infant.

Other conditions and allergies

Patients with certain conditions should use caution when taking hyoscyamine, including those who have some nervous system disorders and anyone with coronary heart disease, arrhythmia (irregular heartbeat), or congestive heart failure. Caution also should be used in patients who have high blood pressure or kidney disease or dysfunction.

Some people are allergic to hyoscyamine, and it is important to let the doctor know about any drug allergies before taking hyoscyamine. Patients with a history of heart disease or kidney disease should inform their doctors about their health histories when considering use of hyoscyamine.

Side effects

Use of hyoscyamine can produce side effects, including:

- dizziness
- drowsiness
- blurred vision
- headache
- warm or flushed skin
- problems urinating
- dry mouth

Some side effects from hyoscyamine can be severe and should be reported to a doctor right away. These include:

- rapid or irregular heartbeat
- skin rash
- diarrhea
- pain in the eyes

Interactions

It is important to tell the doctor about any medication, herbal preparations, or vitamin supplements being taken before using hyoscyamine.

Drugs

Hyoscyamine can interact with some drugs, affecting how well one of the drugs works or worsening side effects. In particular, taking antacids can interfere with the stomach's ability to absorb hyoscyamine. It is helpful to take hyoscyamine before meals and antacids after meals. Other medications that interact with hyoscyamine include:

- amantadine, a medication used to treat Parkinson's disease
- **amitriptyline** (Elavil), **nortriptyline** (Aventyl, Pamelor), and certain other antidepressant medications
- **haloperidol**, an antipsychotic medicine

Resources

PERIODICALS

Schor, Nina F. "Why Our Patients (and We) Need Basic Science Research." *Neurology* 80, no. 22 (2013): 2070–75.

Srinath, Arvind Iyengar. "Pain Management in Patients with Inflammatory Bowel Disease: Insights for the Clinician." *Therapeutic Advances in Gastroenterology* 5, no. 5 (2012): 339–57.

OTHER

Alaven Pharmaceutical. "Levsin." Medapharma.us. http://www.medapharma.us/products/pi/LevsinSLTablets_PI.pdf (accessed February 7, 2015).

WEBSITES

"Hyoscyamine." Drugs.com. <http://www.drugs.com/cdi/hyoscyamine.html> (accessed February 7, 2015).

MedlinePlus. "Hyoscyamine." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a684010.html> (accessed February 7, 2015).

ORGANIZATIONS

American Gastroenterological Association, 4930 Del Ray Avenue, Bethesda, MD 20814, (301) 654-2055, Fax: (301) 654-5920, <http://www.gastro.org/>.

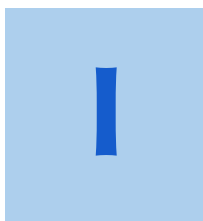
U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) 463-6332, <http://www.fda.gov/ForConsumers/default.htm>.

Teresa G. Odle, BA, ELS

REVIEWED BY KEVIN GLAZA, RPh

Hytrin see **Terazosin**

Hyzaar see **Losartan/hydrochlorothiazide**



Ibandronate

Definition

Ibandronate is a medication called a bisphosphonate. It is used mostly to prevent and manage osteoporosis, a condition related to weakened and brittle bones.

Purpose

People who have osteoporosis have an increased amount of porous bone, which is the basis for the disease's name. The bones begin to lose much of their mass, or density, and become weaker and break easily. The condition occurs most often in older people, especially older women. Bisphosphonates such as ibandronate help slow the bone loss. This can slow the overall progression of osteoporosis and help prevent broken bones. Ibandronate sodium is designed specifically to treat osteoporosis in postmenopausal women, although it may be used for other bone-related conditions.

Description

Ibandronate sodium is available as a tablet taken orally (by mouth) or as a solution for intravenous (IV) administration. It is prescribed either as a high-dose tablet that is taken once a month on the same date each month, or as smaller-dose tablet that is taken daily. The intravenous medication is administered three times monthly.

U.S. brand names

In the United States, ibandronate is sold as the prescription medication Boniva. It is manufactured by Genentech, a part of the Roche Group.

Recommended dosage

Women who take ibandronate once a month take a single 150 mg tablet on the same morning each month by

swallowing it whole with 6 or 8 ounces (oz., or 177 or 237 milliliters [mL]) of water only and while sitting or standing upright. If a woman forgets to take the 150 mg tablet on the scheduled date in a given month, she can take it the next morning after remembering, as long as the next scheduled dose is at least seven days away. If the next scheduled monthly dose is less than seven days away, it is best to wait and take the next month's dose as scheduled.

The daily 2.5 mg tablets should be taken at the same time each day with 6 or 8 oz. (177 or 237 mL) of water. If a woman forgets the daily dose on a given morning, she should skip the dose and continue with her regular schedule of taking the tablets the next morning.

Ibandronate should be taken on an empty stomach.

Precautions

Ibandronate can cause gastrointestinal (GI) symptoms, including irritation of the esophagus, the upper part of the GI tract, which carries food from the mouth to the stomach. Women should not lie down for one hour after taking ibandronate to give the pill time to be absorbed by the stomach and to prevent damage to the esophagus or sores in the mouth. The medication should never be taken at bedtime, the tablets should always be swallowed whole, and women should carefully follow instructions about use of water and foods or liquids when taking ibandronate.

Anyone with low blood calcium levels, problems with digestion, kidney disease, inability to stand up for about an hour, or planned dental surgery should discuss these issues with the doctor before taking ibandronate. Some people are allergic to ibandronate or one of its ingredients.

Geriatric

Overall safety and effectiveness of ibandronate are observed to be similar in older patients to those in all adults. There is a possibility of greater sensitivity to the side effects of the medication among older women.



Ibandronate sodium, 150 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Pregnant or breastfeeding

Ibandronate is in pregnancy category C, meaning it has been tested only in animals; women who are pregnant should use the medication only if the benefits outweigh potential risks. Researchers do not know if the medication is secreted in breast milk.

Other conditions and allergies

Women who already have upper GI conditions, such as gastritis, ulcers, or Barrett's esophagus, should discuss these conditions with their doctor and use ibandronate with caution. The medication can worsen their GI condition.

Side effects

Stomach pain and nausea are among the most common symptoms experienced by people who take ibandronate. Other side effects include:

- constipation
- diarrhea
- dizziness
- headache
- more frequent or painful urination
- sore throat and flulike symptoms

Other side effects may be more serious, and a woman should contact her doctor right away if she experiences:

KEY TERMS

Gastrointestinal—Referring to areas of the digestive system, specifically the stomach and intestines.

Postmenopausal—Describing the time after which a woman has reached menopause or has not had a menstrual period for 12 consecutive months.

- heartburn that is new or gets worse
- trouble with swallowing or pain when swallowing
- severe pain in the joints, bones, muscles, or upper chest
- new or unusual pain in the hip or thigh
- jaw pain or numbness
- a rash
- loose teeth or sore and swollen gums

Interactions

Certain medicines, vitamins, and herbal supplements can interact with ibandronate or cause it work less effectively. Women should avoid taking any vitamins or other medications they use for at least an hour after taking ibandronate.

Drugs

Several drugs cause serious interactions if taken along with ibandronate. Among the most common are **aspirin** and other nonsteroidal anti-inflammatory drugs, or over-the-counter painkillers. Others are antacids, which are used to relieve heartburn. Prescription drugs that interact with ibandronate include antivirals, such as **cidofovir** (Vistide).

Herbs and supplements

Women concerned about bone health often take calcium supplements; certain vitamins and other supplements containing calcium can interfere with the body's ability to absorb ibandronate. It is helpful to continue the use of calcium and vitamin D supplements as directed to maintain bone health, but these supplements must be taken at least 60 minutes after taking ibandronate.

Food and other substances

Ibandronate should always be taken before eating or drinking and before taking any other medication or supplements. The medicine should be taken only with 6 or 8 oz. (177 or 237 mL) of plain water. Some mineral waters contain calcium and should be avoided until at

least one hour after taking ibandronate. Other drinks, such as coffee, tea, soda, and juice, should be avoided for at least one hour. Food can affect how the body absorbs the medicine, which is why ibandronate should be taken in the morning before eating or drinking anything but water. Food should be avoided for an hour after taking the medicine.

Resources

PERIODICALS

Suresh, Ernet, Michael Pazianas, and Bo Abrahamsen. "Safety Issues with Bisphosphonate Therapy for Osteoporosis." *Rheumatology* 53 (2014): 19–31.

Vestergaard, Peter. "New Strategies for Osteoporosis Patients Previously Managed with Strontium Renalate." *Therapeutic Advances in Musculoskeletal Disease* 6, no. 6 (2014): 217–25.

WEBSITES

American Society of Health-System Pharmacists. "Ibandronate." MedlinePlus. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a605035.html> (accessed December 18, 2014).

Drugs.com. "Ibandronate." Drugs.com. <http://www.drugs.com/cdi/ibandronate.html> (accessed December 18, 2014).

Genentech. "Boniva Tablets (Ibandronate Sodium)." Genentech. <http://www.gene.com/patients/medicines/boniva-tablets> (accessed December 18, 2014).

National Osteoporosis Foundation. "Types of Osteoporosis Medications." National Osteoporosis Foundation. <http://nof.org/articles/22> (accessed December 18, 2014).

RXList. "Boniva." RXList. <http://www.rxlist.com/boniva-drug.htm> (accessed December 18, 2014).

ORGANIZATIONS

American Academy of Orthopaedic Surgeons, 9400 West Higgins Road, Rosemont, IL 60018-4262, (847) 823-7186, Fax: (847) 823-8125, <http://www.aaos.org/home.asp>.

National Osteoporosis Foundation, 1150 17th Street, Suite 850, Washington, DC 20036, Fax: (202) 223-2237, (800) 231-4222, info@nof.org, <http://nof.org/>.

Teresa G. Odle, BA, ELS

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC



Ibuprofen (IBU), 800 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Ibuprofen is used to treat mild to moderately severe pain. It is particularly effective against inflammatory diseases (such as rheumatoid arthritis), musculoskeletal conditions (such as osteoarthritis), fever, and menstrual pain.

Off-label uses

Ibuprofen has been used to treat acute episodes of migraine headaches, pain and inflammation due to ankylosing spondylitis or gout, and cystic fibrosis. Ibuprofen has also been used as a preventive drug against the onset of migraine headaches in susceptible individuals.

Description

Adult-strength ibuprofen is available in tablet and capsule forms, in strengths of 200, 400, 600, and 800 milligram (mg). Only the 200 mg strength is available over the counter. Other strengths require a physician's prescription.

Ibuprofen in children's strength is available in scored, chewable tablets containing 100 mg of active drug. Liquid formulations are available in strengths of 50 mg per 1.25 milliliters (mL) (40 mg per mL) for infants and 100 mg per 5 mL for children.

U.S. brand names

Ibuprofen is sold in the United States under many brand names, including Addaprin, Advil, Caldolor,

Ibuprofen

Definition

Ibuprofen is a nonprescription painkiller (analgesic) that belongs to the family of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs).

Motrin, EnovaRX, Genpril, I-Prin, NeoProfen, and Provil. Many generics are also available.

Canadian brand names

Ibuprofen is sold in Canada under many brand names, including CanadaAdvil, Advil, Apo-Ibuprofen, Caldolor, Europrofen, APC-Ibuprofen, Jamp-Ibuprofen, Motrin, Novo-Profen, and Pamprin.

International brand names

Ibuprofen is sold under several hundred brand names internationally, including Abumol (Kenya), Actron (Argentina), Adolorin (Austria), Artofen (Israel), Brufanic (Japan), Cibalginafor (Italy), Dol (Colombia), and Gesica (Thailand). In some countries, ibuprofen is only one component of the medication, and there are other medications included in the formulation.

Recommended dosage

For oral administration of ibuprofen to adults and geriatric patients, the following dosages are recommended:

- inflammatory diseases: 400–800 mg three to four times a day, for a maximum of 3,200 mg per day
- general pain, fever, menstrual pain: 200–400 mg every four to six hours
- migraine headache: 400 mg immediately on start of symptoms, for a maximum of 400 mg per day unless otherwise directed by a physician
- pericarditis: 400–800 mg three to four times a day, for a maximum of 3,200 mg per day

Pediatric

For oral administration of ibuprofen to pediatric patients, the following dosages are recommended:

- juvenile idiopathic arthritis: 30–50 mg per kilogram (kg, or 2.2 lb.) of body weight, divided into three doses given every eight hours, for a maximum of 2,400 mg/day
- pain relief: 4–10 mg/kg/dose given every six to eight hours

To control a fever in children 6 months to 12 years of age:

- temperature less than 102.5°F (39°C): 5 mg/kg/dose every six to eight hours, for a maximum of 40 mg/kg per day
- temperature greater than 102.5°F (39°C): 10 mg/kg/dose every six to eight hours, for a maximum of 40 mg/kg per day

KEY TERMS

Analgesic—A drug used to control pain.

Ankylosing spondylitis—A type of arthritis in the spine that leads to stiffening and fusion of the vertebral (spinal) bones.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Gout—A condition in which the deposition of uric acid crystals in the joints causes swelling and pain.

Migraine headache—A condition that causes episodes of severe headache, usually with light and sound sensitivity, visual changes, nausea, and vomiting.

Pericarditis—Inflammation of the sac around the heart.

Precautions

Ibuprofen carries several boxed warnings:

- Individuals should be aware of an increased risk of life-threatening heart attack or stroke with the use of ibuprofen. Risk elevates over time and in the setting of other cardiovascular risk factors or conditions.
- Individuals should be aware of an increased risk of life-threatening gastrointestinal irritation, inflammation, ulceration, bleeding, or perforation. People with a history of these problems, the elderly, smokers, heavy alcohol drinkers, or those using aspirin, blood thinners, or steroid medications should use particular caution or take an alternate drug.
- Ibuprofen should not be given to patients who have had a recent coronary artery bypass graft (CABG), due to a greatly increased risk of heart attack or stroke.

Ibuprofen increases bleeding time. Patients with clotting disorders or who are taking other medications, such as blood thinners or aspirin, should use particular caution and have regular monitoring for the development of anemia. Individuals who are scheduled to have dental or surgical procedures should avoid the use of ibuprofen in the week prior to the procedure.

Ibuprofen can cause an increased blood level of potassium, especially in older people, patients with kidney disease or diabetes, or individuals taking other drugs that can increase potassium levels.

Ibuprofen can cause skin reactions, including rashes, welts, hives, blisters, and separation/peeling of the skin layers. If this occurs, ibuprofen use should be immediately stopped.

Geriatric

The elderly are at particular risk of complications from ibuprofen use, especially bleeding, heart attack, and stroke. Ibuprofen should be used with extreme caution and close monitoring in this population.

Pregnant or breastfeeding

Ibuprofen is in the U.S. Food and Drug Administration (FDA) pregnancy category C up to 30 weeks' gestation and the category D after 30 weeks' gestation. Category C means that risk cannot be ruled out in pregnant women. If possible, use of this drug should be avoided. Category D means that studies have shown risk to the developing fetus. Ibuprofen should not be used by women in the last trimester of pregnancy.

Research is not conclusive on whether ibuprofen passes into breast milk. It should be avoided by breastfeeding women.

Other conditions and allergies

Ibuprofen can exacerbate certain conditions and should be avoided in people with:

- asthma (may cause severe bronchospasm and wheezing)
- recent CABG surgery
- liver disorders (may cause hepatitis, liver failure)
- high blood pressure (may prompt the onset of high blood pressure or the worsening of preexisting high blood pressure)
- kidney impairment (may worsen preexisting kidney problems or prompt the onset of kidney problems in the elderly or individuals who are dehydrated, have heart or liver failure, or are taking diuretic medications or angiotensin-converting enzyme [ACE] inhibitors)

Ibuprofen should not be taken by individuals who are hypersensitive to ibuprofen or NSAIDs or who have the following cluster of three factors: bronchial asthma, **aspirin** intolerance, and rhinitis. Individuals who have had bronchospasm, asthma, rhinitis, or hives while taking aspirin or other NSAIDs should not take ibuprofen.

Side effects

The most common side effects of ibuprofen treatment include:

- upset stomach
- abdominal pain

- sensation of indigestion
- nausea, vomiting
- gas, flatulence
- constipation or diarrhea
- nervous feelings
- ringing in the ears
- itching, rash, hives
- headache, dizziness, drowsiness
- seizures
- blood test evidence of bone marrow suppression, including low white blood cell count, low platelets, and low hematocrit (red blood cell levels)
- blood test evidence of liver damage
- blood test evidence of kidney damage
- blood in the urine
- yellow cast to skin or whites of eyes

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Concomitant use of ibuprofen may increase potential toxic effects of the following drugs:

- 5-aminosalicylic acid derivatives
- antiplatelet drugs
- aminoglycoside antibiotics
- anticoagulants
- bisphosphonate derivatives
- collagenase
- **cyclosporine**
- desmopressin
- **digoxin**
- **haloperidol**
- lithium
- **methotrexate**
- salicylates
- **tacrolimus**
- tenofovir
- vancomycin

The risk of potential adverse effects from ibuprofen may be increased with concomitant use of the following drugs:

- ACE inhibitors
- angiotensin II receptor blockers
- tricyclic antidepressants
- corticosteroids
- dextetopfen
- **diclofenac**
- floctafenine
- **ketorolac**
- probenecid
- selective serotonin reuptake inhibitors (SSRIs)
- serotonin and norepinephrine reuptake inhibitors (SNRIs)
- treprostinil

The use of ibuprofen may hamper the effectiveness of the following drugs:

- aliskiren
- beta-blockers
- eplerenone
- hydralazine
- loop diuretics
- potassium-sparing diuretics
- thiazide diuretics

Bile acid sequestrants may hamper the effectiveness of ibuprofen.

Food and other substances

The gastrointestinal risks of ibuprofen may be decreased when the drug is taken with food.

Resources

BOOKS

- Aronson, J. K. *Meyler's Side Effects of Analgesics and Anti-inflammatory Drugs*. Oxford, UK: Elsevier, 2010.
- Benzon, Honorio T. *Essentials of Pain Medicine*. 3rd ed. Philadelphia: Saunders, 2011.
- Smith, Howard S. *Current Therapy in Pain*. Philadelphia: Saunders, 2009.
- Waldman, Steven D. *Pain Management*. 2nd ed. Philadelphia: Saunders, 2011.

WEBSITES

- "Ibuprofen." Drugs.com. <http://www.drugs.com/ibuprofen.html> (accessed February 15, 2015).
- MedlinePlus. "Ibuprofen." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682159.html> (accessed February 15, 2015).

U.S. National Library of Medicine. "LactMed: Ibuprofen." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+3099> (accessed February 15, 2015).

ORGANIZATIONS

- American Chronic Pain Association, PO Box 850, Rocklin, CA 95677, (800) 533-3231, APAC@theacpa.org, <http://www.theacpa.org/>.
- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- National Pain Foundation, 14828 W 6 Avenue, Suite 16-B, Room 1, Golden, CO 80401-5000, (720) 541-6808, Fax: (720) 541-6809, <http://www.thenationalpainfoundation.org/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rosalyn S. Carson-Dewitt, MD

REVIEWED BY KEVIN GLAZA, RPh

Ibuprofen/hydrocodone see **Hydrocodone/ibuprofen**

Imatinib

Definition

Imatinib mesylate is an enzyme inhibitor used for cancer therapy.

Purpose

Imatinib was first approved by the U.S. Food and Drug Administration (FDA) to treat a cancer called chronic myeloid leukemia (CML). In 2013, the FDA approved the use of imatinib for treating children who have a specific type of acute lymphoblastic leukemia that is Philadelphia chromosome positive. In this type of leukemia, which can come on suddenly and be life threatening, part of a chromosome moves to another. The drug is also approved to treat leukemia and gastrointestinal stromal tumors (GIST).

Description

Imatinib mesylate is the first drug of its kind developed. It fights cancer by turning off an enzyme called tyrosine kinase, which causes CML cells to multiply at an abnormal rate. Its function is different from that of other cancer drugs, because it specifically targets an enzyme that allows the growth of CML cells.



Imatinib, 100 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

This drug has been shown to significantly reduce the number of cancer cells in the blood and bone marrow of treated patients.

Patients who are diagnosed with CML in the three phases of disease can be treated with imatinib mesylate. Chronic myeloid leukemia appears to respond within one to three months following administration of this drug.

U.S. brand names

Imatinib mesylate is sold under the brand name Gleevec.

Origins

Imatinib mesylate is also known as STI571, a name it was given during early development. STI stands for “signal transduction inhibitor.”

Recommended dosage

To minimize the risk of gastrointestinal irritation, imatinib mesylate should be taken with food and a large glass of water. The recommended dosage varies according to clinical circumstances and stage of disease but generally ranges between 300 and 600 milligrams (mg) per day. As long as the patient continues to benefit, treatment should be continued. A doctor experienced in

the treatment of patients with CML should initiate therapy.

Precautions

Studies have not been performed with imatinib mesylate to determine if it is a carcinogen (cancer causing); therefore, it is not known whether this drug may cause mutations or have cancer-causing effects.

Side effects

Commonly reported side effects include nausea and vomiting, muscle cramps, edema (water retention), skin rash, diarrhea, heartburn, and headache. Serious side effects occur less frequently but may include severe edema, liver toxicity, and the potential for excess bleeding, especially in the elderly.

Interactions

Patients must inform their doctors of any drugs they are taking, including supplements, to avoid drug interactions.

Drugs

Imatinib mesylate interacts with many other drugs. In some cases, side effects may be increased because imatinib mesylate might increase blood levels of certain drugs. Alternatively, imatinib mesylate may decrease blood levels of the drugs, thus reducing their effectiveness. In addition, the blood levels of imatinib mesylate may rise or fall because of other drugs. Therefore, the side effects of imatinib mesylate may be increased, or its effectiveness may be reduced. Patients must discuss all of their medications with their doctor due to many potential drug-drug interactions.

The following drugs or families of drugs may interact with imatinib mesylate:

- the antifungal drugs **ketoconazole** and itraconazole
- **carbamazepine**
- certain HMG-CoA reductase inhibitors
- **cyclosporine**
- dexamethasone
- dihydropyridine calcium channel blockers
- **erythromycin**
- phenobarbital
- **phenytoin**
- pimozide
- rifampicin
- triazolobenzodiazepines

Imatinib mesylate also interacts with the anticoagulant drug warfarin. Patients needing anticoagulant

KEY TERMS

Cancer—A term for diseases in which abnormal cells divide without control. Cancer cells can invade nearby tissues and spread through the bloodstream and lymphatic system to other parts of the body.

Enzyme—Any protein that acts as a catalyst, increasing the rate of a chemical reaction.

Gastrointestinal stromal tumor (GIST)—Tumor of the gastrointestinal tract derived from connective tissue.

Kinase—An enzyme.

Leukemia—A type of cancer in which the bone marrow produces an excessive number of abnormal (leukemic) white blood cells. White blood cells protect the body against infection, but the abnormal cells suppress the production of normal white blood cells.

Tumor—An abnormal mass of tissue that serves no purpose. Tumors may be either benign (non-cancerous) or malignant (cancerous).

Tyrosine—A nonessential amino acid. Amino acids are the building blocks of protein. They are the raw materials used by the body to make protein. Tyrosine is labeled “nonessential” because when the amino acids are lacking in the diet, they can be manufactured by the body.

therapy while taking imatinib mesylate should be prescribed low-molecular-weight or standard heparin.

Other drug interactions may be possible.

Herbs and supplements

Investigators have also evaluated the effect of St. John's wort (an herb used to treat mild to moderate depression) on the pharmacokinetics of imatinib. Studies showed that the administration of St. John's wort along with imatinib mesylate reduced absorption and increased elimination of imatinib, reducing drug exposure by as much as 42%. Since the clinical efficacy of imatinib is dependent on drug dose and concentration, the interaction with St. John's wort could result in a loss of therapeutic effect. Therefore, the concurrent use of St. John's wort and imatinib should be avoided.

Resources

WEBSITES

National Cancer Institute. “Gastrointestinal Stromal Tumors Treatment (PDQ®).” <http://www.cancer.gov/cancertopics/pdq/treatment/gist/Patient> (accessed February 25, 2015).

Novartis. “Gleevec.” http://www.gleevec.com/index.jsp?usertrack.filter_applied=true&NovaId=4029462118440539469 (accessed February 25, 2015).

U.S. Food and Drug Administration. “FDA Approves Gleevec for Children with Acute Lymphoblastic Leukemia.” <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm336868.htm> (accessed February 25, 2015).

ORGANIZATIONS

American Cancer Society, 250 Williams Street NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org/>.

National Cancer Institute, 9609 Medical Center Drive, BG 9609 MSC 9760, Bethesda, MD 20892-9760, (800) 4-CANCER (422-6237), <http://www.cancer.gov/>.

Teresa G. Odle

REVIEWED BY KEVIN GLAZA, RPh

ImDur see **Isosorbide**

Imipramine

Definition

Imipramine is a tricyclic antidepressant.

Purpose

Imipramine is used to relieve symptoms of depression. It is also used in the treatment of enuresis (bed-wetting) in people between the ages of 6 and 25.

Description

Imipramine hydrochloride was the first tricyclic antidepressant to be discovered. Tricyclic antidepressants act to change the balance of naturally occurring chemicals in the brain (called neurotransmitters) that regulate the transmission of nerve impulses between cells. Mental well-being is partially dependent on maintaining a correct balance of these brain chemicals. Imipramine is thought to act primarily by increasing the concentration of norepinephrine and serotonin (both chemicals that stimulate nerve cells) and, to a lesser extent, by blocking the action of another brain chemical, acetylcholine. Imipramine shares most of the properties of other tricyclic antidepressants, such as **amitriptyline**, **amoxapine**, **clomipramine**, **desipramine**, **nortriptyline**, **protriptyline**, and **trimipramine**.



Imipramine hydrochloride, 50 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

The therapeutic effects of imipramine, like those of other antidepressants, appear slowly. Maximum benefit is often not evident for two to three weeks after starting the drug. People taking imipramine should be aware of this and continue taking the drug as directed even if they do not see immediate improvement.

U.S. brand names

Imipramine is sold under the brand name Tofranil in the United States.

Recommended dosage

Imipramine is usually started with a total amount of up to 100 milligrams (mg) per day, divided into several smaller doses. This is generally increased to a total of 200 mg per day divided into several doses. Total dosages for patients who are not hospitalized should be no more than 200 mg per day. The recommended maximum dosage for the drug for all patients is 250–300 mg per day. Before dosages greater than 200 mg per day are taken, an electrocardiogram (ECG) should be done. This should be repeated at regular intervals until a steady-state dosage is reached. Lower dosages are recommended for adolescents and older people (over age 60). The lowest dosage that controls symptoms of depression should be used.

Imipramine should be withdrawn gradually, rather than abruptly discontinued. This will help reduce the possibility of a relapse into depression.

Precautions

Some studies have shown that children and adults up to age 24 are at an increased risk of developing suicidal thoughts or behaviors when taking antidepressants, including imipramine. Any patient taking imipramine should be closely monitored for signs of worsening depression or other risk factors, including panic attacks, difficulty falling asleep, irritability, planning to engage in self-harm or to attempt suicide, or abnormal excitement. Any signs that a person is considering self-harm or suicide warrants an immediate call to the doctor. The risk of suicide may also be increased when imipramine is taken in overdose or combined with alcohol.

A common problem with tricyclic antidepressants is sedation (drowsiness, lack of physical and mental alertness). This side effect is especially noticeable early in therapy. In most patients, sedation decreases or disappears entirely with time, but until then patients taking imipramine should not perform hazardous activities requiring mental alertness or coordination. The sedative effect is increased when imipramine is taken with other central nervous system depressants, such as alcoholic beverages, sleeping medications, other sedatives and related drugs, or antihistamines, and combinations of imipramine with any of these substances should be avoided.

Imipramine may increase heart rate and stress on the heart. It may be dangerous for people with cardiovascular disease, especially those who have recently had a heart attack, to take this drug or other antidepressants in the same pharmacological class. Older people and people with a history of heart disease may develop heart arrhythmias (irregular heartbeat), heart conduction abnormalities, congestive heart failure, heart attack, abnormally rapid heart rates, and strokes. Changes in blood pressure have also been reported.

Manic episodes and the emergence of symptoms of preexisting psychotic states have been reported when imipramine therapy is started.

Patients undergoing surgery should stop taking imipramine at least two weeks before their procedure (if possible) to avoid adverse interactions with the anesthesia.

Other conditions and allergies

Like all tricyclic antidepressants, imipramine should be used cautiously and with close physician supervision in patients, especially the elderly, with benign prostatic hypertrophy, urinary retention, and glaucoma, especially angle-closure glaucoma (the most severe form). Before starting treatment, people with these conditions should discuss the relative risks and benefits of treatment with their doctors to help determine if imipramine is the right antidepressant for them.

Side effects

Imipramine shares side effects common to all tricyclic antidepressants. The most frequent of these are dry mouth, constipation, urinary retention, increased heart rate, sedation, irritability, dizziness, and decreased coordination. As with most side effects associated with tricyclic antidepressants, the intensity is highest at the beginning of therapy and tends to decrease with continued use.

Confusion, disorientation, delusions, insomnia, and anxiety have been reported as side effects in a small percentage of people taking imipramine, as have problems associated with the skin (loss of sensation, numbness and tingling, rashes, spots, itching, and puffiness), seizures, ringing in the ears, nausea, vomiting, loss of appetite, diarrhea, and abdominal cramping.

Dry mouth, if severe to the point of causing difficulty speaking or swallowing, may be managed by dosage reduction or temporary discontinuation of the drug. Patients may also chew sugarless gum or suck on sugarless candy in order to increase the flow of saliva. Some artificial saliva products may provide temporary relief.

Interactions

Individuals should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs and supplements, before starting treatment with imipramine.

Drugs

Methylphenidate may increase the effects of imipramine. This is usually avoided by reducing the dosage of imipramine.

Dangerously high blood pressure has resulted from the combination of tricyclic antidepressants, such as imipramine, and members of another class of antidepressants known as monoamine oxidase inhibitors (MAOIs). Patients taking imipramine should not take monoamine oxidase inhibitors (or vice versa). Patients taking any MAOIs, such as Nardil (phenelzine sulfate) or Parnate (tranylcypromine sulfate), should stop taking the drug and wait at least 14 days before starting treatment with imipramine or any other tricyclic antidepressant. The same holds true when discontinuing imipramine and starting an MAOI.

The sedative effects of imipramine are increased by other central nervous system depressants such as sedatives, sleeping medications, or medications used for other mental disorders such as schizophrenia. The anticholinergic (drying out) effects of imipramine are additive with other anticholinergic drugs such as

KEY TERMS

Depression—A mental state characterized by excessive sadness and loss of interest in life; other symptoms may include altered sleep or eating patterns, loss of concentration, agitation, lack of energy, and, in severe cases, attempts at self-harm or suicide.

Enuresis—Involuntary urination.

Monoamine oxidase inhibitors (MAOIs)—A group of antidepressant drugs that decreases the activity of monoamine oxidase, a neurotransmitter found in the brain that affects mood.

Neurotransmitters—Naturally occurring chemicals in the body that carry chemical messages to nerve cells, often by transmitting nerve impulses. Central nervous system well-being is dependent on a balance among the neurotransmitters acetylcholine, dopamine, serotonin, and norepinephrine.

Relapse—A recurrence of symptoms after a period of improvement or recovery.

benztropine, biperiden, trihexyphenidyl, and antihistamines.

Food and other substances

Imipramine may increase the depressant action of alcohol. For this reason, people taking imipramine should not drink alcoholic beverages.

Resources

BOOKS

- Adams, Michael, and Norman Holland. *Core Concepts in Pharmacology*. 4th ed. Upper Saddle River, NJ: Prentice Hall, 2014.
- van Boxtel, Chris J., Budiono Santoso, and I. Ralph Edwards, eds. *Drug Benefits and Risks: International Textbook of Clinical Pharmacology*. 2nd ed. Amsterdam: IOS Press, 2008.

PERIODICALS

- Baldwin, D. S., M. Green, and S. A. Montgomery. "Lack of Efficacy of Moclobemide or Imipramine in the Treatment of Recurrent Brief Depression: Results from an Exploratory Randomized, Double-Blind, Placebo-Controlled Treatment Study." *International Clinical Psychopharmacology* 29, no. 6 (2014): 339–43.
- Hearn, L., et al. "Imipramine for Neuropathic Pain in Adults." *Cochrane Database of Systematic Reviews* 5, art. no. CD010769 (May 19, 2014). <http://dx.doi.org/10.1002/14651858.CD010769.pub2> (accessed February 25, 2015).

Uguz, F., et al. "Low-Dose Imipramine for Treatment of Panic Disorder during Pregnancy: A Retrospective Chart Review." *Journal of Clinical Psychopharmacology* 34, no. 4 (2014): 513–15.

OTHER

University of Michigan Health System. "Instructions for Use of Imipramine." <http://www.med.umich.edu/1libr/urology/InstructionsImipramine.pdf> (accessed February 25, 2015).

WEBSITES

A.D.A.M. Medical Encyclopedia. "Imipramine." University of Maryland, Baltimore Washington Medical Center. <http://www.mybwmc.org/library/41/067000> (accessed February 25, 2015).

AHFS Consumer Medication Information. "Imipramine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682389.html> (accessed February 25, 2015).

U.S. Food and Drug Administration. "Antidepressant Use in Children, Adolescents, and Adults." <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/UCM096273> (accessed February 25, 2015).

ORGANIZATIONS

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.

National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.

National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 443-4513, (866) 415-8051, Fax: (301) 443-4279, TTY: (301) 443-4279, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Imiquimod cream. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Imiquimod cream is approved by the U.S. Food and Drug Administration (FDA) for the treatment of genital warts, typical AK, and biopsy-confirmed primary sBCC.

Genital warts occur on the skin or adjoining mucous membranes of the genital or anal areas. They are caused by highly contagious, sexually transmitted human papillomavirus (HPV). Imiquimod is approved for the treatment of genital warts in adults and children over age 12. Neither imiquimod nor other treatments cure genital warts, nor are any treatments 100% effective. New warts may develop even during treatment. Treatment may reduce the risk of spreading the virus to others.

AK appears as flat, scaly skin growths caused by sun exposure that may develop into cancer. Imiquimod is approved for treating AK on the face or scalp in people with healthy immune systems (immunocompetent).

BCC is the most common type of skin cancer, affecting at least 800,000 Americans every year. sBCC is one of four BCC subtypes and usually occurs as a result of ultraviolet (UV) exposure on the arms, legs, or trunk. Imiquimod is approved to treat sBCC on the neck, trunk, arms, or legs in immunocompetent patients. It is approved only for tumors of diameters not exceeding 0.8 in. (2 cm) and only when surgical methods are less appropriate and patient follow-up is reasonably assured. Imiquimod is not approved for treating sBCC on the hands or feet, nor is it effective in all patients. Some patients may need to undergo another form of treatment.

Imiquimod

Definition

Imiquimod is a cream for treating genital warts, a precancerous skin condition called actinic keratosis (AK), and superficial basal cell carcinoma (sBCC). Imiquimod is a topical biotherapy or immunotherapy in a class of medications called biological-response or immune-response modifiers.

KEY TERMS

Actinic keratosis (AK)—Dry, scaly lesions or patches on the skin from long-term sun exposure that are considered the earliest stage in the development of squamous cell carcinoma; also known as solar keratosis.

Adjuvant—A substance added to a vaccine to increase the immune response.

Agonist—A drug, such as imiquimod, that binds to a receptor and mimics the effects of the endogenous receptor-binding substance.

Cytokine—A protein associated with inflammation that, at high levels, may be toxic to nerve cells in the developing brain.

Genital warts—Venereal warts, anogenital warts, or condylomata acuminata; painless, pink or grayish growths on the skin and mucous membranes of the genitals and anal area caused by sexually transmitted human papillomavirus.

Human papillomavirus (HPV)—A large family of viruses, some of which cause genital and anal warts.

Immunotherapy—A form of treatment that uses biologic agents to enhance or stimulate normal immune function.

Interferon—A potent immune-defense protein (cytokine) produced by viral-infected cells. Manufactured interferon is used as an anticancer and antiviral drug.

Superficial basal cell carcinoma (sBCC)—A subtype of basal cell carcinoma that originates in basal cells of the skin.

Toll-like receptor 7 (TLR7)—A protein receptor with important roles in immune responses that binds imiquimod.

As of 2015, the long-term effectiveness of imiquimod for sBCC was being evaluated.

Imiquimod is sometimes prescribed for other purposes. It is sometimes used to treat cancerous vulvar lesions and mycosis fungoides (a major type of cutaneous T-cell lymphoma that predominantly affects the skin) as well as certain other skin conditions. In Switzerland, as of 2015, imiquimod was sponsored as an orphan drug for the treatment of bladder carcinoma in situ. It was also being studied for the treatment of other conditions and other types of cancer and as an adjuvant for increasing the potency of some vaccines.

Description

Imiquimod is a biological-response modifier that activates the body's own immune response. Specifically, it is a synthetic agonist of toll-like receptor 7 (TLR7); it binds to TLR7 and initiates the same series of events as substances that naturally bind TLR7. These events include stimulation of immune system cytokine production, especially interferon production, and the proliferation (increase) and recruitment of immune cells to the site of imiquimod application.

Imiquimod's exact mode of action against genital warts, AK, and sBCC is not known. Imiquimod does not have direct antiviral activity against HPV or other viruses. However, interferon has activity against viruses and tumors, especially skin (cutaneous) cancers. Imiquimod appears to cause cell death (apoptosis) in susceptible tumor cells. As part of the sBCC healing process, imiquimod induces local skin reactions, including redness, swelling, erosion, scabbing, scaling, and crusting.

Imiquimod is stored in the container it came in at room temperature and away from excess heat and moisture (not in the bathroom). Packets are to be discarded if all of the cream is not used immediately.

U.S. brand names

Imiquimod is sold in the United States under the brand names Aldara and Zyclara. Generic imiquimod is also available.

Aldara is a 5% cream supplied in single-use packets, 12 packets per box. Each packet has 250 milligrams (mg) of cream containing 12.5 mg of imiquimod in an off-white, oil-in-water, vanishing-cream base. Zyclara is supplied as 2.5% and 3.75% creams in packets or a pump.

Canadian brand names

Imiquimod is sold in Canada under the brand names Aldara, Zyclara, and Vyloma.

International brand names

Aldara is the most common international brand name for imiquimod, although it is sold under a number of other brand names.

Origins

Imiquimod was first approved by the FDA in 1997 for the treatment of AK and external genital warts. In 2004, approval was extended to the treatment of sBCC.

Recommended dosage

Because Zyclara has a lower dose of imiquimod, it can be applied daily to a larger surface area than Aldara.

- For external genital warts, Aldara is applied at bedtime three times per week (such as Monday, Wednesday, and Friday or Tuesday, Thursday, and Saturday) until the warts are completely cleared or for a maximum of 16 weeks, using one packet per application. Zyclara is applied once daily for up to 8 weeks, using one packet or one full actuation of the pump. It is left on for six to ten hours. Uncircumcised men treating warts under the foreskin must pull the foreskin back and clean it daily and before each treatment.
- For AK, Aldara is applied twice weekly (such as Monday and Thursday or Tuesday and Friday) for a full 16 weeks, even if the AK disappears. It is applied to an area no larger than about 2 in. by 2 in. (25 cm²) and left on for about eight hours. Zyclara is applied once daily to the entire face or balding scalp for two 2-week treatment cycles separated by a 2-week break. The treatment cycle is not extended due to missed doses or breaks.
- For sBCC, Aldara is applied to the carcinoma and immediately surrounding area (about a 1 cm, or 0.4 in., margin) five times per week (such as Monday through Friday) and left on for about eight hours. It is used for a full 6 weeks even if the sBCC appears to be gone. Zyclara is not used for sBCC.

Imiquimod cream is applied at bedtime as follows:

- The hands are washed.
- The target area is washed with mild soap and water and allowed to dry.
- A Zyclara pump is primed only before the first use by repeatedly depressing the actuator until the cream is dispensed.
- A thin layer of cream is rubbed into the skin until it is no longer visible.
- The hands are washed.
- The cream is left on without bathing, showering, or swimming for the designated time.
- Following the designated treatment time, the area is washed with mild soap and water to remove any remaining cream.
- A missed dose should be applied as soon as possible unless it is almost time for the next dose, in which case the dose should be skipped and the regular schedule resumed.

Precautions

Imiquimod is for use only on the skin. It cannot be used for internal viral treatment (urethral, intravaginal, cervical, rectal, or intra-anal), and it must not be applied in or near the eyes, lips, nostrils, vagina, or anus. If it gets in the mouth or eyes, it must be rinsed away with water immediately.

Additional precautions include:

- Treated areas should not be covered with a tight bandage or dressing, although cotton gauze dressings or cotton underwear may be worn.
- Sexual activity should be avoided while the cream is on the skin.
- Imiquimod may weaken condoms and vaginal diaphragms.
- Imiquimod can sensitize skin to sunlight. Exposure to sunlight, sunlamps, and tanning beds should be avoided, and protective clothing, including a hat, sunglasses, and sunscreen, should be worn when outside in daylight. Imiquimod should not be used on a sunburned area.
- Imiquimod may permanently alter skin color.
- The appearance of flulike symptoms, including fever, nausea, muscle pain and stiffness, and malaise, may require dosing interruption.
- The safety and effectiveness of repeated treatment of AK in the same area have not been established.
- Imiquimod is not recommended for treatment of BCC subtypes other than sBCC.
- Surgical removal of sBCC is usually more effective, so imiquimod is used only when surgery is less appropriate.
- Treatment for sBCC requires regular return visits to the healthcare provider.
- Symptoms of imiquimod overdose can include fainting, dizziness, blurred vision, and nausea.

Pediatric

The safety and effectiveness of imiquimod for treating external genital/perianal warts have not been established in children under age 12. AK and sBCC do not usually affect children, and the safety and effectiveness of imiquimod have not been established for treating these conditions in patients under age 18.

Geriatric

Clinical studies and experience have not shown any overall differences in safety and effectiveness between older and younger patients, although it is possible that

some older patients may be more sensitive to imiquimod effects.

Pregnant or breastfeeding

Imiquimod is in the FDA pregnancy category C, which means there have been no adequate studies in pregnant women, but animal studies have indicated potential harm. Imiquimod should not be used during pregnancy unless potential benefits outweigh potential risks to the fetus. It is not known whether imiquimod is excreted in human milk. It should be administered to nursing mothers with caution.

Other conditions and allergies

The healthcare provider and pharmacist should be notified if the patient is allergic to imiquimod, any ingredients in imiquimod cream, or any other medications. The safety and effectiveness of imiquimod have not been established in patients with impaired immune systems. Patients should inform their healthcare providers if they have or have ever had:

- any condition that affects the immune system, such as HIV/AIDS
- recent surgery to the affected area
- unusual sensitivity to sunlight
- any skin disease, such as psoriasis
- graft-versus-host disease

Side effects

The most common side effects of imiquimod, affecting more than 28% of patients, are local skin or application-site reactions. These may include itching, burning or stinging, pain, redness, flaking or peeling, scaling or dryness, skin thickening, scabbing or crusting, hardness, lesions or erosion, ulcers, swelling, sores or blisters, bleeding, or bumps. At least 1% of patients experience fatigue, fever, or headache. Most patients treated for sBCC experience skin reactions. There have been a few reports of headache, upper respiratory tract infection, or back pain. If any of these symptoms or diarrhea are severe or persistent, the healthcare provider should be consulted. The provider should be called immediately if flulike symptoms or skin breakdown or draining sores occur, especially during the first week of treatment.

Interactions

It is very important that the healthcare provider and pharmacist be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used or planning to be

used by the patient, as well as any medications that the patient stops taking while using imiquimod. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Drugs

Imiquimod may interact with other treatments for genital or anal warts, AK, or sBCC.

Resources

BOOKS

Hengge, Ulrich R. *Specialized Dermatological Treatment Options with Imiquimod*. New York: Thieme, 2012.

OTHER

U.S. Food and Drug Administration. "Full Prescribing Information: Aldara." http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020723s020lbl.pdf (accessed February 10, 2015).

WEBSITES

American Academy of Dermatology. "Immunotherapy: What It Is and How It Can Help Fight Cancer." <http://www.skincarephysicians.com/skincancernet/immunotherapy.html> (accessed February 11, 2015).

"Imiquimod (Rx)—Aldara, Zyclara." Medscape.com. <http://reference.medscape.com/drug/aldara-zyclara-imiquimod-343508> (accessed February 11, 2015).

National Cancer Institute. "Imiquimod." <http://www.cancer.gov/cancertopics/druginfo/imiquimod> (accessed February 11, 2015).

Pazdur, Richard. "FDA Approval for Imiquimod." National Cancer Institute. <http://www.cancer.gov/cancertopics/druginfo/fda-imiquimod> (accessed February 11, 2015).

ORGANIZATIONS

American Academy of Dermatology, PO Box 4014, Schaumburg, IL 60168, (847) 240-1280, Fax: (847) 240-1859, (866) 503-SKIN (7546), <http://www.aad.org/>.

National Cancer Institute, 9609 Medical Center Drive, Bethesda, MD 20892-9760, (800) 4-CANCER (422-6237), <http://www.cancer.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Imitrex see **Sumatriptan**

Imodium see **Loperamide**

Inderal see **Propranolol**

Indocin see **Indomethacin**

Indomethacin

Definition

Indomethacin is a prescription painkiller (analgesic) that belongs to the family of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs).

Purpose

Indomethacin is used to treat mild to moderate pain. It is particularly effective against moderate to severe cases of osteoarthritis, rheumatoid arthritis, gouty arthritis, ankylosing spondylitis, and acute painful shoulder conditions such as bursitis and tendinitis.

Off-label uses

Indomethacin has been used to treat pericarditis (inflammation of the heart sac), to prevent inflammation of the pancreas (pancreatitis) after the diagnostic scoping procedure called endoscopic retrograde cholangiopancreatography (ERCP), and in the setting of preterm labor.

Description

Adult-strength indomethacin is available in capsule form in strengths of 25 and 50 milligrams (mg). An extended-release capsule form is also available in 75 mg strength. A pineapple-coconut-mint flavored liquid suspension is available in 25 mg per 5 milliliters (mL).



Indomethacin ER (extended release), 75 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

U.S. brand names

In the United States, indomethacin is sold under the brand names Indocin, Indocin SR, and Tivorbex. Many generics are also available.

Canadian brand names

In Canada, indomethacin is sold under the brand names Indocid, Ratio-Indomethacin, and Rhodacine.

International brand names

Indomethacin is sold under several hundred brand names internationally, including Betacin (South Africa), Fiacin (Spain), Patetin (Taiwan), Sportflex (Belgium), Hapstar (Japan), Vonum (Austria), Rheumadolor (Greece), and Rheumacin (New Zealand). In some countries, indomethacin is only one component of the medication, and there are other medications included in the formulation.

Recommended dosage

In all cases, the lowest possible effective dose should be used.

For oral administration of indomethacin to adults and geriatric patients, the following dosages are recommended:

- inflammatory diseases: 25–50 mg per dose, two to three times a day, for a maximum of 200 mg per day
- bursitis or tendinitis: 75–150 mg per day divided into three or four doses, or one to two doses if the extended-release preparation is used; duration of use is usually 7–14 days
- acute gouty arthritis: 50 mg, three times per day, decreasing the dosage when pain improves; duration of use is usually under 3–5 days
- acute pain: 20 mg per dose, three times per day, or 40 mg per dose two times per day

Pediatric

To treat pediatric patients over 2 years old for inflammatory arthritis, the dosing of indomethacin depends on the weight of the child and should be 1–2 mg per kilogram (kg, or 2.2 lb.) of body weight per day, divided into two to four equal doses. The maximum dosage is 4 mg/kg/day and should not exceed 150–200 mg each day.

Children over the age of 14 are dosed as adults.

Precautions

Indomethacin carries a boxed warning, which states that:

- Individuals should be aware of an increased risk of life-threatening heart attack or stroke with the use of

KEY TERMS

Analgesic—A drug used to control pain.

Ankylosing spondylitis—A type of arthritis in the spine that leads to stiffening and fusion of the vertebral (spinal) bones.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Bursitis—Inflammation of a fluid-filled sac within a joint.

Gout—A condition in which the deposition of uric acid crystals in the joints causes swelling and pain.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Osteoarthritis—A type of arthritis marked by chronic degeneration of the cartilage of the joints, leading to pain and sometimes loss of function.

Parkinsonism—A progressive nervous system disorder that affects normal movement.

Rheumatoid arthritis—A joint disease of unknown origins that may begin at an early age, causing deformity and loss of function in the joints.

Tendinitis—Inflammation of a tendon.

indomethacin. Risk elevates over time and in the setting of other cardiovascular risk factors or conditions.

- Individuals should be aware of an increased risk of life-threatening gastrointestinal irritation, inflammation, ulceration, bleeding, or perforation. People with a history of these problems, the elderly, smokers, heavy alcohol drinkers, or those using **aspirin**, blood thinners, or steroid medications should use particular caution or take an alternate drug.
- Indomethacin should not be given to patients who have had a recent coronary artery bypass graft (CABG) due to a greatly increased risk of heart attack or stroke.

Indomethacin increases bleeding time. Patients with clotting disorders or who are taking other medications such as blood thinners or aspirin should use particular

caution and have regular monitoring for the development of anemia. Individuals who are scheduled to have dental or surgical procedures should avoid the use of indomethacin in the week prior to the procedure.

Indomethacin can cause vision problems, including blurring, decreased vision, blind spots, and problems discerning color. If these symptoms occur, patients should stop indomethacin use and go to an eye doctor (ophthalmologist).

Indomethacin can cause an increased blood level of potassium, especially in older people, patients with kidney disease or diabetes, or individuals taking other drugs that can increase potassium.

Indomethacin can cause skin reactions, including rashes, welts, hives, blisters, and separation/peeling of the skin layers. If this occurs, indomethacin use should be immediately stopped.

Geriatric

The elderly are at particular risk of complications from indomethacin use, especially bleeding, heart attack, and stroke. Indomethacin should be used with extreme caution and close monitoring in this population.

Pregnant or breastfeeding

Indomethacin is in the U.S. Food and Drug Administration (FDA) pregnancy category C up to 30 weeks' gestation and the category D after 30 weeks' gestation. Category C means that risk cannot be ruled out in pregnant women. If possible, use of this drug should be avoided. Category D means that studies have shown risk to the developing fetus. Indomethacin should not be used by women in the last trimester of pregnancy.

Research is not conclusive on whether indomethacin passes into breast milk. It should be avoided by breastfeeding women.

Other conditions and allergies

Indomethacin may exacerbate specific conditions, and its use should be avoided in individuals with:

- asthma (may cause severe bronchospasm and wheezing)
- recent CABG surgery
- liver disorders (may cause hepatitis, liver failure)
- high blood pressure (may prompt the onset of high blood pressure or the worsening of preexisting high blood pressure)
- kidney impairment (may worsen preexisting kidney problems or prompt the onset of kidney problems in the elderly or individuals who are dehydrated, have heart or

liver failure, or are taking diuretic medications or angiotensin-converting enzyme [ACE] inhibitors)

- depression (may worsen depressive symptoms)
- seizure disorders (may worsen symptoms)
- parkinsonism (may worsen symptoms)

Indomethacin should not be taken by individuals who are hypersensitive to indomethacin or NSAIDs or who have bronchial asthma, aspirin intolerance, or rhinitis.

Individuals who have experienced bronchospasm, asthma, rhinitis, or hives while taking aspirin or other NSAIDs should not take indomethacin.

Side effects

The most common side effects of indomethacin treatment include:

- upset stomach
- abdominal pain
- sensation of indigestion
- nausea, vomiting
- gas, flatulence
- constipation or diarrhea
- nervous feelings
- ringing in the ears
- itching, rash, hives
- headache, dizziness, drowsiness
- seizures
- blood test evidence of bone marrow suppression, including low white blood cell count, low platelets, and low hematocrit (red blood cell levels)
- blood test evidence of liver damage
- blood test evidence of kidney damage
- blood in the urine
- yellow cast to skin or whites of eyes

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Concomitant use of indomethacin may increase potential toxic effects of the following drugs:

- 5-aminosalicylic acid derivatives

- antiplatelet drugs
- aminoglycoside antibiotics
- anticoagulants
- bisphosphonate derivatives
- collagenase
- **cyclosporine**
- desmopressin
- **digoxin**
- **haloperidol**
- lithium
- **methotrexate**
- salicylates
- **tacrolimus**
- tenofovir
- vancomycin

The risk of potential adverse effects from indomethacin may be increased with concomitant use of the following drugs:

- ACE inhibitors
- angiotensin II receptor blockers
- tricyclic antidepressants
- corticosteroids
- dexamethasone
- **diclofenac**
- floctafenine
- **ketorolac**
- probenecid
- selective serotonin reuptake inhibitors (SSRIs)
- serotonin and norepinephrine reuptake inhibitors (SNRIs)
- treprostinil

The use of indomethacin may hamper the effectiveness of the following drugs:

- aliskiren
- beta-blockers
- eplerenone
- hydralazine
- loop diuretics
- potassium-sparing diuretics
- thiazide diuretics

Bile acid sequestrants may hamper the effectiveness of indomethacin.

Food and other substances

Gastrointestinal risks may be decreased when indomethacin is taken with food.

Resources

BOOKS

- Aronson, J. K. *Meyler's Side Effects of Analgesics and Anti-inflammatory Drugs*. Oxford: Elsevier, 2010.
- Benzon, Honorio T. *Essentials of Pain Medicine*. 3rd ed. Philadelphia: Saunders, 2011.
- Smith, Howard S. *Current Therapy in Pain*. Philadelphia: Saunders, 2009.
- Waldman, Steven D. *Pain Management*. 2nd ed. Philadelphia: Saunders, 2011.

WEBSITES

- "Indomethacin." Drugs.com. <http://www.drugs.com/mtm/indomethacin.html> (accessed February 15, 2015).
- MedlinePlus. "Indomethacin." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a681027.html> (accessed February 15, 2015).
- U.S. National Library of Medicine. "LactMed: Indomethacin." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+145> (accessed February 15, 2015).

ORGANIZATIONS

- American Chronic Pain Association, PO Box 850, Rocklin, CA 95677, (800) 533-3231, APAC@theacpa.org, <http://www.theacpa.org/>.
- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- National Pain Foundation, 14828 W 6 Avenue, Suite 16-B, Room 1, Golden, CO 80401-5000, (720) 541-6808, Fax: (720) 541-6809, <http://www.thenationalpainfoundation.org/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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REVIEWED BY KEVIN GLAZA, RPh

Infliximab

Definition

Infliximab is a tumor necrosis factor-alpha (TNF-alpha) inhibitor that is used to treat a variety of autoimmune disorders by blocking the action of TNF, an immune-system protein that causes widespread inflammation. Infliximab is in a medication class called biologics, because it is based on naturally occurring proteins. Because it is used to treat rheumatoid arthritis (RA), it is also classified as a disease-modifying antirheumatic drug (DMARD).



Remicade (infliximab). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Autoimmune disorders are caused by immune-system attacks on the body's own healthy tissues, which can result in inflammation, swelling, pain, loss of function, and permanent damage. TNF inhibitors do not cure autoimmune disorders, but they can control symptoms; prevent progressive structural damage; reduce severe complications, hospitalizations, and surgeries; and improve patient quality of life. Infliximab is used alone or in combination with other medications to treat:

- RA that is also being treated with **methotrexate** (MTX)
- juvenile idiopathic arthritis (JIA) that delays growth and development
- chronic plaque psoriasis, in which red, scaly patches form on the skin
- psoriatic arthritis (PsA), a serious complication of plaque psoriasis
- ankylosing spondylitis—RA of the joints of the spine
- moderate to severe Crohn's disease (CD) in adults and children that has not improved with other medications
- ulcerative colitis (UC) in adults and children when other treatments are ineffective or not tolerated

Infliximab is very effective. The infliximab/MTX combination prevents progressive structural damage and deterioration of function in RA patients who have not responded adequately to MTX alone. Infliximab clears the skin of psoriasis and reduces toe- and finger-joint

swelling, decreases tendon and ligament inflammation, and improves the range of activities and quality of life in psoriatic arthritis patients. It is used to manage both newly diagnosed and advanced Crohn's disease and ulcerative colitis. It can reduce the use of steroids, induce remission, and maintain remission with long-term therapy in both adults and children with moderate to severe Crohn's disease that has not responded adequately to conventional therapy. Infliximab reduces the number of draining fistulas (small tunnels that connect intestinal loops to another part of the intestine or another organ) and maintains fistula closure in adults. Infliximab also reduces signs and symptoms of moderate to severe UC in patients who have not responded adequately to conventional therapy, induces remission and mucosal healing, and eliminates the need for corticosteroids.

Off-label use

Infliximab may be prescribed for other conditions. For example, it is sometimes used to treat Behcet's syndrome, which causes ulcers in the mouth and on the genitals and inflammation elsewhere in the body.

Description

Biologic DMARDs, such as infliximab, are similar to antibodies produced by the immune system, but they are genetically engineered to target specific disease-promoting substances. Infliximab is a monoclonal antibody that specifically binds to and blocks the action of both soluble and membrane-bound TNF, an immune-system protein that promotes inflammation in the joints, spine, skin, and digestive tract. Because infliximab is a powerful immune-system suppressant, it is used only for moderate to severe disease that has not responded well to conventional therapy.

Infliximab and other TNF- α inhibitors are among the ten best-selling drugs in the United States. They effectively treat diverse conditions that are both common and chronic and so are usually used long term.

Infliximab is very expensive. Depending on the patient's weight, treatment with 200–500 milligrams (mg) twice a month can cost \$3,725–\$9,300 per month.

U.S. brand names

In the United States, infliximab is sold under the brand name Remicade.

Canadian brand names

In Canada, infliximab is sold under the brand name Remicade.

International brand names

Internationally, infliximab is sold under the brand names Remicade and Revellex.

Origins

In 1998, infliximab became the first drug approved by the U.S. Food and Drug Administration (FDA) specifically for treating Crohn's disease. It was approved for RA treatment in 1999. It was subsequently approved for other uses, including induction of remission and maintenance therapy for ulcerative colitis in adults, in 2005. In 2011, it became the first biologic approved to treat ulcerative colitis in children.

Infliximab is about 1,000 times larger than chemically synthesized drugs, too large to be well absorbed by the gastrointestinal tract. Therefore, it must be infused into a vein in a medical office or clinic over a period of up to two hours. Infliximab is supplied as a powder that is mixed with sterile water.

Recommended dosage

Infliximab dosage is based on body weight. The most common dosage is 5 mg per kilogram (kg, or 2.2 lb.) of body weight at 0, 2, and 6 weeks, followed by maintenance doses every 8 weeks. RA is generally treated with 3 mg/kg, in combination with MTX, at 0, 2, and 6 weeks, followed by maintenance doses every 8 weeks, or up to 10 mg/kg every 4 weeks for incomplete responses. However, many patients receive a single dose and then wait a few months or longer before requiring another dose. Effectiveness is not usually evaluated until the patient has had at least two infusions. Treatment is usually halted if Crohn's disease has not improved after 14 weeks. Crohn's disease fistula therapy is supplemented with oral azathioprine treatment.

Pediatric

The usual dose for children six years and older is 5 mg/kg—or 3 mg/kg for JIA in children ten years and older—on the same schedule as for adults.

Precautions

Patients should discuss the risks of infliximab with their doctor. Infliximab comes with a boxed warning:

- It can decrease the body's ability to fight infection and increase the risk of severe or life-threatening fungal, bacterial, and viral infections that could spread through the body.
- Doctors should be informed of any infections, including open cuts or sores, intermittent infections such as cold sores, or chronic infections. Patients should be monitored

KEY TERMS

Ankylosing spondylitis—Rheumatoid arthritis of the spine.

Autoimmune disorders—Conditions caused by inappropriate immune-system activity.

Biologics—Naturally occurring compounds in the human body, usually proteins, that are used to treat disease.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Crohn's disease (CD)—A chronic inflammatory autoimmune disease of the gastrointestinal tract, especially the large intestine, with scarring and thickening of the bowel wall.

Disease-modifying antirheumatic drug (DMARD)—A drug, such as infliximab, that suppresses the immune system to decrease inflammation from rheumatoid arthritis.

Fistula—An abnormal passageway between tissues and organs.

Inflammation—The body's reaction to invasion by foreign matter, particularly infection. The result is swelling and redness from an increase in water and blood, and pain from the chemical activity of the reaction.

Juvenile idiopathic arthritis (JIA)—A type of autoimmune arthritis that affects children aged 16 and younger and that can delay growth and development.

Methotrexate (MTX)—A drug used to treat severe psoriasis and rheumatoid arthritis.

Monoclonal antibody—Identical antibodies produced in the laboratory that recognize and bind to a specific protein.

Plaque psoriasis—An autoimmune disorder that causes patches of inflamed skin.

Psoriatic arthritis (PsA)—Joint inflammation that develops in some psoriasis patients.

Rheumatoid arthritis (RA)—A chronic autoimmune disease that causes pain, stiffness, inflammation, swelling, and sometimes destruction of joints.

Tuberculosis (TB)—A highly variable chronic bacterial infection that affects the lungs and can spread to other parts of the body.

Tumor necrosis factor (TNF)-alpha—A protein called a cytokine that mediates inflammation throughout the body and activates immune-system cells; inhibited by infliximab.

Ulcerative colitis (UC)—A chronic, episodic, inflammatory autoimmune disease of the large intestine and rectum characterized by bloody diarrhea.

for any signs of infection before and after treatment. Infections during treatment require halting infliximab.

- Patients should inform their doctor if they have diabetes.
- Doctors should be informed of any current or past conditions or medications that affect the immune system and whether patients have ever lived in areas such as the Ohio or Mississippi River valleys, where fungal infections are common.
- Doctors should be informed if patients have ever had tuberculosis (TB), ever been in a country where TB is common, or been around someone who has ever had TB.
- Patients should be tested for inactive TB and hepatitis B infection before treatment. Infections must be treated before beginning infliximab.
- Doctors should be informed immediately of any of the following symptoms before, during, or shortly after treatment: sweating; sore throat; cough; coughing up

bloody mucus; fever; weight loss; weakness; loss of muscle tone; yellowing of the skin or eyes; loss of appetite; nausea or vomiting; muscle aches; dark urine; clay-colored bowel movements; chills; stomach pain; rash; extreme fatigue; diarrhea; warm, red, or painful skin; painful, difficult, or frequent urination; or other signs of infection.

Rarely, infliximab and some other biologic DMARDs, as well as MTX, have been associated with severe infections such as TB, fungal infections, pneumonia, food-borne diseases such as listeriosis, and cancers, especially lymphoma and skin cancer. Occasionally, nervous system disorders have occurred with infliximab and, rarely, blood disorders.

Infliximab should be continued to maintain disease remission; it should not be stopped and then restarted. Doctors and dentists should be informed of infliximab treatment before performing any type of surgery. Patients

should not have any **vaccinations** while receiving infliximab without talking to their doctor.

Pediatric

Children should have all of their required vaccinations before beginning treatment with infliximab. Some children, teens, and young adults treated with infliximab or similar medications have developed severe or life-threatening cancers, including lymphoma. Some adolescents and young adult males treated with infliximab or similar medications (usually for Crohn's disease or ulcerative colitis, along with the drugs azathioprine or 6-mercaptopurine) have developed hepatosplenic T-cell lymphoma, which is often rapidly fatal.

Pregnant or breastfeeding

Infliximab is in the FDA pregnancy category B. Although infliximab injection during pregnancy has not been well studied, there have been no reports of increased rates of miscarriage or birth defects. Because it is a large protein, significant amounts are not expected to reach the placenta until the second or third trimester of pregnancy. On average, it takes about seven weeks after the last injection for infliximab to completely clear the body. Women who are pregnant or breastfeeding, planning to become pregnant, or become pregnant while taking infliximab should consult with their healthcare provider. Babies whose mothers received infliximab during pregnancy may need to have some vaccinations delayed.

Because infliximab is a very large protein, very little passes into breast milk. Furthermore, infliximab is not well absorbed by the gut, so any present in breast milk would not be well absorbed by the baby's digestive system. Premature infants with underdeveloped digestive systems may absorb more.

Other conditions and allergies

Patients should inform their doctor if they are allergic to infliximab, any medications containing mouse (murine) proteins, any other infliximab ingredients, or any other medications. Delayed allergic reactions can occur 3 to 12 days after infliximab infusion.

Infliximab can cause serious allergic reactions during or for about two hours after an infusion. Patients are monitored for reactions and may be given medications to prevent or treat reactions. Symptoms of an infusion reaction include:

- hives
- rash

- itching
- swelling of the face, eyes, mouth, throat, tongue, lips, hands, feet, ankles, or lower legs
- difficulty breathing or swallowing
- flushing
- dizziness
- fainting
- fever
- chills
- seizures
- chest pain

Doctors should be informed if patients have ever had:

- congestive heart failure, which may preclude use of infliximab
- heart disease
- light therapy for psoriasis
- numbness, burning, or tingling in any part of the body or any disease that affects the nervous system, such as multiple sclerosis, Guillain-Barré syndrome, or optic neuritis
- seizures
- chronic obstructive pulmonary disease
- any type of cancer
- bleeding problems or diseases that affect the blood

Side effects

The most common side effects of infliximab are:

- infusion-site reactions, such as redness, rash, swelling, itching, or bruising
- respiratory infections, such as sinus infections and sore throat
- headache
- coughing
- stomach pain
- nausea
- back pain

Symptoms that require medical attention if severe or long lasting include:

- flushing
- stomach pain
- nausea
- heartburn
- headache
- runny nose
- back pain

- white patches in the mouth
- vaginal itching, burning, and pain or other signs of a yeast infection

The most serious potential side effects of infliximab are TB, sepsis (a life-threatening blood infection), and, rarely, cancers such as lymphoma. In addition to the symptoms in the boxed warning, uncommon side effects that require immediate medical attention include:

- any type of rash, including a rash on the cheeks or arms that worsens in the sun
- chest pain
- swelling of the feet, ankles, stomach, or lower legs
- sudden weight gain
- shortness of breath
- blurred vision or vision changes
- weakness in arms or legs
- muscle or joint pain
- numbness or tingling in any part of the body
- seizures
- pain in the upper-right part of the stomach
- unusual bruising or bleeding
- blood in the stool
- pale skin
- red, scaly patches or pus-filled bumps on the skin

Interactions

Patients should tell their doctor and pharmacist about all of their prescription and nonprescription medications, vitamins, nutritional supplements, and herbal products.

Drugs

Medications that decrease immune-system activity and may require changing infliximab dosages or monitoring for side effects include:

- abatacept
- anakinra
- tocilizumab
- MTX
- steroids such as dexamethasone, **methylprednisolone**, **prednisone**, or prednisolone

Other drugs that may require changing dosages or careful monitoring for side effects include **warfarin** (Coumadin), **cyclosporine**, and theophylline.

Resources

BOOKS

Koo, John Y. M., et al, eds. *Moderate-to-Severe Psoriasis*. Boca Raton, FL: CRC, 2014.

Medrano Acevedo, Antonio D., and Montserrat Fajardo Gaitan, eds. *Infliximab: Pharmacology, Uses & Limitations*. Hauppauge, NY: Nova Science, 2012.

PERIODICALS

Curtis, Jeffrey R., et al. "Estimating Effectiveness and Cost of Biologics for Rheumatoid Arthritis: Application of a Validated Algorithm to Commercial Insurance Claims." *Clinical Therapeutics* 36, no. 7 (2014): 996–1004.

Shader, Richard I. "Rheumatoid Arthritis and More." *Clinical Therapeutics* 36, no. 7 (2014): 993–94.

Tanaka, Yoshiya, and Shintaro Hirata. "Is It Possible to Withdraw Biologics from Therapy in Rheumatoid Arthritis?" *Clinical Therapeutics* 35, no. 12 (2013): 2028–35.

Tkacz, Joseph, et al. "Utilization and Adherence Patterns of Subcutaneously Administered Anti-Tumor Necrosis Factor Treatment among Rheumatoid Arthritis Patients." *Clinical Therapeutics* 36, no. 5 (2014): 737–47.

OTHER

Janssen Biotech, Inc. "Medication Guide Remicade (Rem-cikad) (Infliximab)." U.S. Food and Drug Administration. <http://www.fda.gov/downloads/Drugs/DrugSafety/ucm089023.pdf> (accessed February 11, 2015).

WEBSITES

Agency for Healthcare Research and Quality. "Medicines for Psoriatic Arthritis: A Review of the Research for Adults." <http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1312> (accessed February 11, 2015).

MedlinePlus. "Infliximab Injection." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a604023.html> (accessed February 11, 2015).

Organization of Teratology Information Specialists. "Infliximab (Remicade) and Pregnancy." <http://www.mothersbaby.org/infliximab-remicade-and-pregnancy--p150080> (accessed February 11, 2015).

ORGANIZATIONS

Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, (301) 427-1364, <http://www.ahrq.gov/>.

Crohn's & Colitis Foundation of America, 733 Third Avenue, Suite 510, New York, NY 10017, (800) 932-2423, info@ccfa.org, <http://www.ccfa.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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REVIEWED BY GREGORY A. PRATT, RPh

InnoPran see **Propranolol**

Insulin aspart

Definition

Insulin aspart is a short-acting insulin analogue used in the treatment of type 1 and type 2 diabetes in adults and type 1 diabetes in children. Its name is derived from the substitution of the amino acid aspartic acid for proline at one point in the human insulin molecule. This substitution allows insulin aspart to act more rapidly than normal human insulin. It also has a shorter duration of activity. Insulin aspart begins to act within 15 minutes of administration, reaches peak activity in 45–90 minutes, and has a total duration of activity between three and five hours.

Purpose

Insulin aspart is used to manage the spike in blood sugar levels that occurs after meals in treating type 1 diabetes in children and adults and type 2 diabetes in adults. It is most often used together with a basal insulin or an intermediate-acting insulin such as insulin aspart protamine, which delays insulin absorption and prolongs insulin's activity. This allows individuals to maintain glycemic control over the course of the day with fewer injections. The insulin aspart protamine/insulin aspart combination is used to treat type 1 diabetes in adults. It is not recommended for use in children. Insulin aspart can be used only to manage diabetes; it cannot be used to cure it.



Novolog (insulin aspart). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Insulin aspart and insulin aspart protamine/insulin aspart work best when combined with an appropriate dietary and exercise plan.

Off-label use

Insulin aspart is used off label to manage gestational diabetes.

Description

Insulin aspart is available as a vial of 100 U/mL (units per milliliters) of NovoLog insulin, as a FlexPen containing 100 U/mL NovoLog insulin, and as a NovoLog PenFill cartridge containing 100 U/mL insulin. The pens must be used with special pen needles that can be used only once.

Insulin aspart protamine/insulin aspart is available as a vial of NovoLog Mix 70/30 100 U/mL solution and as a FlexPen containing 100 U/mL NovoLog Mix 70/30.

Insulin aspart protamine/insulin aspart is manufactured as a suspension that settles between doses. The patient must be careful to restore the suspension before each injection. If the vial is used, the patient must roll the vial horizontally ten times between the hands; the liquid in the vial should look uniformly white and cloudy. If the patient is using the FlexPen, the pen should be rolled horizontally between the hands ten times, then shaken ten times to mix the solution inside.

Insulin aspart vials may be safely stored at room temperature or a cool place after they are opened, or they may be refrigerated, as the patient prefers. They must, however, be used within 28 days after opening. Insulin aspart must be discarded if its temperature rises above 98°F. Insulin aspart protamine/insulin aspart cartridges may be stored at room temperature after their first use but must be used within 14 days.

U.S. brand names

Insulin aspart is sold in the United States under the brand names NovoLog, NovoLog FlexPen, NovoPen Junior (children's size), NovoPen Echo (combines half-unit dosing with a memory function), and NovoLog FlexTouch.

Insulin aspart protamine/insulin aspart is marketed in the United States under the brand names NovoLog Mix 50/50, NovoLog Mix 70/30, and NovoLog Mix 70/30 FlexPen.

Canadian brand names

Insulin aspart is sold under the trade name NovoRapid in Canada.

International brand names

Insulin aspart is sold under the trade names Insulina Novorapid (Argentina) and NovoRapid (Australia, New

KEY TERMS

Angioedema—A condition marked by the sudden and rapid swelling of subcutaneous tissues and mucous membranes, often as an allergic reaction to some foods or drugs.

Basal insulin—A term that refers to long-acting insulins that are released slowly and provide 24 hours or more of background insulin in diabetic patients.

Biphasic insulin—An insulin formulation consisting of a mixture of short-acting and intermediate-acting insulin. Insulin aspart comes in two biphasic formulations as well as its simple form.

Glucagon—A peptide hormone produced in the alpha cells of the pancreas that quickly raises the level of blood sugar. An injectable form of glucagon is a necessary part of first aid in assisting a diabetic patient with severe hypoglycemia.

Hypoglycemia—Abnormally low blood sugar; it is a common complication of treating diabetes with insulin or oral diabetes medications.

Insulin analogue—An insulin that has been altered by genetic engineering to affect its absorption, distribution, metabolism, and excretion rates but can still be used by the human body to maintain glycemic control.

Subcutaneous—Below the skin.

Zealand, Europe, Indonesia; South Africa, Singapore, Japan, Turkey, and Thailand).

Origins

Insulin aspart was developed in the late 1990s by Novo Nordisk, a multinational pharmaceutical company headquartered in Denmark, and was approved by the U.S. Food and Drug Administration (FDA) for use in June 2000. The biphasic formulations were approved by the FDA in August 2008.

Recommended dosage

The dosage of insulin aspart is individualized according to the patient's response to treatment and concurrent medical conditions. Daily monitoring of blood glucose levels is essential because changes in diet, infections, travel, stressful events, and similar factors can affect the patient's response to insulin. Patients should

never change their insulin dosage without consulting their healthcare provider.

Insulin aspart may be administered by subcutaneous injection (into the skin), by intravenous infusion in a hospital setting, or by an insulin pump. Insulin aspart protamine/insulin aspart, however, is to be administered only by subcutaneous injection. None of the forms of insulin aspart should be mixed with other insulins.

Recommended dosages for adults include:

- Type 1 diabetes, insulin aspart: The patient may self-administer insulin aspart 0.2–0.6 units per kilogram (kg, or 2.2 lb.) of body weight per day in divided doses, although lower doses of 0.2–0.4 unit/kg/day are often recommended to reduce the risk of hypoglycemia. Fifty to seventy percent of the daily insulin requirement may be provided by aspart and the remainder by an intermediate or long-acting insulin. The total maintenance daily dose is usually between 0.5 and 1 unit/kg/day.
- Type 1 diabetes, insulin aspart protamine/insulin aspart: The daily dose varies according to the patient's metabolic requirements but is usually between 0.5 and 1 unit/kg/day. The patient should administer the dose every 12 hours, usually before breakfast and before dinner. Each dose should cover two meals or a meal plus a snack.
- Type 2 diabetes, insulin aspart: 10 units per day, or 0.1–0.2 units/kg/day in the evening. Fifty to seventy percent of the patient's daily insulin requirement may be provided by insulin aspart and the remainder by an intermediate or long-acting insulin.
- If an insulin pump is used, the patient should divide the number of units per day by 24 to obtain the basal rate per hour.

Pediatric

For type 1 diabetes in children two years and older, up to 0.8–1.2 units/kg/day may be given during growth spurts. Adolescents may require less than 1.2 units/kg/day; otherwise, the child or teenager may use 0.5–1 unit/kg/day. Between 50% and 75% of the child's daily insulin may be supplied by intermediate- or long-acting insulin. The remainder is divided and supplied at or before mealtimes by insulin aspart.

There are insulin pens designed for children and adolescents (NovoPen Echo and NovoPen Junior) that allow for dosage increases or decreases as small as half a unit. Children between the ages of two and four must use insulin aspart by subcutaneous injection; children over four years may use an insulin pump.

The insulin aspart protamine/insulin aspart combination is not recommended for use in children.

Precautions

Patients should be instructed about the proper way to inject themselves, to care for their injection devices, and to dispose of used needles and expired insulin properly:

- Insulin aspart and its biphasic (combination) formulations act rapidly to lower the patient's blood sugar levels. To prevent hypoglycemia, patients must eat a meal within 5 to 10 minutes of injecting the insulin.
- Patients should rotate the injection site (upper arm, thigh, abdomen) and avoid using the same site twice in a row.
- Patients should never share their hypodermic needles or injection pens with others and should use each syringe or pen needle only once.
- Used needles should be stored in a puncture-proof container, kept away from children and pets, and disposed of in accordance with state or local laws. A pharmacist can provide information about obtaining such containers and disposing of them properly.
- Patients using an insulin pump with insulin aspart must remove unused insulin at least every six days and change the infusion set and insertion site at least every three days to prevent degradation of the insulin and loss of the preservative.
- Patients with diabetes should always keep a supply of insulin and syringes or an insulin pen with them in case of an episode of high blood sugar. They should also carry candy or another form of quickly digested sugar with them in case of a hypoglycemic episode. In addition, they should keep a glucagon kit and syringe with them in case of an episode of severe hypoglycemia.

Pregnant or breastfeeding

Insulin aspart is in the FDA pregnancy category B, which means that animal reproduction studies have failed to demonstrate a risk to the human fetus. Insulin aspart protamine/insulin aspart, however, is in the FDA pregnancy category C, which means that risk of harm to a human fetus cannot be ruled out. Pregnant women should consult their healthcare provider before using the biphasic form of insulin aspart. It is not known whether these insulins pass into human breast milk, but nursing mothers are advised to consult a healthcare provider before using these insulins.

Other conditions and allergies

Patients with any of the following conditions should consult their healthcare provider before using insulin aspart, as they may affect the amount of insulin the patient will need:

- chronic emotional disturbances
- an active viral, bacterial, or fungal infection

- high stress levels, which typically increase blood sugar levels
- kidney disease
- liver disease, which may lower the amount of insulin required

Side effects

Common side effects of insulin aspart and insulin aspart protamine/insulin aspart include:

- lowered blood potassium levels (hypokalemia)
- episodes of hypoglycemia
- pitting or thickening of the skin at the injection site
- skin rash or irritation at the injection site
- anxiety

Less common side effects include:

- flulike symptoms
- itching
- sweating
- mental confusion
- redistribution of body fat (lipodystrophy)
- dry mouth
- increased hunger or thirst
- loss of appetite
- unusual tiredness

The following side effects of insulin aspart or symptoms of severe hypoglycemia should be reported to a healthcare provider immediately:

- Symptoms of angioedema, an allergic reaction to insulin, may include sudden swelling of the face, arms, legs, eyes, lips, or tongue or problems with swallowing or breathing.
- Symptoms of hypoglycemia may include anxiety; behavioral changes that resemble those of alcohol intoxication; difficulty in thinking clearly; cold sweats; nervousness; difficulty sleeping; tremor; slurred speech; tingling sensations in the hands, feet, or tongue; excessive hunger; drowsiness; or lightheadedness or dizziness.
- Symptoms of severe hypoglycemia may include convulsions or unconsciousness.
- Symptoms of edema (fluid retention) may include rapid weight gain; shortness of breath; chest pain or discomfort; extreme tiredness or weakness; uneven heartbeat; or severe swelling of the hands, wrists, ankles, or feet. Edema is most often caused by using insulin aspart together with the type 2 diabetes drugs **pioglitazone** or **rosiglitazone**.

Interactions

Insulin aspart is known to interact with various drugs, herbs, and other substances.

Drugs

Insulin aspart is known to interact with the following drugs:

- angiotensin-converting enzyme (ACE) inhibitors (e.g., lisinopril, **captopril**, **fosinopril**, **ramipril**)
- beta-blockers (e.g., **sotalol**, **timolol**, **propranolol**, **atenolol**)
- fibrates (**gemfibrozil** and **fenofibrate**)
- disopyramide (drug given to treat abnormal heart rhythms)
- monoamine oxidase inhibitors (MAOIs, e.g., phenelzine, selegiline, isocarboxazid)
- oral diabetes medications (e.g., **metformin**, **glipizide**, glyburide, **glimepiride**)
- propoxyphene (pain medication)
- salicylates (**aspirin**, diflunisal)
- sulfonamide antibiotics (e.g., sulfadiazine, sulfadoxine, sulfamethoxazole)
- thiazolidinediones (pioglitazone, rosiglitazone)
- fluoroquinolone antibiotics (e.g., norfloxacin, gatifloxacin, **levofloxacin**)

Herbs and supplements

Patients using insulin aspart should avoid the herbs and spices cinnamon, bitter melon, gotu kola, elderberry, American ginseng, nettle, juniper, horse chestnut, willow bark, and Siberian or panax ginseng because of an increased risk of hypoglycemia.

Food and other substances

Diabetic patients using insulin aspart should avoid alcoholic beverages because of an increased risk of hypoglycemia and possible loss of glycemic control because of the added calories in alcoholic beverages.

Patients using insulin aspart should also avoid smoking or ingesting marijuana or food products containing marijuana, as this recreational drug lowers the effectiveness of insulin.

Resources

BOOKS

- Morris, Deborah Gray. *Calculate with Confidence*. 6th ed. St. Louis, MO: Mosby Elsevier, 2014.
- Strachan, Mark W. J., and Brian M. Frier. *Insulin Therapy: A Pocket Guide*. New York: Springer, 2013.

PERIODICALS

- Rasmussen, C. H., et al. "Insulin Aspart Pharmacokinetics: An Assessment of Its Variability and Underlying Mechanisms." *European Journal of Pharmaceutical Sciences* 62 (2014): 65–75.
- Simmons, D. "Safety Considerations with Pharmacological Treatment of Gestational Diabetes Mellitus." *Drug Safety* 38, no. 1 (2015): e-pub ahead of print. <http://dx.doi.org/10.1007/s40264-014-0253-9> (accessed February 11, 2015).
- Tibaldi, J. M. "Evolution of Insulin: From Human to Analog." *American Journal of Medicine* 127, no. 10 (suppl.): S25–S38.

WEBSITES

- "Insulin Aspart." Drugs.com. <http://www.drugs.com/monograph/insulin-aspart.html> (accessed February 11, 2015).
- "Insulin Aspart and Insulin Aspart Protamine." Drugs.com. <http://www.drugs.com/mtm/insulin-aspart-and-insulin-aspart-protamine.html> (accessed February 11, 2015).
- "Insulin Aspart Protamine/Insulin Aspart (Rx)." Medscape.com. <http://reference.medscape.com/drug/novolog-mix-50-50-novolog-mix-70-30-insulin-aspart-protamine-insulin-aspart-999552> (accessed February 11, 2015).
- "Insulin Aspart (Rx)." Medscape.com. <http://reference.medscape.com/drug/novolog-insulin-aspart-999001> (accessed February 11, 2015).
- Micromedex. "Insulin Aspart Protamine and Insulin Aspart (Subcutaneous Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/insulin-aspart-protamine-and-insulin-aspart-subcutaneous-route/description/drg-20072450> (accessed February 11, 2015).
- Micromedex. "Insulin Aspart, Recombinant (Subcutaneous Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/insulin-aspart-recombinant-subcutaneous-route/description/drg-20067762> (accessed February 11, 2015).

ORGANIZATIONS

- American Diabetes Association (ADA), 1701 North Beauregard Street, Alexandria, VA 22311, (800) DIABETES (342-2383), <http://www.diabetes.org/>.
- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Insulin detemir

Definition

Insulin detemir is a long-acting insulin analogue produced by recombinant DNA technology. It is used in



Levemir (insulin detemir). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

the treatment of adults with type 1 and type 2 diabetes, and children and adolescents with type 1 diabetes. Insulin detemir is considered a basal insulin because its sustained release and length of action allow it to maintain a steady baseline level of insulin in the body without sharp peaks or troughs in blood glucose levels.

Purpose

Insulin detemir is used to lower blood sugar levels (maintain glycemic control) in adults with type 1 or type 2 diabetes mellitus and in children over the age of two with type 1 diabetes. It is not used to cure diabetes.

Insulin detemir is used together with other, shorter-acting insulins or oral diabetes medications to control sudden spikes in blood glucose levels after meals.

Description

Insulin detemir is available in the United States as a vial of 100 U/mL (units per milliliter) solution or as a FlexTouch insulin pen containing 3 mL of 100 U/mL insulin. The solution is clear, watery, and colorless.

U.S. brand names

Insulin detemir is marketed in the United States by Novo Nordisk under the brand names Levemir and Levemir FlexTouch.

International brand names

Insulin detemir is sold worldwide under the trade name Levemir.

Origins

Insulin detemir was developed in the early 2000s by Novo Nordisk, a Danish multinational pharmaceutical company. It was approved by the FDA in June 2005.

Recommended dosage

The dosage of insulin detemir is individualized according to the patient's response to treatment and concurrent medical conditions. Daily monitoring of blood glucose levels is essential because changes in diet, infections, travel, stressful events, and similar factors can affect the patient's response to insulin. Patients should never change their insulin dosage or switch to another type of insulin without consulting their physician.

Adults with type 1 diabetes should administer a single daily dose subcutaneously with the evening meal or at bedtime. If two daily doses are used, inject the first dose at breakfast and the second dose 12 hours later. The initial dose of insulin detemir should supply about one-third of the patient's daily requirements, with rapid- or short-acting premeal insulin used to supply the remaining two-thirds. The usual daily maintenance range is 0.5–1 unit per kilogram (kg, or 2.2 lb.) of body weight, given in divided doses; obese patients may require 0.6–1.2 U/kg/day. Insulin dosage may be adjusted as needed.

Adults with type 2 diabetes who are inadequately controlled on oral medication should inject 10 U/day of insulin detemir subcutaneously (or 0.1–0.2 U/kg/day) in the evening or divided into two doses administered every 12 hours. If the patient is inadequately controlled on a glucagon-like peptide-1 (GLP-1) receptor agonist, he or she should inject 10 U/day of insulin detemir subcutaneously once daily in the evening.

Pediatric

For children and adolescents two years and older with type 1 diabetes, the daily dose of insulin detemir should supply about one-third of the patient's needs, with the remaining two-thirds supplied by a rapid- or short-acting insulin injected before meals, as in adults. The normal dosage range for teenagers is equal to or less than 1.2 U/kg/day during growth spurts.

Precautions

Patients should check the appearance of their insulin before each use. Insulin detemir is a colorless solution with a watery texture; it should not be used if it looks

KEY TERMS

Basal insulin—A term that refers to long-acting insulins that are released slowly and provide 24 hours or more of background insulin in diabetic patients.

Diabetes mellitus—A disease in which insufficient insulin is made by the body to metabolize sugars. In type 1 diabetes, the pancreas does not produce sufficient amounts of insulin. In type 2 diabetes, the body does not properly utilize glucose (blood sugar).

Diabetic ketoacidosis (DKA)—A potentially life-threatening complication of diabetes in which a shortage of insulin causes the body to burn fatty acids and produce acidic ketone bodies, resulting in such symptoms as nausea, vomiting, and intense thirst.

GLP-1 receptor agonists—A group of newer medications for the treatment of type 2 diabetes that works by stimulating insulin secretion by the pancreas. They are also called incretin mimetics.

Glucagon—A peptide hormone produced in the alpha cells of the pancreas that quickly raises the

level of blood sugar. An injectable form of glucagon is a necessary part of first aid in assisting a diabetic patient with severe hypoglycemia.

Glucose—A simple sugar produced when carbohydrates are broken down in the small intestine. It is the primary source of energy for the body.

Hypoglycemia—Abnormally low blood sugar; it is a common complication of treating diabetes with insulin or oral diabetes medications.

Insulin—A hormone secreted by the pancreas in response to high blood glucose levels that induces hypoglycemia. Insulin regulates the body's use of glucose and the levels of glucose in the blood by acting to open the cells so that they can intake glucose.

Insulin analogue—An insulin that has been altered by genetic engineering to affect its absorption, distribution, metabolism, and excretion rates but can still be used by the human body to maintain glycemic control.

Subcutaneous—Below the skin.

cloudy or thickened or has changed color. Unopened vials or insulin pens should be stored in the refrigerator but not allowed to freeze. Opened vials or pens may be stored at room temperature for up to 42 days but should be kept as cool as possible and away from heat and light. Insulin detemir that has passed its expiration date or become frozen should be discarded.

Patients should be instructed about the proper way to inject themselves, to care for their injection devices, and to dispose of used needles properly:

- Because insulin detemir is intended to maintain steady levels of blood glucose over a 24-hour period, it should be injected once daily at the same time each day, preferably with the evening meal or at bedtime. Patients who are instructed by the doctor to use two daily doses should inject the first dose with the morning meal and the second dose 12 hours later.
- Patients should rotate the injection site (upper arm, thigh, abdomen) and avoid using the same site twice in a row.
- Patients should never share their hypodermic needles or injection pens with others and should use each syringe or pen needle only once.

- Insulin detemir is intended only for subcutaneous injection. It should never be used with an insulin pump or injected into a vein or muscle.
- Used needles should be stored in a puncture-proof container, kept away from children and pets, and disposed of in accordance with state or local laws. A pharmacist can provide information about obtaining such containers and disposing of them properly.
- Patients with diabetes should always keep a supply of insulin detemir and syringes or an insulin pen with them in case of an episode of high blood sugar; they should also carry candy or another form of quickly digested sugar with them in case of a hypoglycemic episode. In addition, they should keep a glucagon kit and syringe with them in case of an episode of severe hypoglycemia.
- In case of an accidental or intentional overdose of insulin detemir, which will result in severe hypoglycemia, the patient should call the poison control center hotline at 1-800-222-1222 if still conscious. An unconscious patient should be taken to a hospital emergency department for treatment with intravenous glucose solution and a glucagon injection.

Pediatric

Insulin detemir is not recommended for use in children younger than two years.

Pregnant or breastfeeding

Insulin detemir is classified as a pregnancy category B drug, which means that adequate studies in humans have failed to demonstrate a risk to the fetus. There were also no studies as of early 2015 that indicated potential harm to nursing infants. Women should tell their doctor, however, if they are pregnant, plan to become pregnant, or plan to breastfeed.

Other conditions and allergies

Insulin detemir should not be used by patients who are allergic to this form of insulin or who are in a state of diabetic ketoacidosis (DKA). DKA is a medical emergency and requires treatment with a short-acting insulin, among other measures.

Patients with any of the following conditions should consult their doctor before using insulin detemir, as they may affect the amount of insulin the patient will need:

- chronic emotional disturbances
- an active viral, bacterial, or fungal infection
- high stress levels, which typically increase blood sugar levels
- frequent episodes of hypoglycemia
- history of digestive malabsorption
- kidney disease
- thyroid disorders
- liver disease; this condition may lower the amount of insulin required

Side effects

Insulin detemir is usually well tolerated. Some of its more common side effects include:

- episodes of hypoglycemia
- pitting or thickening of the skin at the injection site
- skin rash or irritation at the injection site
- low blood potassium levels (hypokalemia)

Less common side effects that have been reported include:

- headache
- diarrhea
- muscle weakness
- redistribution of body fat (lipodystrophy)
- pallor

- heart palpitations or a rapid heartbeat
- flu-like symptoms
- hunger
- mental confusion

The following side effects of insulin detemir or symptoms of severe hypoglycemia should be reported to a doctor immediately:

- symptoms of angioedema (an allergic reaction), which may include sudden swelling of the face, arms, legs, eyes, lips, or tongue; hives; wheezing; and problems with swallowing or breathing
- symptoms of edema (fluid retention), which may include rapid weight gain; shortness of breath; chest pain or discomfort; extreme tiredness or weakness; uneven heartbeat; and severe swelling of the hands, wrists, ankles, or feet; most often caused by using insulin detemir together with the type 2 diabetes drugs **pioglitazone** or **rosiglitazone**
- symptoms of hypoglycemia, which may include anxiety; behavioral changes that resemble those of alcohol intoxication; difficulty in thinking clearly; cold sweats; nervousness; difficulty sleeping; tremor; slurred speech; tingling sensations in the hands, feet, or tongue; excessive hunger; drowsiness; and lightheadedness or dizziness
- symptoms of severe hypoglycemia, which may include convulsions and unconsciousness

Interactions

The doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

Insulin detemir interacts with a large number of drugs. The following types of drugs increase the patient's risk of hypoglycemia when used together with this insulin:

- angiotensin-converting enzyme (ACE) inhibitors (e.g., lisinopril, **captopril**, **fosinopril**, **ramipril**)
- beta-blockers (e.g., **sotalol**, **timolol**, **propranolol**, **atenolol**)
- fibrates (**gemfibrozil** and **fenofibrate**)
- disopyramide (drug given to treat abnormal heart rhythms)
- sulfonamide antibiotics (e.g., sulfadiazine, sulfadoxine, sulfamethoxazole)

- monoamine oxidase inhibitors (MAOIs, e.g., phenelzine, selegiline, isocarboxazid)
- oral diabetes medications (e.g., **metformin**, **glipizide**, glyburide, **glimepiride**)
- propoxyphene (pain medication)
- salicylates (**aspirin**, diflunisal)
- **octreotide** (used to treat pituitary tumors and growth hormone-producing tumors)
- thiazolidinediones (drugs used to treat type 2 diabetes, including pioglitazone and rosiglitazone)

Insulin detemir should never be mixed with any other insulin prior to administration.

Herbs and supplements

Patients using insulin detemir should avoid cinnamon, bitter melon, prickly pear, and American ginseng because they increase the effects of this insulin.

Food and other substances

Patients using insulin detemir should avoid drinking alcohol because it can lower blood sugar levels and increase the patient's risk of hypoglycemia.

Patients using insulin detemir should also avoid smoking or ingesting marijuana or food products containing marijuana, as this recreational drug lowers the effectiveness of insulin.

Resources

BOOKS

- Morris, Deborah Gray. *Calculate with Confidence*. 6th ed. St. Louis, MO: Mosby Elsevier, 2014.
- Strachan, Mark W. J., ed. *Insulin Therapy: A Pocket Guide*. New York: Springer, 2013.

PERIODICALS

- Eldred, A. E., et al. "Problem Based Review: The Patient Who Has Taken an Overdose of Long-acting Insulin Analogue." *Acute Care* 12, no. 3 (2013): 167–72.
- Keating, G. M. "Insulin Detemir: A Review of Its Use in the Management of Diabetes Mellitus." *Drugs* 72, no. 17 (2012): 2255–87.
- Lambert, K., and R. I. Holt. "The Use of Insulin Analogues in Pregnancy." *Diabetes, Obesity and Metabolism* 15, no. 10 (2013): 888–900.
- Tibaldi, J. M. "Evolution of Insulin: From Human to Analog." *American Journal of Medicine* 127, no. 10 (suppl.) (2014): S25–S38.

WEBSITES

- "Insulin Detemir." Drugs.com. <http://www.drugs.com/mtm/insulin-detemir.html> (accessed February 28, 2015).
- "Insulin Detemir (Rx)." Medscape.com. <http://reference.medscape.com/drug/levemir-insulin-detemir-999002> (accessed February 28, 2015).

- Micromedex. "Insulin Detemir (Subcutaneous Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/insulin-detemir-subcutaneous-route/description/drg-20067537> (accessed February 28, 2015).
- U.S. Food and Drug Administration (FDA). "Public Health Advisory Regarding Levemir Insulin." <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm166358.htm> (accessed February 28, 2015).

ORGANIZATIONS

- American Diabetes Association (ADA), 1701 North Beauregard Street, Alexandria, VA 22311, (800) DIABETES (342-2383), <http://www.diabetes.org/>.
- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rebecca J. Frey, PhD

REVIEWED BY GREGORY A. PRATT, RPh

Insulin glargine

Definition

Insulin glargine is a long-acting insulin analogue produced by recombinant DNA technology. It is used in the treatment of adults with type 1 and type 2 diabetes and children with type 1 diabetes. Insulin glargine is considered a basal insulin because its sustained release and length of action allow it to maintain a steady baseline level of insulin in the body without sharp peaks or troughs. It is thought that the "peakless" profile of this insulin's activity lowers the patient's risk of hypoglycemia (low blood sugar).

Purpose

Insulin glargine is used to lower blood sugar levels (glycemic control) in adults with type 1 or type 2 diabetes mellitus and in children over the age of six with type 1 diabetes. It is not used to cure diabetes.

Insulin glargine may be used by itself to control blood sugar levels, or with other shorter-acting insulins or oral diabetes medications used to control sudden spikes in blood glucose levels after meals.

Description

Insulin glargine is a clear liquid intended for subcutaneous injection with a hypodermic needle. It is



Lantus (insulin glargine). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

available as a vial containing 100 units per milliliter (mL) of solution (U100) or as a Lantus SoloStar pen that contains a total of 300 units of insulin. The pen can be set to deliver from 1 to 80 units of insulin with each press of the injection button. The SoloStar pen must be used with special pen needles that can be used only once. Insulin glargine should never be diluted or mixed with any other type of insulin either in the vial or within a hypodermic needle. The bottle should not be shaken before use.

Insulin glargine should be stored in the refrigerator after the vial is opened but should not be allowed to freeze. It can be used for up to 28 days after opening, but any unused insulin should be discarded after that time period. The SoloStar pen should not be stored in the refrigerator after a new cartridge of insulin is inserted, but, as with the vial form of insulin glargine, any insulin remaining in the cartridge should be discarded after 28 days.

A new concentrated form of insulin glargine that contains 300 units/mL (U300 glargine) is not on the market as of early 2015 but has been evaluated in several clinical trials in Europe and the United States with good results. It offers the advantage of more evenly sustained release, lower risk of hypoglycemia during the overnight hours, and even less variability in blood sugar levels than U100 glargine.

U.S. brand names

Insulin glargine is manufactured by Sanofi (formerly Sanofi-Aventis), a drug company headquartered in

France, and sold in the United States under the trade name Lantus.

International brand names

Insulin glargine is sold worldwide under the trade name Lantus.

Origins

Insulin glargine was developed in Sanofi's biotechnology center in Germany in the late 1990s and approved for use in treating diabetes by the European Union in 2000 and the U.S. Food and Drug Administration (FDA) in the same year. It is currently Germany's largest and most important drug manufactured for export; it is sold in 100 countries around the world and used by nearly four million patients worldwide.

Recommended dosage

The dosage of insulin glargine is individualized according to the patient's response to treatment and concurrent medical conditions. Daily monitoring of blood glucose levels is essential because changes in diet, infections, travel, stressful events, and similar factors can affect the patient's response to insulin. Patients should never change their insulin dosage without consulting their physician.

Patients with type 1 diabetes must use a short-acting insulin as part of their regimen along with insulin glargine.

Adult dosages include:

- Initial dose, type 1 diabetes: The starting dose of insulin glargine should be about one-third of the patient's daily insulin requirement, with a short-acting insulin supplying the remaining two-thirds. The usual daily maintenance range is 0.5–1 units per kilogram (kg, or 2.2 lb.) of body weight per day, given in divided doses.
- Initial dose, type 2 diabetes: Dosing is 10 units (or 0.2 unit/kg) once daily for patients who are not currently taking insulin.

Pediatric

For children over six years of age with type 1 diabetes, the initial dose of insulin glargine should supply one-third of the patient's daily insulin requirement, with a short-acting insulin supplying the remaining two-thirds. The usual daily maintenance range in adolescents is 1.2 units/kg/day during growth spurts.

Precautions

Patients should be instructed about the proper way to inject themselves, to care for their injection devices, and to dispose of used needles properly:

KEY TERMS

Angioedema—A condition marked by sudden and rapid swelling of subcutaneous tissues and mucous membranes, often as an allergic reaction to some foods or drugs.

Basal insulin—A term that refers to long-acting insulins that are released slowly and provide 24 hours or more of background insulin in diabetic patients. Insulin glargine is one type of basal insulin.

Glucagon—A peptide hormone produced in the alpha cells of the pancreas that quickly raises the level of blood sugar. An injectable form of glucagon is a necessary part of first aid in assisting a diabetic patient with severe hypoglycemia.

Hypoglycemia—Abnormally low blood sugar; it is a common complication of treating diabetes with insulin or oral diabetes medications.

Insulin—A hormone secreted by the pancreas in response to high blood sugar levels that induces hypoglycemia. Insulin regulates the body's use of

glucose and the levels of glucose in the blood by acting to open the cells so that they can intake glucose.

Insulin analogue—An insulin that has been altered by genetic engineering to affect its absorption, distribution, metabolism, and excretion rates but can still be used by the human body to maintain glycemic control.

Subcutaneous—Below the skin.

Type 1 diabetes—A chronic immune system disorder in which the pancreas does not produce sufficient amounts of insulin, a hormone that enables cells to use glucose for energy. Also called juvenile diabetes, it must be treated with insulin injections.

Type 2 diabetes—A form of diabetes that typically develops later in life. The disease prevents the body from properly using glucose (sugar), but it can often be controlled with diet and exercise.

- Because insulin glargine is a basal insulin intended to maintain steady levels of blood glucose over a 24-hour period, it should be injected once daily at the same time each day, preferably at bedtime.
- Patients should rotate the injection site (upper arm, thigh, abdomen) and avoid using the same site twice in a row.
- Patients should never share their hypodermic needles or injection pens with others and should use each syringe or pen needle only once.
- Insulin glargine is intended only for subcutaneous injection (into the skin). It should never be used with an insulin pump or injected into a vein or muscle.
- Used needles should be stored in a puncture-proof container, kept away from children and pets, and disposed of in accordance with state or local laws. A pharmacist can provide information about obtaining such containers and disposing of them properly.
- Patients with diabetes should always keep a supply of insulin glargine and syringes or an insulin pen with them in case of an episode of high blood sugar, and they should carry candy or another form of quickly digested sugar with them in case of a hypoglycemic episode. In addition, they should keep a glucagon kit and syringe with them in case of an episode of severe hypoglycemia.
- In case of an accidental or intentional overdose of insulin glargine, which will result in severe hypoglycemia, the

patient should call the Poison Control Center hotline at 1 (800) 222-1222 if still conscious. An unconscious patient should be taken to a hospital emergency department for treatment with intravenous glucose solution and a glucagon injection.

Pediatric

Insulin glargine is not approved for use in children younger than six years old.

Pregnant or breastfeeding

Insulin glargine is a pregnancy category C drug, which means that animal studies have shown potential harm to the fetus, but there are no adequate and well-controlled studies in humans. In general, uncontrolled diabetes is more likely to cause harm to the fetus than the use of insulin during pregnancy under the supervision of a physician.

There are no data as of 2015 regarding the excretion of insulin glargine into human milk. The manufacturer recommends caution in the use of insulin in nursing women.

Other conditions and allergies

Patients with known allergies to insulin glargine or to any of the inactive ingredients used to make the medication cannot use this form of insulin.

Patients with any of the following conditions should consult their doctor before using insulin glargine, as they may affect the amount of insulin the patient will need:

- chronic emotional disturbances
- an active viral, bacterial, or fungal infection
- high stress levels, which typically increase blood sugar levels
- kidney disease
- liver disease, which may lower the amount of insulin required

Side effects

Insulin glargine is usually well tolerated. Some of its side effects include:

- episodes of hypoglycemia
- pitting or thickening of the skin at the injection site
- skin rash or irritation at the injection site

Less common side effects that have been reported include:

- headache
- diarrhea
- back pain
- redistribution of body fat (lipodystrophy)
- swelling of the hands or feet
- pallor
- heart palpitations or speeded-up heartbeat
- flulike symptoms
- hypokalemia (low levels of potassium in the blood)

The following side effects of insulin glargine or symptoms of severe hypoglycemia should be reported to a doctor immediately:

- symptoms of the allergic reaction angioedema, which include sudden swelling of the face, arms, legs, eyes, lips, or tongue and problems with swallowing or breathing
- symptoms of hypoglycemia, which may include anxiety; behavioral changes that resemble those of alcohol intoxication; difficulty in thinking clearly; cold sweats; nervousness; difficulty sleeping; tremor; slurred speech; tingling sensations in the hands, feet, or tongue; excessive hunger; drowsiness; lightheadedness; and dizziness
- symptoms of severe hypoglycemia, which may include convulsions and unconsciousness

Interactions

Drugs

Insulin glargine interacts with a large number of drugs. The following types of drugs increase the patient's

risk of hypoglycemia when used together with insulin glargine:

- angiotensin-converting enzyme (ACE) inhibitors (**lisinopril**, captopril, **fosinopril**, **ramipril**, etc.)
- beta-blockers (**sotalol**, **timolol**, **propranolol**, **atenolol**, etc.)
- fibrates (**gemfibrozil** and **fenofibrate**)
- disopyramide (drug given to treat abnormal heart rhythms)
- sulfonamide antibiotics (sulfadiazine, sulfadoxine, sulfamethoxazole, etc.)
- monoamine oxidase inhibitors (MAOIs: phenelzine, selegiline, isocarboxazid, etc.)
- oral diabetes medications (**metformin**, **glipizide**, glyburide, **glimepiride**, etc.)
- propoxyphene (pain medication)
- salicylates (**aspirin**, diflunisal)
- **octreotide** (used to treat pituitary tumors and growth hormone-producing tumors)

Herbs and supplements

Cinnamon, eucalyptus, agrimony, juniper, devil's claw, nettle, willow bark, elderberry, panax ginseng, and American ginseng are known to intensify the effects of insulin glargine. Patients using insulin glargine should not use any herbal preparations without consulting their doctor.

Food and other substances

Diabetic patients using insulin glargine should avoid alcoholic beverages because of an increased risk of hypoglycemia.

Resources

BOOKS

- Morris, Deborah Gray. *Calculate with Confidence*. 6th ed. St. Louis, MO: Mosby Elsevier, 2014.
- Strachan, Mark W. J., and Brian M. Frier. *Insulin Therapy: A Pocket Guide*. New York: Springer, 2013.

PERIODICALS

- Garber, A. J. "Will the Next Generation of Basal Insulins Offer Clinical Advantages?" *Diabetes, Obesity and Metabolism* 16, no. 6 (2014): 483–91.
- Roomp, K., and J. S. Rand. "Management of Diabetic Cats with Long-Acting Insulin." *Veterinary Clinics of North America Small Animal Practice* 43, no. 2 (2013): 251–66.
- Segal, A. R., and N. El Sayed. "Are You Ready for More Insulin Concentrations?" *Journal of Diabetes Science and Technology* 9, no. 2 (2015): 331–38.
- Steintraesser, A., et al. "Investigational New Insulin Glargine 300 U/mL Has the Same Metabolism as Insulin Glargine

100 U/mL." *Diabetes, Obesity and Metabolism* 16, no. 9 (2014): 873–76.

Svingos, R. S., et al. "Life-Threatening Hypoglycemia Associated with Intentional Insulin Ingestion." *Pharmacotherapy* 33, no. 3 (2013): e28–33.

WEBSITES

- "Insulin Glargine." Drugs.com. <http://www.drugs.com/mtm/insulin-glargine.html> (accessed February 15, 2015).
- Medscape. "Insulin Glargine (Rx)." <http://reference.medscape.com/drug/lantus-insulin-glargine-999003> (accessed February 15, 2015).
- Micromedex. "Insulin Glargine, Recombinant (Subcutaneous Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/insulin-glargine-recombinant-subcutaneous-route/description/drg-20067770> (accessed February 15, 2015).

ORGANIZATIONS

- American Diabetes Association (ADA), 1701 North Beauregard Street, Alexandria, VA 22311, 800-DIABETES (342-2383), <http://www.diabetes.org/>.
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 9000 Rockville Pike, Bethesda, MD 20892-2560, (301) 496-3583, <http://www.niddk.nih.gov/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Rebecca J. Frey, PhD

REVIEWED BY JAMES E. WAUN, MD, RPh

Insulin lispro

Definition

Insulin lispro is a rapid-acting insulin analog used in the treatment of adults with type 1 and type 2 diabetes and children with type 1 diabetes. The advantage of using a rapid-acting insulin like insulin lispro is that it allows the patient to start eating a meal within a short period of time after the insulin injection, whereas regular insulins require a longer waiting period before eating.

Insulin lispro is also available as a biphasic insulin, which is an insulin formulation consisting of a fixed combination of a short-acting and an intermediate-acting insulin. Insulin lispro is formulated together with insulin lispro protamine, an intermediate-acting insulin, in two combinations: insulin lispro protamine/insulin lispro 75/25, and insulin lispro protamine/insulin lispro 50/50. The biphasic insulins allow patients to maintain glycemic control with fewer insulin injections during the day.



Humalog (insulin lispro). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Insulin lispro is used to manage the spike in blood sugar levels that occurs after meals in individuals with diabetes. It is most often used together with an intermediate-acting insulin, a basal insulin, or (for type 2 diabetics) oral diabetes medications to maintain glycemic control over the course of the day. Insulin lispro protamine/insulin lispro is used to treat type 1 diabetes in adults; it is not recommended for use in children. Both insulin lispro and its biphasic formulations can be used only to manage diabetes; they cannot be used to cure it.

Insulin lispro and insulin lispro protamine/insulin lispro work best when combined with an appropriate dietary and exercise plan.

Off-label use

Insulin lispro is used off label as preventive treatment for diabetic nephropathy (kidney disease), diabetic neuropathy (nerve damage), and cardiovascular complications of diabetes.

Description

Both insulin lispro and its two biphasic formulations are available as 100 U/mL (units per milliliter) vials for injection with standard hypodermic needles and as insulin pens or Kwikpens for use with special needles. Insulin lispro is a clear, watery liquid. The Kwikpen

contains 3 mL of 100 U/mL insulin lispro and can be adjusted to deliver 1–60 U in a single injection.

Insulin lispro protamine/insulin lispro is manufactured as a suspension that settles between doses. The patient must be careful to restore the suspension before each injection. If the vial is used, the patient must roll the vial horizontally ten times between the hands; the liquid in the vial should look uniformly white and cloudy. For the pen or Kwikpen, the patient should follow the instructions packaged with the specific device.

Insulin lispro vials may be safely stored at room temperature or a cool place after they are opened, or they may be refrigerated, as the patient prefers. They must, however, be used within 28 days after opening. An insulin lispro vial must be discarded if it becomes frozen or has not been used within 28 days. Insulin lispro cartridges or injection pens must be stored at room temperature, away from heat and bright light. In-use cartridges or injection pens should not be refrigerated; they should be kept at room temperature. A Kwikpen that has been opened must be used within 10 days.

U.S. brand names

Insulin lispro is marketed by Eli Lilly in the United States under the brand names HumaLOG, HumaLOG Cartridge, HumaLOG Pen, and HumaLOG Kwikpen. The biphasic forms of the insulin are sold under the brand names HumaLOG Mix 50/50, HumaLOG Mix 50/50 KwikPen, HumaLOG Mix 50/50 Pen; HumaLOG Mix 75/25, HumaLOG Mix 75/25 KwikPen, and HumaLOG Mix 75/25 Pen.

Canadian brand names

Insulin lispro is marketed by Lilly in Canada under the brand name HumaLOG. The biphasic insulins are sold under the brand names HumaLOG Mix 25 and HumaLOG Mix 50.

International brand names

Lilly markets insulin lispro in most countries as HumaLOG or HumaLOG Kwikpen; in the Baltic countries, Lilly sells insulin lispro under the brand names Liprolog and Liprolog Kwikpen. The biphasic insulins are sold in most countries as HumaLOG Mix 25, HumaLOG Mix 50, HumaLOG Mix 25 Kwikpen, and HumaLOG Mix 50 Kwikpen.

Origins

Insulin lispro was the first insulin analog to receive U.S. Food and Drug Administration (FDA) approval. It was

KEY TERMS

Basal insulin—A term that refers to long-acting insulins that are released slowly and provide 24 hours or more of background insulin in diabetic patients. Insulin detemir and insulin glargine are examples of basal insulins.

Biphasic insulin—An insulin formulation consisting of a fixed combination of short-acting and intermediate-acting insulin. Insulin lispro comes in two biphasic formulations as well as its simple form.

Glucagon—A peptide hormone produced in the alpha cells of the pancreas that quickly raises the level of blood sugar. An injectable form of glucagon is a necessary part of first aid in assisting a diabetic patient with severe hypoglycemia.

Hypoglycemia—Abnormally low blood sugar; it is a common complication of treating diabetes with insulin or oral diabetes medications.

Insulin analogue—An insulin that has been altered by genetic engineering to affect its absorption, distribution, metabolism, and excretion rates but can still be used by the human body to maintain glycemic control.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Subcutaneous—Below the skin.

developed by Eli Lilly and approved by the FDA in June 1996. The two biphasic forms of insulin lispro, also developed by Lilly, were approved by the FDA in December 1999. The FDA approvals included the pen and Kwikpen versions of the insulin as well as the standard vials.

Recommended dosage

The dosage of insulin lispro is individualized according to the patient's response to treatment and concurrent medical conditions. Daily monitoring of blood glucose levels is essential because changes in diet, infections, travel, stressful events, and similar factors can affect the patient's response to insulin. Patients should never change their insulin dosage without consulting their physician.

Insulin lispro may be administered by subcutaneous injection (into the skin), by intravenous infusion in a hospital setting, or by an insulin pump. Insulin lispro protamine/insulin lispro, however, is to be administered only by subcutaneous injection. None of the forms of insulin lispro should be mixed with other insulins.

Adults

Recommended dosages for adults include:

TYPE 1 DIABETES, INSULIN LISPRO. The usual daily maintenance range is 0.5–1 unit per kilogram (kg, or 2.2 lb.) of body weight per day in divided doses, one before breakfast and the second before the evening meal. Patients who are not obese may require 0.4–0.6 U/kg per day; obese patients may require 0.8–1.2 U/kg per day.

TYPE 2 DIABETES, INSULIN LISPRO. Intermediate- or long-acting insulins are generally preferred for adults with type 2 diabetes who cannot maintain glycemic control on oral medications alone. If insulin lispro is used in this type of patient, the dose must be carefully adjusted for each individual.

TYPE 1 OR TYPE 2 DIABETES, INSULIN LISPRO PROTAMINE/INSULIN LISPRO. There is no standard dose for the biphasic insulins that is suitable for all patients or for the same patient in different situations. The typical daily insulin requirements for adults range between 0.5 and 1 U/kg. The patient should self-administer the insulin subcutaneously twice daily, usually before breakfast and before the evening meal. Each dose should cover two meals or a meal and a snack.

For all doses, if an insulin pump is used, the patient should divide the number of units per day by 24 to obtain the basal rate per hour.

Pediatric

For managing type 1 diabetes with insulin lispro, most children and teenagers ages three and over require 0.8–1.2 U/kg per day during growth spurts; otherwise, they are given adult doses (0.5–1 U/kg per day).

Precautions

Patients using injectable insulins should be instructed about the proper way to inject themselves, to care for their injection devices, and to dispose of used needles and expired insulin properly:

- Insulin lispro and its biphasic formulations act rapidly to lower the patient's blood sugar levels. To prevent hypoglycemia, patients must eat a meal within 10–15 minutes of injecting the insulin.

- Patients should rotate the injection site (upper arm, thigh, abdomen) and avoid using the same site twice in a row.
- Patients using an insulin pump with insulin lispro must remove unused insulin at least every six days and change the infusion set and insertion site at least every three days to prevent degradation of the insulin and loss of the preservative.
- Patients should never share their hypodermic needles or injection pens with others and should use each syringe or pen needle only once.
- Used needles should be stored in a puncture-proof container, kept away from children and pets, and disposed of in accordance with state or local laws. A pharmacist can provide information about obtaining such containers and disposing of them properly.
- Patients with diabetes should always keep a supply of insulin and syringes or an insulin pen with them in case of an episode of high blood sugar; they should carry candy or another form of quickly digested sugar with them in case of a hypoglycemic episode. In addition, they should keep a glucagon kit and syringe with them in case of an episode of severe hypoglycemia.
- Patients with diabetes should also carry a medical identification card with them at all times; the card should state that they have diabetes, the type of insulin they use, and a list of all other medications they are currently taking.
- Insulin lispro may affect judgment and clear thinking; patients using this insulin should avoid driving or operating hazardous machinery until they know how the insulin affects them.

Insulin lispro, whether in a vial or a pen, should not be used if it looks thick or discolored or has visible particles or lumps floating in it.

Pediatric

Insulin lispro is not recommended for use in children with type 1 diabetes who are younger than three years. In addition, the biphasic forms of insulin lispro are not recommended for use in children or adolescents.

Pregnant or breastfeeding

Both insulin lispro and its biphasic formulations are in the FDA pregnancy category B, which means that animal reproduction studies have failed to demonstrate a risk to the human fetus. It is not known whether these insulins pass into human breast milk, but nursing mothers are advised to consult their healthcare provider before using these insulins.

Other conditions and allergies

Patients with any of the following conditions should consult their doctor before using insulin lispro, as they may affect the amount of insulin the patient will need:

- chronic emotional disturbances
- repeated episodes of hypoglycemia
- hypokalemia (low blood potassium level)
- an active viral, bacterial, or fungal infection
- high stress levels, which typically increase blood sugar levels
- kidney disease
- liver disease, which may lower the amount of insulin required

Side effects

Common side effects of insulin lispro and insulin lispro protamine/insulin lispro include:

- episodes of hypoglycemia
- pitting or thickening of the skin at the injection site
- skin rash or irritation at the injection site
- anxiety

The following side effects of insulin lispro or symptoms of severe hypoglycemia should be reported to a doctor immediately:

- Symptoms of angioedema, an allergic reaction to insulin, may include sudden swelling of the face, arms, legs, eyes, lips, or tongue or problems with swallowing or breathing.
- Symptoms of hypoglycemia may include anxiety; behavioral changes that resemble those of alcohol intoxication; difficulty in thinking clearly; cold sweats; nervousness; difficulty sleeping; tremor; slurred speech; tingling sensations in the hands, feet, or tongue; excessive hunger; drowsiness; or lightheadedness or dizziness.
- Symptoms of severe hypoglycemia may include convulsions or unconsciousness.
- Symptoms of edema (fluid retention) may include rapid weight gain; shortness of breath; chest pain or discomfort; extreme tiredness or weakness; uneven heartbeat; or severe swelling of the hands, wrists, ankles, or feet. Edema is most often caused by using insulin lispro together with the type 2 diabetes drugs **pioglitazone** or **rosiglitazone**.
- Symptoms of hypokalemia (low blood potassium levels) may include mental confusion, uneven heart rate, extreme thirst, increased urination, leg pain, muscle weakness, or a generally limp feeling.

Interactions

Insulin lispro interacts with a wide variety of other medications.

Drugs

The following categories of drugs increase the patient's risk of hypoglycemia when used together with insulin lispro or its biphasic formulations:

- angiotensin-converting enzyme (ACE) inhibitors (e.g., lisinopril, **captopril**, **fosinopril**, **ramipril**)
- beta-blockers (e.g., **sotalol**, **timolol**, **propranolol**, **atenolol**)
- fibrates (**gemfibrozil** and **fenofibrate**)
- gliptins (a newer class of oral medications used to treat type 2 diabetes, e.g., alogliptin, saxagliptin, **sitagliptin**, linagliptin)
- monoamine oxidase inhibitors (MAOIs, e.g., phenelzine, selegiline, isocarboxazid)
- oral diabetes medications (e.g., **metformin**, **glipizide**, glyburide, **glimepiride**)
- propoxyphene (pain medication)
- salicylates (**aspirin**, diflunisal)
- sulfonamide antibiotics (e.g., sulfadiazine, sulfadoxine, sulfamethoxazole)
- thiazolidinediones (pioglitazone, rosiglitazone)
- fluoroquinolone antibiotics (e.g., norfloxacin, gatifloxacin, gemifloxacin, ofloxacin, **levofloxacin**)

Other drugs that interact with insulin lispro include some antipsychotic medications (**clozapine** and **olanzapine**), which increase the difficulty of maintaining glycemic control, and pramlintide, a relatively new injectable drug used to treat both type 1 and type 2 diabetes. Pramlintide and insulin lispro should never be used together.

Herbs and supplements

Patients using insulin lispro should avoid such herbs and spices as cinnamon, bitter melon, prickly pear, American ginseng, devil's claw, eucalyptus, sage, nettle, horse chestnut, gotu kola, willow bark, or Siberian or panax ginseng because of an increased risk of hypoglycemia.

Food and other substances

Diabetic patients using insulin lispro should avoid alcoholic beverages because of an increased risk of hypoglycemia and possible loss of glycemic control because of the added calories in alcoholic beverages.

Patients using insulin lispro should also avoid smoking or ingesting marijuana or food products containing marijuana, as this recreational drug lowers the effectiveness of the insulin.

Resources

BOOKS

Morris, Deborah Gray. *Calculate with Confidence*. 6th ed. St. Louis, MO: Mosby Elsevier, 2014.

Strachan, Mark W. J., and Brian M. Frier. *Insulin Therapy: A Pocket Guide*. New York: Springer, 2013.

PERIODICALS

Esposito, K., A. Capuano, and G. Giugliano. "Humalog (Lispro) for Type 2 Diabetes." *Expert Opinion on Biological Therapy* 12, no. 11 (2012): 1541–50.

Home, P. D. "The Pharmacokinetics and Pharmacodynamics of Rapid-Acting Insulin Analogues and Their Clinical Consequences." *Diabetes, Obesity and Metabolism* 14, no. 9 (2012): 780–88.

King, A. "Integrating Advances in Insulin into Clinical Practice: Advances in Insulin Formulations." *Journal of Family Practice* 62, no. 9 suppl. (2013): S9–S17.

Tibaldi, J. M. "Evolution of Insulin: From Human to Analog." *American Journal of Medicine* 127, no. 10 suppl. (2014): S25–S38.

WEBSITES

"Insulin Lispro." Drugs.com. <http://www.drugs.com/mtm/insulin-lispro.html> (accessed February 16, 2015).

"Insulin Lispro and Insulin Lispro Protamine." Drugs.com. <http://www.drugs.com/mtm/insulin-lispro-and-insulin-lispro-protamine.html> (accessed February 16, 2015).

"Insulin Lispro Protamine/Insulin Lispro (Rx)." Medscape.com. <http://reference.medscape.com/drug/humalog-mix-50-50-insulin-lispro-protamine-insulin-lispro-999553> (accessed February 16, 2015).

"Insulin Lispro (Rx)." Medscape.com. <http://reference.medscape.com/drug/humalog-insulin-lispro-999005> (accessed February 16, 2015).

Micromedex. "Insulin Lispro (Intravenous Route, Subcutaneous Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/insulin-lispro-intravenous-route-subcutaneous-route/description/drg-20064334> (accessed February 16, 2015).

Micromedex. "Insulin Lispro Protamine and Insulin Lispro (Subcutaneous Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/insulin-lispro-protamine-and-insulin-lispro-subcutaneous-route/description/drg-20072458> (accessed February 16, 2015).

ORGANIZATIONS

American Diabetes Association, 1701 North Beauregard Street, Alexandria, VA 22311, (800) DIABETES (342-2383), <http://www.diabetes.org/>.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 9000 Rockville Pike, Bethesda, MD 20892-2560, (301) 496-3583, <http://www.niddk.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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REVIEWED BY KEVIN GLAZA, RPh

Interferon beta 1a

Definition

Interferon beta 1a is an injected immune system protein for treating multiple sclerosis (MS). It is in the immunomodulator drug class because it directly affects immune system activity. Interferon beta 1a is also known as a disease-modifying drug (DMD).

Purpose

MS is an autoimmune disease in which the body's immune system attacks and destroys the myelin sheaths that surround nerve cells. Interferon beta 1a is used to treat relapsing-remitting MS, in which symptoms occur in episodes or attacks—defined as worsening of symptom(s) or the appearance of new symptoms lasting at least 24 hours and occurring at least one month after the last exacerbation. Interferon beta 1a does not cure MS, but it



Avonex (interferon beta 1a). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

may decrease the frequency of relapses by 18%–38%. It also decreases the severity of attacks and slows the development of disabilities—weakness, numbness, loss of muscle coordination, and speech, vision, and bladder control problems that result from damage to nerve axons. Magnetic resonance imaging (MRI) shows that interferon beta 1a reduces the occurrence and size of lesions in the brain and spinal cord and may even eliminate them altogether. Because brain shrinkage (atrophy) can occur early in the course of MS, even in the absence of attacks, interferon beta 1a treatment may be initiated after a first clinical episode. It is generally used long term. Interferon beta 1a and other MS DMDs are not effective against chronic progressive MS, in which symptoms are always present and worsen over time.

Off-label use

Interferon beta 1a may be prescribed for other purposes. For example, it is sometimes used to treat severe neuritis (nerve inflammation).

Description

Interferon beta 1a is a 166-amino-acid human glycoprotein (protein with attached sugars) in the interferon family of cytokines. The drug is produced from the human interferon beta 1a gene in genetically engineered animal cells. It is not known exactly how interferon beta 1a treats the symptoms of MS, but it promotes production of anti-inflammatory cytokines and reduces production of pro-inflammatory cytokines by reducing the trafficking of inflammatory cells within the central nervous system. This reduction in inflammation apparently reduces the frequency of attacks and the formation of new lesions. Interferon beta 1a may also stimulate the production of nerve growth factor, so it may function in nerve cell repair.

U.S. brand names

There are two brand-name interferon beta 1a formulations available in the United States and internationally—Avonex for intramuscular injection and Rebif for subcutaneous (under the skin) injection. There are no generic forms available in the United States.

Avonex is supplied in three forms for once-per-week intramuscular injection: 33 micrograms (mcg) or 6.6 million units of lyophilized (freeze-dried) powder, a premixed-liquid syringe kit, and an injection pen. The vials of powder (which include albumin, a serum protein) are reconstituted in 1 milliliter (mL) of supplied sterile water for injection (SWFI) and come with an access pin, sterile needle, and alcohol wipes. The kit includes a syringe with 30 mcg interferon beta 1a in 0.5 mL (albumin-free), a syringe cap (contains latex), alcohol

wipes, a gauze pad, and adhesive bandages. The vials and prefilled syringes should be kept refrigerated. The vials may be stored at room temperature, away from heat and light, for up to 30 days, but once the powder is mixed, it should be refrigerated and used within 6 hours. The prefilled syringes must be used within 12 hours of removal from the refrigerator.

Rebif is supplied in a preservative-free combination package containing six prefilled syringes of 8.8 mcg in 0.2 mL solution, or 22 or 44 mcg in 0.5 mL solutions. The package can be stored at room temperature for up to 30 days.

Origins

As of 2015, interferon beta 1a was one of ten DMDs approved by the U.S. Food and Drug Administration (FDA) for treating relapsing forms of MS. Avonex was approved in the United States in 1996 and in Europe in 1997. Rebif was approved in Europe in 1998 and in the United States in 2002. Both drugs are registered in more than 80 countries worldwide. Avonex is the leading MS drug in the United States, with an overall market share of approximately 40%. Avonex has about 30% of the overall European market.

Recommended dosage

Avonex is a once-weekly, 30 mcg injection into a muscle, given on the same day each week at about the same time, usually in the late afternoon or evening. Rebif is a 22 mcg or a 44 mcg subcutaneous injection given three times per week, with doses at least 48 hours apart. If the target Rebif dosage is 44 mcg, the initial dose is 8.8 mcg (20%) three times per week for eight weeks, followed by 22 mcg three times a week for eight weeks. If the target dosage is 22 mcg, the initial dose is 4.4 mcg three times per week for eight weeks, followed by 11 mcg three times per week for eight weeks. Rebif is injected at the same time of day on the same three days of the week: for example, late afternoon or evening of Monday, Wednesday, and Friday. A missed dose should be injected as soon as possible, but the drug should not be injected on two consecutive days.

The initial dose is injected in the doctor's office. Subsequently, the patient or a friend or relative performs the injections. A new, unopened vial or prefilled syringe and needle are used for each injection. Used syringes and needles are discarded in a puncture-resistant container. Interferon beta 1a is warmed to room temperature without heating before use. Avonex is usually injected into an upper arm or thigh at a different site each time. Rebif injections are performed where there is a layer of fat between the skin and muscle—such as the thigh, outer

KEY TERMS

Anemia—A deficiency in red blood cells, in the hemoglobin component of red blood cells, or in total blood volume.

Autoimmune disease—A condition, such as multiple sclerosis, caused by inappropriate immune-system activity.

Chronic—Progressing slowly but persisting or recurring over time.

Cytokines—Proteins, such as interferons, that regulate immune responses and mediate intercellular communication.

Disease-modifying drug (DMD)—A drug, such as interferon beta 1a, that modulates the immune system to decrease inflammation.

Immunomodulators—A class of drugs, including interferon beta 1a, that acts by altering the immune response.

Inflammation—The body's reaction to invasion by foreign matter, particularly infection. The result is swelling and redness from an increase in water and blood, and pain from the chemical activity of the reaction.

Leukopenia—Condition characterized by an abnormally low number of circulating white blood cells.

Magnetic resonance imaging (MRI)—A diagnostic technique that provides cross-sectional images of structures within the body via a magnetic imaging device.

Multiple sclerosis (MS)—A central nervous system autoimmune disorder causing progressive paralysis, usually marked by periods of exacerbation and remission.

Myelin sheath—A protective cover that surrounds nerve cells and helps to increase the speed by which information travels along the nerve.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Subcutaneous—Into the skin.

surface of the upper arm, stomach, or buttocks. Very thin people should inject only into the thigh or arm. Injections should not be near the navel or waistline. A record is kept

of the date and site of each injection. Injections should not be made into skin that is sore, red, bruised, scarred, irritated, infected, or otherwise abnormal. Injection instructions should be followed carefully. The injection site is checked after two hours for redness, swelling, or tenderness. A cold compress or ice pack helps reduce these symptoms.

Other conditions and allergies

If liver function tests increase or leukopenia (low white blood cell count) develops in patients with liver impairment, the Rebif dose is decreased by 20%–50%.

Precautions

Some precautions to be aware of while taking interferon beta 1a include:

- Patients will need to have tests to monitor treatment responses, as well as baseline and periodic liver-function testing and complete blood cell counts.
- Doctors and dentists must be informed of interferon usage before any type of surgery.
- Patients should not stop using interferon without consulting their doctor.
- Immunity may develop to interferon beta 1a.

Pediatric

The safety and effectiveness of interferon beta 1a have not been established in pediatric patients.

Geriatric

It is not known whether elderly patients respond differently than younger patients to interferon beta 1a. Initial treatment should be at the low end of the dosing range due to the possibility of decreased liver, kidney, and cardiac function in the elderly, as well as the existence of other diseases and medication use.

Pregnant or breastfeeding

Interferon beta 1a is in the FDA pregnancy category C. In most cases, women should not use it during pregnancy because it may harm the fetus. It is not known whether interferon beta 1a is excreted in breast milk, but its use by nursing mothers is not recommended.

Other conditions and allergies

Rare but significant allergic reactions have been reported with interferon beta 1a. The doctor and pharmacist should be informed of allergies to any interferon products; any ingredients in interferon beta 1a injection, including human albumin; any other medications; natural rubber; or latex. Patients with a

history of depression, seizures, or heart problems should be closely monitored. The doctor should be told if the patient drinks or has ever drunk large amounts of alcohol or has ever had:

- HIV/AIDS
- an autoimmune disease other than MS
- blood conditions such as anemia, leukopenia, or easy bruising or bleeding
- cancer
- anxiety, mood disorders, or mental illness
- difficulty falling or staying asleep
- angina (recurring chest pain)
- heart, liver, or thyroid disease

Side effects

The most common side effects of interferon beta 1a are flulike symptoms—including headache, fever, chills, sweating, muscle aches, nausea, vomiting, and fatigue—lasting for about one day postinjection. Injecting at bedtime and taking over-the-counter pain and fever relievers may help. These symptoms often lessen or disappear over time. Other common side effects are injection-site reactions, mild leukopenia, and reversible thyroid and liver dysfunction. Less common symptoms are depression, mild anemia, allergic reactions, and heart problems.

Patients should consult their doctor if any of the following symptoms are severe or persistent:

- tight muscles
- dizziness
- numbness, burning, tingling, or pain in hands or feet
- joint pain
- stomach pain
- eye problems
- runny nose
- toothache
- hair loss
- bruising, pain, redness, swelling, bleeding, or irritation at the injection site
- dry eyes
- dry mouth
- nausea
- vomiting

Uncommon but serious side effects that require immediately contacting the doctor are:

- depression
- thoughts of self-harm or suicide

- extreme emotion
- anxiety
- hallucinations
- seizures
- unexplained weight gain or loss
- consistently feeling cold or hot
- difficulty breathing when lying flat
- increased nighttime urination
- painful or difficult urination
- decreased ability to exercise
- lack of energy
- excessive tiredness
- chest tightness or pain
- fast or irregular heartbeat
- pale skin
- loss of appetite
- unusual bleeding or bruising
- pain or swelling in the upper-right stomach
- yellowing of the skin or eyes
- dark-brown urine
- light-colored bowel movements
- hives
- rash
- itching
- flushing
- swelling of the face, throat, tongue, lips, eyes, hands, arms, feet, ankles, or lower legs
- difficulty breathing or swallowing
- hoarseness
- lightheadedness
- fainting
- loss of coordination
- vision problems
- difficulty sleeping
- swollen neck glands
- sore throat, cough, fever, chills, or other signs of infection
- blackening of skin or drainage at the injection site

Interactions

The doctor and pharmacist should be informed of all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used or planning to be used by the patient. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

The following drugs may require changing dosages or carefully monitoring for side effects:

- acetaminophen
- antidepressants
- azathioprine
- cancer chemotherapy drugs
- **carbamazepine**
- chloramphenicol
- cholesterol-lowering medications (statins)
- **cyclosporine**
- gold compounds such as auranofin and aurothioglucose
- heparin
- iron products
- isoniazid
- HIV/AIDS medications
- **methotrexate**
- penicillamine
- **phenytoin**
- **rifampin**
- salicylate pain relievers such as **aspirin**, choline magnesium trisalicylate, choline salicylate, diflunisal, magnesium salicylate, and salsalate
- sirolimus
- sulfa antibiotics such as sulfamethoxazole and sulfisoxazole
- **tacrolimus**
- thyroid medications

Herbs and supplements

Interferon beta 1a may interact with niacin (nicotinic acid).

Food and other substances

Alcohol may increase the risk of serious side effects. Patients should discuss safe use of alcohol with their doctors.

Resources

PERIODICALS

- Carrithers, Michael D. "Update on Disease-Modifying Treatments for Multiple Sclerosis." *Clinical Therapeutics* 36, no. 12 (2014): 1938–45.
- Hupperts, Raymond, et al. "The STAR Study: A Real-World, International, Observational Study of the Safety and Tolerability of, and Adherence to, Serum-Free Subcutaneous Interferon [beta]-1a in Patients with Relapsing Multiple Sclerosis." *Clinical Therapeutics* 36, no. 12 (2014): 1946–57.

Prosperini, Luca, et al. "Interferon Beta Failure Predicted by EMA Criteria or Isolated MRI Activity in Multiple Sclerosis." *Multiple Sclerosis Journal* 20, no. 5 (2014): 566–76.

Rudick, Richard A., et al. "Multiple Sclerosis Outcome Assessments Consortium: Genesis and Initial Project Plan." *Multiple Sclerosis Journal* 20, no. 1 (2014): 12–17.

Tavazzi, Eleonora, Rovaris, Marco, and Loradana La Mantia. "Drug Therapy for Multiple Sclerosis." *Canadian Medical Association Journal* 186, no. 11 (2014): 833–40.

Vermersch, Patrick, et al. "Teriflunomide Versus Subcutaneous Interferon Beta-1a in Patients with Relapsing Multiple Sclerosis: A Randomised, Controlled Phase 3 Trial." *Multiple Sclerosis Journal* 20, no. 6 (2014): 705–16.

OTHER

National Multiple Sclerosis Society. "The MS Disease-Modifying Medications: General Information." <http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Brochure-The-MS-Disease-Modifying-Medications.pdf> (accessed December 28, 2014).

U.S. Food and Drug Administration. "Full Prescribing Information." http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103780s5178s51791bl.pdf (accessed February 15, 2015).

WEBSITES

MedlinePlus. "Interferon Beta-1a Intramuscular Injection." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a693040.html> (accessed February 15, 2015).

MedlinePlus. "Interferon Beta-1a Subcutaneous Injection." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a604005.html> (accessed February 15, 2015).

University of Maryland Baltimore Washington Medical Center. "Interferon Beta-1a." <http://www.mybwmc.org/library/41/071127> (accessed February 15, 2015).

ORGANIZATIONS

National Institute of Neurological Disorders and Stroke, NIH Neurological Institute, PO Box 5801, Bethesda, MD 20824, (301) 496-5751, (800) 352-9424, <http://www.ninds.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY JAMES E. WAUN, MD, RPH

Invega see **Paliperidone**

Ionamin see **Phentermine**

Ipratropium

Definition

Ipratropium is a medication that is inhaled to help prevent problems associated with chronic obstructive pulmonary disease (COPD), a group of diseases that affect the lungs and airways and the ability to breathe. Ipratropium is a bronchodilator that belongs to a class of drugs called anticholinergics. The full name of ipratropium is ipratropium bromide.

Purpose

People who have COPD have chronic, or ongoing, problems related to their lungs and airways. Typically, they have emphysema, which is a progressive condition caused by damage to the lungs' air sacs, or chronic bronchitis, which is characterized by swollen airways leading to the lungs. Shortness of breath, a tight feeling in the chest, coughing, and difficulty breathing are some of the symptoms of COPD. Anticholinergic drugs work by preventing the muscles around the airways from tightening, which helps keep the airways open and makes it easier for people who have COPD to breathe.

Description

Ipratropium is an aerosol that must be inhaled into the airways before it can take action, often from a metered-dose inhaler. The drug is also available in a

liquid solution that can be used as part of a nebulizer treatment. Ipratropium is considered a short-acting anticholinergic, which means begins to take effect in about 15 minutes and lasts six to eight hours.

U.S. brand names

In the United States, ipratropium is sold as Atrovent.

Recommended dosage

Metered dose inhalers have premeasured doses. For COPD, most adults start ipratropium at a dose of two inhalations four times a day. Depending on symptom severity and doctor instructions, patients may take more doses, but they should not take more than 12 inhalations within a 24-hour period.

When using the nebulizer solution, adults may have one vial, which is a unit dose containing 500 micrograms (mcg) of ipratropium, three to four times a day.

Pediatric

Children ages 3 to 12 who have COPD may use one to two inhalations three times a day but no more than six inhalations a day. Beginning at age 12, they may have two inhalations four times a day, with no more than 12 inhalations in a 24-hour period.

Newborns should receive only 25 mcg per kilogram (kg, or 2.2 lb.) of their body weight in a nebulizer up to three times per day. Infants and children up to 12 years old who use a nebulizer may use 125–250 mcg up to three times a day. Children older than age 12 may use a full-dose vial (500 mcg) three to four times a day.

Precautions

It is important to prime an inhaler before using it for the first time. This is accomplished by releasing two test sprays. When testing or using the inhaler, patients should always be careful to avoid pointing the sprayer toward their eyes.

Some people are allergic or hypersensitive to ipratropium and similar medications. It is important to inform the doctor of any known drug allergies before starting ipratropium treatment. Some people react to use of ipratropium with a paradoxical bronchospasm, or sudden and worse tightening of the airway muscles that is potentially life threatening.

To ensure that ipratropium works as it should, it is important to follow the directions that accompany the medication and any instructions provided by the healthcare provider. Breathing correctly during ipratropium inhaler treatment and properly using inhalers and nebulizers ensures safe and more effective results.



Atrovent HFA (ipratropium). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Bronchodilator—A medicine that relaxes the airways or the muscles around the airways to make breathing easier for people who have asthma or chronic obstructive pulmonary disease.

Chronic obstructive pulmonary disease (COPD)—Refers to several progressive diseases of the lungs and airways, including emphysema, chronic bronchitis, and nonreversible asthma.

Nebulizer—A machine, usually run by a small compressor, that delivers a fine liquid mist with medicine through a mouth tube or face mask. The nebulizer provides a breathing treatment for people who have COPD and other types of lung diseases.

Ipratropium is not intended as a rescue medication for rapid response to a breathing problem such as bronchospasm. Instead, the medicine is intended for maintenance and prevention of symptoms.

Pregnant or breastfeeding

Ipratropium is a pregnancy category B drug. There are no thorough studies of the drug's possible effects on a fetus, so pregnant women should use the medication only if the benefit of doing so clearly outweighs potential risk to the fetus. It is not known whether ipratropium passes through breast milk, so any new mother who wants to breastfeed should discuss use of ipratropium with her doctor and use the medication with caution or choose not to breastfeed.

Side effects

Ipratropium causes side effects, including:

- heartburn
- nausea and constipation
- dizziness
- pain when urinating and difficult or frequent urination
- back pain
- dry mouth

Some side effects can be severe. Individuals should contact their healthcare provider immediately if they experience any of the following symptoms while taking ipratropium:

- hives or rash
- itching

- swollen eyes, lips, tongue, throat, face, hands, or lower limbs
- problems with breathing or swallowing
- rapid or pounding heartbeat
- chest pain

Other conditions and allergies

Some studies have shown serious side effects from using ipratropium in people who have certain cardiovascular diseases. These risks may not be explained in all of the literature accompanying ipratropium prescriptions, and individuals with a history of heart conditions should consult with their physician.

Interactions

Drugs can interact with each other or with other substances. Individuals taking ipratropium should inform their doctor of any and all herbal remedies, supplements, or other medications being taken before starting ipratropium therapy.

Drugs

Ipratropium does not cause severe interactions with other drugs, but anyone taking ipratropium should not take other anticholinergics at the same time, because the drugs can increase effects of one another. Anticholinergic drugs may be used to treat irritable bowel disease, motion sickness, ulcers, or Parkinson's disease in addition to COPD, so patients should be sure their healthcare provider has a complete and up-to-date medical and medication history.

Resources

PERIODICALS

- Cheyne, Leanne, Melanie J. Irvin-Sellers, and John White. "Tiotropium versus Ipratropium Bromide for Chronic Obstructive Pulmonary Disease." *Cochrane Database of Systematic Reviews* 9, art. no. CD009552 (2013). <http://dx.doi.org/10.1002/14651858.CD009552.pub2> (accessed February 10, 2015).
- Coad, Felicity. "Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease." *InnovAiT* 6, no. 4 (2013): 232–39.
- Singh, Sonal, et al. "Pro-Arrhythmic and Pro-Ischaemic Effects of Inhaled Anticholinergic Medications." *Thorax* 68, no. 1 (2012): 114–16.

WEBSITES

- AHFS Consumer Medication Information. "Ipratropium." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a695021.html> (accessed February 7, 2015).
- American Lung Association. "COPD." <http://www.lung.org/lung-disease/copd/> (accessed February 10, 2015).

Cincinnati Children's Hospital. "Ipratropium Bromide Inhalation." <http://www.cincinnatichildrens.org/health/i/ipratropium-bromide/> (accessed February 10, 2015).

ORGANIZATIONS

American Lung Association, 55 W. Wacker Drive, Suite 1150, Chicago, IL 60601, (800) LUNGUSA (586-4872), Fax: (202) 452-1805, <http://www.lung.org/>.

American Thoracic Society, 25 Broadway, New York, NY 10004, (212) 315-8600, Fax: (212) 315-6493, <http://www.thoracic.org/>.

COPD Foundation, 20 F Street NW, Suite 200-A, Washington, DC 20001, (866) 316-2673, info@copdfoundation.org, <http://www.copdfoundation.org/>.

Teresa G. Odle, BA, ELS
REVIEWED BY KEVIN GLAZA, RPh

Ipratropium/albuterol see **Albuterol/ipratropium**

Irbesartan

Definition

Irbesartan is an antihypertensive drug in the class of drugs known as angiotensin II receptor antagonists, also called angiotensin receptor blockers.



Irbesartan, 300 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Irbesartan is used to treat high blood pressure, which is known medically as hypertension. Irbesartan is used to control or reduce blood pressure, but is not expected to cure high blood pressure. Irbesartan use in diabetics with high blood pressure is proven to help delay diabetes-related kidney disease, known as diabetic nephropathy.

Off-label uses

Irbesartan is sometimes used to treat congestive heart failure, which occurs when the heart is not able to effectively pump blood throughout the body. In using irbesartan to treat high blood pressure, it was found that the specific action of irbesartan in reducing blood pressure and smoothing blood flow also eased the pumping action of the heart.

Description

High blood pressure refers to the outward pressure of blood flow against the walls of blood vessels throughout the body. As an angiotensin II receptor antagonist, irbesartan works by blocking the activity of specific substances that narrow or tighten blood vessels. Angiotensin II is one of a family of peptides that constrict blood vessels. This constriction results in narrowing the diameters of blood vessels, which increases the outward pressure exerted by flowing blood on blood vessel walls. Angiotensin II antagonists block that action, allowing blood to flow more smoothly and the heart to pump blood more efficiently.

Controlling blood pressure is important because high blood pressure increases the risk of heart disease and stroke. Irbesartan is often used in combination with other blood pressure-lowering drugs that work in different ways. Physicians also advise that lifestyle measures such as a healthy diet, avoiding salt and caffeine, managing weight, and getting sufficient exercise will help irbesartan work more effectively.

Irbesartan is a white to off-white crystalline powder that is prepared as tablets to be taken by mouth. The tablets come in dosages of 150 milligrams (mg) and 300 mg.

U.S. brand names

In the United States, irbesartan is sold under the brand name Avapro.

Canadian brand names

In Canada, irbesartan is sold under the brand name Avapro.

KEY TERMS

Antagonist—Drugs that act against, block, or inhibit a specific biochemical activity in the body.

Antihypertensive—A medication intended to reduce blood pressure.

Hypotension—Low blood pressure.

Nephropathy—Kidney damage or disease that can affect kidney function. Diabetic nephropathy refers to kidney damage caused by diabetes, which can lead to kidney failure.

International brand names

Internationally, irbesartan is sold under a wide variety of brand names. In some countries, irbesartan is only one component of the medication, and there are other medications included in the formulation.

Recommended dosage

The recommended dosage of irbesartan may be low initially and increased gradually. Irbesartan is taken once a day, with or without food, and at the same time every day. For blood pressure reduction, the starting dose is 150 mg, which will usually be increased to 300 mg after the patient has adjusted to the medication. For a hypertensive patient with diabetes-associated nephropathy, the starting dose is 300 mg and will usually be maintained.

Lowering blood pressure or reducing the effects of high blood pressure may not be noticed until two or more weeks after starting treatment. Patients should not take more or less irbesartan than their doctor has prescribed, and it should never be discontinued without the doctor's knowledge and permission.

Precautions

Inactive ingredients in the irbesartan tablet may cause allergic reactions in some patients. Before taking irbesartan, patients should tell their physician about any known allergies and previous reactions to certain medications. All medications being taken regularly should also be reported to the physician, as well as the patient's history of diseases or conditions such as liver or kidney disease, heart disease, or dehydration.

Irbesartan may cause dizziness. Patients should not drive, operate machinery, or perform any tasks requiring alertness until they are sure these activities can be done safely, without dizziness. Alcohol consumption should be limited while taking irbesartan.

Taking irbesartan may increase potassium levels in the blood. Patients should consult their physician about using supplements or salt substitutes containing potassium, as increased levels may disturb electrolyte balance, which can lead to changes in heart rate.

Patients experiencing certain clinical conditions such as diarrhea, vomiting, dehydration, and profuse sweating may have significant reductions in blood pressure levels (hypotension), which may result in dizziness and even fainting. Patients should inform their physician immediately if any such conditions or symptoms develop while they are taking irbesartan. To avoid these conditions and symptoms, patients must be sure to drink sufficient water throughout the day and night.

Initial doses of irbesartan may cause a feeling of lightheadedness, dizziness, and fainting. To avoid these symptoms, patients should get up slowly from a sitting position or after lying down. Dizziness on rising can be minimized by resting the feet on the floor for a few minutes before standing.

In rare instances, irbesartan may break down skeletal muscle tissue, which leads to kidney failure. If symptoms such as muscle pain, tenderness or weakness accompanied by fever, extreme fatigue, and darker-than-normal urine color are noticed, the patient should stop taking irbesartan and should report symptoms to the physician immediately.

Pregnant or breastfeeding

Irbesartan is in the U.S. Food and Drug Administration (FDA) pregnancy category D, meaning that there is positive evidence of risk to the fetus. Irbesartan should not be taken during pregnancy. If a woman becomes pregnant while taking irbesartan, the drug should be discontinued immediately to avoid injury to the developing fetus.

It is not known if irbesartan passes into breast milk. Women who are breastfeeding should consult with their physician before taking irbesartan.

Side effects

Allergic reactions to irbesartan are rare but may include rash; hives; difficulty breathing; or swelling of the face, lips, tongue, or throat. If any of these symptoms are noticed, patients should stop taking irbesartan and should get immediate emergency help.

Dizziness, lightheadedness, and upset stomach may occur when first taking irbesartan but will likely subside or disappear completely as the body adjusts to the medication. If any of these symptoms persist, patients should report the symptoms to their physician.

Side effects such as flushing of the face, heart symptoms such as murmur or heart attack, constipation, sleep disturbance, lung congestion, and vision or hearing abnormalities have been reported in fewer than 1% of people taking irbesartan. Orthostatic hypertension that occurs with rising from sitting or lying down may occur more often in diabetes patients being treated for nephropathy and high blood pressure than in patients being treated for hypertension alone.

Serious side effects of irbesartan are unlikely. However, potentially serious side effects such as fainting; muscle weakness; a slow, irregular heartbeat; or unusual changes in the amount of urine excreted should be reported to the physician as soon as noticed.

Interactions

To avoid unwanted drug interactions, patients must inform their physician of any previous allergic reactions to drugs or other substances, even foods, and report any known allergies. Patients must also inform their physician about all drugs being taken, including prescription drugs and over-the-counter drugs such as **aspirin**, **ibuprofen**, or naproxen. The use of all supplements, especially potassium, should be reported. It is also important to let the physician know about any preexisting diagnoses of diabetes, heart disease, or kidney or liver disease.

Drugs

Interactions may occur between irbesartan and potassium-sparing diuretics such as amiloride (Midamor), eplerenone (Inspra), spironolactone (Aspirant), and triamterene (Dyrenium) and loop or thiazide diuretics such as **atenolol** (Tenormin), **furosemide** (Lasix), bendroflumethiazide (Aprinox), chlorthalidone (Thalitone) and **hydrochlorothiazide** (Microzide), among others. **Digoxin** (Cardigox, Digicor, Lanoxin, and other trade names), and blood thinners such as **warfarin** (Coumadin, Jantoven) may also interact with irbesartan. Before taking irbesartan, patients should inform their physician if they are taking any of these drugs so that the dosage can be determined appropriately.

Irbesartan cannot be taken by patients with diabetes who are also taking the antidiabetic drug aliskiren (Tekturna, Teklamo).

Certain drugs may increase or decrease the activity of irbesartan. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen (Motrin, Advil), **indomethacin** (Indocin), naproxen (Aleve, Anaprox, Naprosyn), oxaprozin (Daypro), and piroxicam (Feldene) and selective COX-2 inhibitors such as **celecoxib**

(Celebrex) may weaken the action of irbesartan. This may lead to symptoms such as headaches, dizziness, blurred vision, or deterioration of kidney function or acute kidney failure, especially in adults over age 65. Kidney function is usually monitored closely in patients taking irbesartan.

Food and other substances

Since dizziness is a frequent side effect of taking irbesartan, concomitant use of stimulants such as alcohol and tobacco is discouraged.

Resources

BOOKS

American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda, MD: ASHP, 2015.

Porter, Robert S., MD, and Justin L. Kaplan, MD, editors. "Cardiovascular Disorders; Section 15." In *The Merck Manual of Diagnosis and Therapy*. 19th ed., pp. 2015–2242. Whitehouse Station, NJ: Merck Research Laboratories, 2011.

WEBSITES

MedlinePlus. "Irbesartan." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a698009.html> (accessed March 6, 2015).

ORGANIZATIONS

American Society for Clinical Pharmacology and Therapeutics, 528 N Washington Street, Alexandria, VA 22314, (703) 836-6981, info@ascpt.org, <http://www.ascpt.org/>.

American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, MD 20814-3995, (301) 634-7060, <http://www.aspet.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

L. Lee Culvert

REVIEWED BY GREGORY A. PRATT, RPH

ISMO see **Isosorbide**

Isoptin SR see **Verapamil SR**

Isosorbide

Definition

Isosorbide mononitrate is a medication that helps angina. It is in a class of drugs called nitrates, which are also called vasodilators because they relax blood vessels.



Isosorbide mononitrate, 20 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

When too little blood flows to the heart muscle, it causes chest pain. The medical term for this condition is angina. The pain from angina is a symptom of coronary artery disease. Isosorbide relaxes, or widens, the blood vessels to allow improved blood flow and help prevent angina attacks. Isosorbide mononitrate is not intended for use during an angina attack.

Description

Isosorbide mononitrate comes in several forms, but most often it is prescribed as a tablet with extended-release, or long-lasting, action. Taking isosorbide by mouth regularly can help prevent an angina attack.

U.S. brand names

In the United States, isosorbide mononitrate is sold under the brand name Monoket. Previous brand names include Ismo and Imdur, but these have been discontinued. Generic forms of isosorbide mononitrate are available.

Canadian brand names

In Canada, isosorbide mononitrate is sold under the brand names Apo-ISMN and PMS-ISMN.

International brand names

Internationally, isosorbide mononitrate is sold under a variety of other brand names.

Recommended dosage

Adults taking isosorbide mononitrate to prevent angina usually begin with a 30-milligram (mg) tablet taken by mouth. If the medication is the extended-release form, it is taken once a day. Doctors may increase the dose after several days, once it is known how well the patient handles any adverse effects of isosorbide mononitrate and how well the lower dose prevents chest pain. Doctors may increase the dosage to 120 mg a day or, rarely, as high as 240 mg each day. The tablets come in 30 mg, 60 mg, and 120 mg strengths, so patients may have to split a 60 mg or 120 mg tablet. If this is done, they should swallow the cut tablet whole. If patients take isosorbide mononitrate in tablets that are not extended release, they should space the doses at least seven hours apart.

Precautions

Taking isosorbide mononitrate can cause severe hypotension, or low blood pressure.

Using nitrates such as isosorbide mononitrate can actually worsen some types of angina. Use of isosorbide mononitrate is intended for people who have angina caused by coronary artery disease.

Geriatric

Studies have not been extensive enough in older patients to show whether extra precautions are necessary. Doctors typically begin older patients on the lowest effective dose of isosorbide mononitrate until they are certain of the drug's effects.

Pregnant or breastfeeding

Isosorbide mononitrate is in the FDA pregnancy category C, which means that animal studies have shown possible harm to fetuses, but no clinical trials have been conducted with pregnant women. Women who are pregnant should take isosorbide mononitrate only if the possible benefits of using the drug clearly outweigh the potential risks.

Side effects

Isosorbide mononitrate can cause side effects, including:

- rash
- nausea
- headache and dizziness
- flushed or warm feeling

Some side effects of isosorbide mononitrate can be severe and should be reported to the doctor immediately. These include:

KEY TERMS

Angina—Chest pain caused by lack of blood flow to the heart muscle. The blood flow is usually limited by narrowing arteries caused by coronary artery disease.

Coronary artery disease—A condition in which the arteries that supply blood to the heart narrow and close. The narrowing is caused by plaque that builds up on the walls of the arteries because of too much cholesterol in the blood.

Nitrates—Drugs that dilate, or widen, blood vessels. Dilating vessels helps improve blood flow and blood pressure in the arteries.

- chest pain
- dry mouth
- blurred vision
- feeling faint or fainting

Interactions

Some drugs or substances can interact with each other, making one of the drugs work less effectively or worsening the side effects of a drug. It is important to tell a doctor about all drugs, herbal remedies, and vitamins and supplements being taken when isosorbide mononitrate is prescribed.

Drugs

Taking isosorbide mononitrate along with other nitrates or vasodilators increases the drugs' effects.

Individuals taking isosorbide mononitrate should not take drugs used to treat erectile dysfunction (e.g., **sildenafil**).

Food and other substances

Alcohol adds to the effects of isosorbide mononitrate, and drinking alcohol while taking the drug can make adverse effects of the medication much worse.

Resources

PERIODICALS

Jia, Yongliang, and Siu-Wai Leung. "Drug Efficacy in Treating Stable Angina Pectoris: A Protocol for Network Meta-Analysis of Randomized Controlled Trials." *British Medical Journal Open* 4 (June 19, 2014). <http://dx.doi.org/10.1136/bmjopen-2014-005453> (accessed February 16, 2015).

Munzel, Thomas, Andreas Daiber, and Tomaso Gori. "More Answers to the Still Unresolved Question of Nitrate Tolerance." *European Heart Journal* 34, no. 34 (2013): 2666–73.

OTHER

Merck. "Imdur." https://www.merck.com/product/usa/pi_circulars/i/imdur/imdur_pi.pdf (accessed February 16, 2015).

WEBSITES

MedlinePlus. "Isosorbide." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682348.html> (accessed February 16, 2015).

Physicians' Desk Reference. "Isosorbide Mononitrate." PDR Health. <http://www.pdrhealth.com/drugs/isosorbide-mononitrate> (accessed March 4, 2015).

U.S. Food and Drug Administration. "Monoket (Isosorbide Mononitrate) Tablets." <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm422928.htm> (accessed March 4, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.

National Heart, Lung, and Blood Institute (NHLBI), PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbiinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov/>.

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REVIEWED BY JAMES E. WAUN, MD, RPh

Isotretinoin

Definition

Isotretinoin (pronounced EYE-so-TRET-ih-noyn) is an oral medication for the treatment of severe nodular or cystic acne. Also known as 13-cis retinoic acid, it is classified as a retinoid, a member of a class of chemicals related to vitamin A.

The drug's mechanism of action is not completely understood, but it is thought to work by inducing apoptosis (programmed cell death) in the cells of the sebaceous glands. The sebaceous glands play an important role in the development of acne because they secrete sebum, a waxy substance that can accumulate and block the opening of the gland when the gland is overactive. These blocks or plugs can become infected by the bacterium *Propionibacterium acnes*, become inflamed, and produce the skin lesions characteristic of acne.



Amnesteem (isotretinoin). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Isotretinoin is used primarily as a treatment for severe acne that has not responded to such other medications as topical retinoids (adapalene or tretinoin), topical antibiotics (**clindamycin**, **erythromycin**), oral antibiotics (**doxycycline**, **minocycline**), or antiseptics containing benzoyl peroxide. Isotretinoin is not considered a first-line treatment because of its risks, and its availability in the United States has been severely restricted by the U.S. Food and Drug Administration (FDA) since 2006.

Off-label use

Isotretinoin has several off-label uses to treat the following conditions:

- Lesser degrees of acne severity; some dermatologists support this use of isotretinoin on the ground that many adolescents suffer severe psychological trauma resulting from acne.
- Hidradenitis suppurativa (HS), a chronic skin disorder characterized by sebaceous cysts, abscesses, and epidermoid cysts in areas supplied by apocrine sweat glands, such as the armpits, the inner thighs, and the areas under the breasts and buttocks.
- Rosacea, a chronic skin condition characterized by reddening of the skin and sometimes pimples or papules.

- Harlequin ichthyosis, the most severe form of congenital ichthyosis, in which the baby's skin forms massive, thick, diamond-shaped patches of keratin, like the scales of a fish. The child's features are poorly developed and may be completely absent. Isotretinoin is considered an orphan drug for the treatment of this condition.
- Keratoses (abnormal deposits of keratin on the skin surface) that develop in patients with xeroderma pigmentosum (XP), a rare skin disorder in which the skin lacks the ability to repair damage caused by the ultraviolet rays in sunlight.
- Neuroblastoma, a cancer of the nervous system found primarily in children. The high-risk form of the malignancy is the one most commonly treated with isotretinoin.
- Genital warts; isotretinoin has been used primarily experimentally to treat this condition, as there are other, more effective therapies available.

Description

Isotretinoin is taken by mouth in the form of 10, 20, 30, or 40 milligram (mg) capsules.

U.S. brand names

Isotretinoin is sold in the United States under the brand names Amnesteem (Mylan, Inc.), Roaccutane (Hoffman-LaRoche), Claravis (Teva Pharmaceuticals), Absorica (Ranbaxy), Isotroin (Cipla), Epuris (Cipher), Myorisan (VersaPharm), and Zenatane (Promius Pharma).

Absorica capsules are red in color and available only in the three larger dosages. Amnesteem capsules are also red and are available in 10 mg, 20 mg, and 40 mg dosages. Claravis is available in all four strengths; the 10 mg capsules are grey, the 20 mg are red, and the 30 mg and 40 mg capsules are orange. Myorisan is available as 20 mg, 20 mg, and 40 mg yellowish capsules. Zenatane is available as 10 mg teal-colored capsules, 20 mg red capsules, or 40 mg bright-green capsules.

Origins

Isotretinoin has a complex regulatory history. It was originally approved by the FDA in May 1982, with a new formulation approved in May 2012. Isotretinoin was distributed in the United States by the Swiss firm Hoffman-La Roche during the 1980s under the trade name Accutane. In the early 2000s, however, the company was sued by consumers who claimed that Accutane had caused inflammatory bowel disease. Roche removed Accutane from the U.S. market in 2009 and reintroduced it several years later under the trade name Roaccutane.

KEY TERMS

Apocrine sweat glands—Sweat glands found under the armpits, the breasts, the inner thighs, and a few other body areas that secrete an oily fluid that produces a characteristic body odor when degraded by bacteria.

Apoptosis—Programmed cell death.

Benign intracranial hypertension—A condition in which the pressure around the brain increases in the absence of a tumor or other diseases. It is characterized by headache, nausea and vomiting, ringing in the ears, and visual disturbances. It is also known as pseudotumor cerebri.

Boxed warning—A warning label required by the U.S. Food and Drug Administration (FDA) for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Ichthyoses (singular, ichthyosis)—A group of about 28 skin disorders, mostly genetic in origin, in which the person's skin forms heavy or thick flakes or patches of dry skin resembling the scales of a fish. The name of the group of disorders is derived from the Greek word for "fish."

Keratin—A structural protein that is the primary material making up the outer layer of human skin.

Nodular acne—Severe acne characterized by large papules (elevated areas of skin without visible fluid) that may be as much as 5–10 millimeters (0.2–0.4 inches) in size.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the FDA. It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Orphan drug—A medication that has been developed to treat a rare disease, defined in the United States as a disease or disorder affecting fewer than 200,000 people.

Sebaceous glands—Tiny structures in the skin that produce oil (sebum). If they become plugged, sebum collects inside and forms a nurturing place for germs to grow.

Teratogen—Any drug or other agent capable of interfering with the development of a fetus, causing birth defects or loss of the pregnancy. Isotretinoin is a known teratogen.

Isotretinoin is off-patent, and while Accutane is no longer sold in the United States, several generic brands of isotretinoin are available.

Recommended dosage

For severe nodular acne in adults: 0.5–1 mg per kilogram (kg, or 2.2 lb.) of body weight per day is taken by mouth, divided into two daily doses for 15–20 weeks. The dose may be increased to 2 mg/kg per day (as tolerated) if the acne is very severe with scarring or if it is present primarily on the trunk.

After a period of two months or longer has elapsed after treatment, the patient may undergo a second course of isotretinoin therapy if the acne recurs. If the number of acne nodules has decreased by more than 70% during the first course of therapy before the 15–20 weeks have elapsed, the patient may discontinue taking the drug.

Amnesteem, Claravis, and Myorisan should be taken with food, as a small meal significantly improves absorption of the drug. Absorica may be taken with or without food, as the patient prefers. Patients should be

instructed to swallow the capsules whole and to avoid breaking, crushing, or chewing them. They should also be warned never to share the drug with anyone else because of the drug's potential to cause birth defects.

Isotretinoin should be stored in a closed container away from heat, moisture, and direct light and kept away from children and pets. It should be kept at room temperature and not allowed to freeze. Unused or expired isotretinoin should be discarded.

Precautions

Women of childbearing age must have two pregnancy tests before taking isotretinoin to make sure they are not pregnant. They must also have a pregnancy test each month while taking the medication and a pregnancy test one month after treatment is completed. If they become pregnant while taking isotretinoin, they must go to a gynecologist for counseling and evaluation.

Patients taking isotretinoin should have their blood monitored regularly while they are taking the drug for lipid values, liver function, pregnancy, and other factors.

Women, persons with diabetes, and those with a history of liver disorders should have their blood monitored particularly carefully.

Patients taking isotretinoin should not use wax depilatories or undergo dermabrasion or laser cosmetic procedures while they are taking the drug and for a period of six months after treatment is stopped. The reason for this precaution is that isotretinoin makes the skin relatively fragile, increasing the risk of scarring from depilatories or other procedures that affect the upper layer of skin.

Pediatric

Isotretinoin is not recommended for use in children younger than 12 years.

Pregnant or breastfeeding

Isotretinoin is a pregnancy Category X drug (contraindicated during pregnancy because it is a known teratogen) and must carry a boxed warning. The FDA has instituted very strict limitations on the use of isotretinoin to ensure that women of childbearing age do not become pregnant. These restrictions were put in place in 2006 because about 2,000 women in the United States became pregnant while taking the drug between 1982 and 2003, and almost all their pregnancies ended in abortion or miscarriage. Because isotretinoin is chemically similar to vitamin A, which governs the normal development of the human embryo, it can affect development in harmful ways, causing such defects as impaired vision and hearing, missing ears or earlobes, facial malformation, and intellectual disability.

Patients being prescribed isotretinoin can obtain it only by registering with an FDA-mandated website called iPLEDGE. Dermatologists who prescribe the drug and pharmacists who dispense it must also be registered in the system. Women of childbearing age are required to commit to abstaining from sex or to using two forms of effective contraception simultaneously for the duration of isotretinoin therapy, as well as for a month immediately preceding and a month immediately following therapy. Women not of childbearing age and men are also required to register in the iPLEDGE system to prevent sharing of the drug with patients who may become pregnant. Prescriptions are filled for no more than 30 days at a time. In spite of the system's restrictions, about 150 women in the United States taking isotretinoin become pregnant each year because of noncompliance in using effective contraception.

Patients of either sex taking isotretinoin should not donate blood while they are taking the drug or for at least

one month after treatment is ended, to avoid the risk of the donated blood being given to a pregnant woman.

Other conditions and allergies

People with the following conditions must inform their doctor before taking isotretinoin:

- history of alcoholism
- history of eating disorders
- diabetes or other metabolic disorder
- osteoporosis
- history of hepatitis, pancreatitis, liver, or kidney disease
- history of psychosis or severe depression
- heart disease
- hearing or vision problems
- asthma

Side effects

Common side effects of isotretinoin include:

- dry skin, lips, and mouth
- increased levels of triglycerides in the blood
- itching or skin rash
- increased sensitivity to sun exposure; patients should use sunscreen and protective clothing to prevent sunburn
- muscle cramps
- headache
- lowered number of platelets in the blood

Less common side effects include:

- fatigue
- loss of appetite
- hair loss
- increased appetite
- thirst
- nausea and vomiting

Patients who experience any of the following side effects should notify their doctor at once:

- signs of a severe allergic reaction (hives; itching; sudden and unexplained swelling of the lips, mouth, or throat; difficulty breathing)
- sudden loss of night vision; patients should avoid driving at night if this side effect occurs
- aggressive behavior, suicidal ideation, or symptoms of psychosis (hallucinations, delusions, thought disorders)
- jaundice, dark-colored urine, pain in the upper abdomen, or other signs of a liver disorder

- severe upper abdominal pain accompanied by nausea and vomiting, which may indicate pancreatitis
- in diabetic patients, difficulty controlling blood sugar levels
- impaired hearing; in some cases, this side effect persists after discontinuation of therapy
- abdominal pain, severe diarrhea, or rectal bleeding; these symptoms may indicate inflammatory bowel disease (IBD)
- severe skin reactions

Interactions

Drugs

Isotretinoin interacts with the following drugs:

- **tetracycline** antibiotics (tetracycline, doxycycline, demeclocycline, minocycline, etc., increase the risk of benign intracranial hypertension)
- fluoroquinolone antibiotics (**levofloxacin**, ofloxacin, ciprofloxacin, norfloxacin, etc.)
- **methotrexate** and mipomersen (increase the toxicity of isotretinoin)
- teriflunomide and mifepristone (increase the level or effects of isotretinoin)
- corticosteroids (**triamcinolone**, **prednisone**, prednisolone, dexamethasone, hydrocortisone, etc.)
- progestin-only “mini” birth control pills (Errin, Jolivet, Ortho Micronor); these are an inadequate method of contraception while taking isotretinoin
- **phenytoin**

Herbs and supplements

Patients should not take vitamin A supplements or St. John’s wort while taking isotretinoin because of the risk of increasing the drug’s side effects.

Food and other substances

Patients taking isotretinoin should avoid consuming alcoholic beverages because alcohol increases the risk of elevated triglyceride levels.

Resources

BOOKS

Danby, F. William. *Acne: Causes and Practical Management*. Hoboken, NJ: John Wiley and Sons, 2015.

Zouboulis, Christos C., editor. *Pathogenesis and Treatment of Acne and Rosacea*. New York: Springer, 2014.

PERIODICALS

Collins, M. K., et al. “Compliance with Pregnancy Prevention Measures during Isotretinoin Therapy.” *Journal of the American Academy of Dermatology* 70, no. 1 (2014): 55–59.

Das, S., and R. V. Reynolds. “Recent Advances in Acne Pathogenesis: Implications for Therapy.” *American Journal of Clinical Dermatology* 15, no. 6 (2014): 479–88.

Lam, C., and A. L. Zaenglein. “Contraceptive Use in Acne.” *Clinics in Dermatology* 32, no. 4 (2014): 502–15.

Nickle, S. B., Peterson, N., and M. Peterson. “Updated Physician’s Guide to the Off-label Uses of Oral Isotretinoin.” *Journal of Clinical and Aesthetic Dermatology* 7, no. 4 (2014): 22–34.

Rashtak, S., et al. “Isotretinoin Exposure and Risk of Inflammatory Bowel Disease.” *JAMA Dermatology* 150, no. 12 (2014): 1322–26.

WEBSITES

iPLEDGE.com. <https://www.ipledgeprogram.com/> (accessed February 15, 2015).

“Isotretinoin.” Drugs.com. <http://www.drugs.com/mtm/isotretinoin.html> (accessed February 15, 2015).

Mayo Clinic staff. “Isotretinoin (Oral Route).” MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/isotretinoin-oral-route/description/drg-20068178> (accessed February 15, 2015).

Medscape. “Isotretinoin (Rx).” Reference.medscape.com. <http://reference.medscape.com/drug/amnesteem-claravis-isotretinoin-343544> (accessed February 15, 2015).

ORGANIZATIONS

American Academy of Dermatology (AAD), PO Box 4014, Schaumburg, IL 60168, (847) 240-1280/(866) 503-SKIN, (847) 240-1859 <http://www.aad.org/>.

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rebecca J. Frey, PhD

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Janumet see **Sitagliptin/metformin**

Januvia see **Sitagliptin**

K-Dur see **Potassium chloride**

Keflex see **Cephalexin**

Kenalog see **Triamcinolone**

Keppra see **Levetiracetam**

Ketoconazole

Definition

Ketoconazole is a topical and oral antifungal agent. It is an azole antifungal in the drug class of imidazoles.

Purpose

Topical ketoconazole creams and shampoos are used to treat:

- tinea corporis, a fungal (ringworm) skin infection that causes red, scaly rashes
- tinea cruris or “jock itch,” a fungal skin infection of the groin or buttocks
- tinea pedis or “athlete’s foot,” a fungal infection of the skin on the feet and between the toes
- tinea versicolor, a fungal skin infection that causes light-colored or brown spots on the chest, back, arms, legs, or neck
- onychomycosis, a fungal infection of the fingernail or toenail bed
- other dermatophytoses—parasitic fungi infections of the skin, nails, or hair
- seborrheic dermatitis—red, scaly, itchy skin on the face, scalp, or chest that may be caused, in part, by yeast that normally live on the skin

- cutaneous candidiasis or yeast infections of the skin
- in combination with other medications, skin conditions that are frequently worsened by fungal infections, such as diaper rash, eczema (an allergic reaction), impetigo (a bacterial infection), and psoriasis (an autoimmune disorder)

In 2013, the U.S. Food and Drug Administration (FDA) limited the use of oral ketoconazole, as well as adding labels warning of potentially severe liver injury, adrenal gland problems, and harmful drug interactions. Ketoconazole tablets are only indicated when other treatments are not tolerated or have failed for:

- blastomycosis—a potentially serious disease of the skin, lymph nodes, and lungs caused by yeast-like fungi of the genus *Blastomyces*
- coccidioidomycosis or valley fever—a rare disease caused by inhaling microscopic spores of the soil fungus *Coccidioides immitis* or cocci, which is on the increase in the southwestern United States
- histoplasmosis—a respiratory disease caused by the fungus *Histoplasma capsulatum*
- chromomycosis—a fungal skin disease caused by various pigmented fungi
- paracoccidioidomycosis—the South American form of blastomycosis, caused by the fungus *Paracoccidioides brasiliensis*

Oral ketoconazole is no longer indicated for candida or dermatophyte infections unless other drugs are not available or tolerated. Ketoconazole cannot treat fungal meningitis since it does not penetrate the cerebrospinal fluid.

Off-label use

High doses may be used for other non-FDA-approved purposes, including Cushing syndrome (a condition caused by excess corticosteroid hormone) and advanced prostate cancer.



Ketoconazole, 200 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

Ketoconazole is an imidazole derivative that slows the growth of fungal pathogens. Topical ketoconazole can be quite effective, with symptoms improving upon first application. For internal and systemic infections, the triazole antifungal oral medications, **fluconazole** and itraconazole, have higher affinity for fungal cell membranes and usually are more effective at lower doses with fewer adverse effects. However, some of the side effects of ketoconazole can be useful for treating other conditions. In humans, ketoconazole inhibits enzymes that convert cholesterol to steroid hormones such as cortisol and testosterone. Thus, ketoconazole can suppress glucocorticoid synthesis in patients with Cushing syndrome. At very high oral doses (400 milligrams [mg] three times daily), ketoconazole acts as an antiandrogen to block testosterone production in advanced androgen-dependent prostate cancer. It also acts as a weak androgen receptor antagonist, preventing testosterone and dihydrotestosterone from binding to their receptors.

U.S. brand names

In addition to various generic ketoconazole products, U.S. brand names include:

- Ketozole cream
- Nizoral cream
- Extina foam
- Xolegel

- Nizoral shampoo
- Nizoral AD shampoo
- Nizoral oral tablets

Canadian brand names

Canadian brand names include Nizoral, Apo-Ketoconazole, and Ketoderm.

International brand names

There are many international brand names for ketoconazole, including:

- Arcolane
- Cetoconazol
- Dezor
- Diazon
- Fungoral
- Ketozol
- Nizoral
- Oronazol

Origins

The FDA approved prescription Nizoral 2% topical shampoo in 1990. Generic 2% topical shampoos, creams, and aerosol foams and 200 mg oral tablets were approved in 1999. Ketozole 2% topical prescription cream was approved in 2002. Xolegel 2% topical prescription gel was approved in 2006. Extina 2% topical prescription aerosol foam was approved in 2007. Ketoconazole shampoo is available without a prescription for treating dandruff.

Topical ketoconazole is on the list of essential medicines of the World Health Organization (WHO), and 50 mg capsules are on WHO's list of essential medicines for children. However, the European Medicines Agency banned oral ketoconazole in 2013. It was previously banned in France and Australia.

Recommended dosage

The affected area and surrounding skin are covered with ketoconazole cream, usually once daily for two to six weeks. Prescription ketoconazole shampoo is generally used once (over-the-counter ketoconazole shampoo can be used every three to four days for up to eight weeks and as needed). The affected skin is wetted with a small amount of water, and the prescription shampoo is applied to the affected skin and a large surrounding area. It is lathered with the fingers, left on for five minutes, and then rinsed off with water.

KEY TERMS

Blastomycosis—Either of two infectious diseases (North American and South American) caused by yeast-like fungi of the genus *Blastomyces* or *Paracoccidioides*.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Candidiasis—Yeast infection caused by *Candida* spp.

Chromomycosis—A fungal skin disease usually caused by pigmented fungi in the genera *Phialophora*, *Cladosporium*, or *Fonsecaea*.

Coccidioidomycosis—Valley fever; disease caused by the fungus *Coccidioides immitis* or *cocci*.

Cushing syndrome—A condition caused by excess cortisol production.

Dermatophytoses—Diseases of the skin, hair, or nails caused by parasitic fungi.

Fluconazole—An antifungal agent similar to ketoconazole but more effective for systemic infections and less toxic.

Histoplasmosis—A respiratory disease with flu-like symptoms caused by the fungus *Histoplasma capsulatum*, endemic to the Mississippi and Ohio River valleys.

Itraconazole—An antifungal agent similar to ketoconazole but more effective for systemic infections and less toxic.

Meningitis—Inflammation of the meninges—membranes covering the brain and spinal cord—that can be caused by fungi.

Onychomycosis—A fungal disease of the fingernails or toenails.

Paracoccidioidomycosis—South American blastomycosis caused by the fungus *Paracoccidioides brasiliensis*.

Pathogens—Disease-causing organisms.

QT prolongation—A heart arrhythmia that can be caused by ketoconazole.

Ringworm—Any of several contagious fungal diseases of the skin, hair, or nails characterized by ring-shaped patches.

Seborrheic dermatitis—A red, scaly, itchy skin infection of the face, scalp, or chest.

Tinea corporis—A fungal infection (ringworm) of the skin.

Tinea cruris—“Jock itch”; a fungal infection of the groin and perineum.

Tinea pedis—“Athlete’s foot”; ringworm of the feet.

Tinea versicolor—A chronic skin infection caused by the fungus *Pityrosporum orbiculare*.

The usual adult dosage of oral ketoconazole for blastomycosis, chromomycosis, coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis is 200 mg once daily for six months. The dosage may be increased to 400 mg. Ketoconazole tablets should be taken with a meal and an acidic drink such as non-diet cola.

Pediatric

The usual oral dosages in children two years and older—when other antifungal therapy is not available or tolerated and benefits outweigh risks—is 3.3–6.6 mg per kilogram (kg, or 2.2 lb.) of body weight once daily for six months.

Precautions

Use of ketoconazole cream should continue even after symptoms improve to completely cure the infection. Ketoconazole shampoo may remove the curl from “permed” hair.

Oral ketoconazole comes with a boxed warning:

- It should only be used when other medications are unavailable or not tolerated.
- It may cause liver damage requiring a liver transplant or leading to death, even in patients without liver disease or risk factors for liver damage.
- Alcohol should be avoided during treatment because it can increase the risk of liver damage.
- Patients should tell their doctors if they drink or have ever drunk large amounts of alcohol or have ever had liver disease.
- The doctor should be called immediately if any of the following symptoms occur: extreme tiredness, loss of appetite, weight loss, nausea, vomiting, yellowing of the skin or eyes, dark yellow urine, pale stools, pain in the upper-right stomach, fever, or rash.
- Ketoconazole can cause an irregular heart rhythm called QT prolongation that can lead to fainting, seizures,

unconsciousness, or sudden death. The doctor should be called immediately if any of the following symptoms occur: fast, pounding, or irregular heartbeat; dizziness, light-headedness, or fainting; loss of consciousness.

- Patients must not take disopyramide, dofetilide, dronedarone, pimozide, quinidine, cisapride, **methadone**, or ranolazine while taking ketoconazole.
- Tests are required to check responses to ketoconazole.
- Patients should discuss the risks of ketoconazole with their doctor.

Patients should tell their doctors, laboratory personnel, and dentists that they are taking ketoconazole before having any laboratory tests or surgery. Ketoconazole should be continued until the doctor orders it stopped, since stopping too soon may cause the infection to quickly return. Ketoconazole may decrease sperm production, especially at high doses.

Pregnant or breastfeeding

Ketoconazole is in FDA pregnancy category C—animal studies indicate adverse effects on a fetus from oral ketoconazole. It should only be used during pregnancy if potential benefits outweigh potential risks to the fetus. Topical ketoconazole should be used with caution during breastfeeding. Oral ketoconazole is excreted in human milk, and its use is not recommended while breastfeeding.

Other conditions and allergies

Patients should tell their doctor and pharmacist if they are allergic to ketoconazole, any ingredients in ketoconazole tablets, or any other medications, creams, or shampoos. If using ketoconazole cream, patients should tell their doctor if they are allergic to sulfites or have ever had asthma. Patients should tell their doctor if they have ever had any medical condition, especially liver disease or adrenal insufficiency in which the adrenal glands do not make sufficient steroid hormones. Patients with acute or chronic liver disease should not take oral ketoconazole.

Oral ketoconazole absorption is decreased in patients with reduced stomach acidity from disease or medication.

Side effects

Patients should consult their doctors if any of the following side effects of topical ketoconazole are severe or persistent:

- irritation, itching, or stinging
- dry skin
- oily or dry hair or scalp

- changes in hair texture
- scalp blisters

The doctor should be contacted immediately if any of the following uncommon side effects occur with topical ketoconazole:

- redness, tenderness, swelling, pain, or warmth
- rash
- hives
- difficulty breathing or swallowing

The doctor should be contacted if any of the following symptoms of oral ketoconazole are severe or persistent:

- headache
- stomach pain
- diarrhea
- constipation
- heartburn
- gas
- changes in food tastes
- dry mouth
- change in tongue color
- difficulty falling or staying asleep
- nervousness
- numbness, burning, or tingling of the hands or feet
- muscle pain
- hair loss
- flushing
- chills
- light sensitivity
- nosebleeds
- breast enlargement in males
- decrease in sexual ability

The following uncommon but serious side effects of oral ketoconazole require immediately contacting the doctor or obtaining emergency medical treatment:

- symptoms listed in the boxed warning
- rash
- hives
- itching
- swelling of the eyes, face, lips, tongue, hands, feet, ankles, or lower legs
- hoarseness
- difficulty breathing or swallowing
- tiredness or weakness

Interactions

The doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

In addition to the medications listed in the boxed warning, oral ketoconazole should not be taken by patients taking:

- **alprazolam**
- eplerenone
- ergot alkaloids such as ergotamine, dihydroergotamine, or methylergonovine
- felodipine
- irinotecan
- **lovastatin**
- lurasidone
- midazolam
- nisoldipine
- **simvastatin**
- tolvaptan
- **triazolam**

Many medications can interact with ketoconazole. The following drugs may require changing dosages and/or carefully monitoring for side effects:

- aliskiren
- anticoagulants such as dabigatran, **rivaroxaban**, and **warfarin**
- aprepitant
- **aripiprazole**
- **atorvastatin**
- bosentan
- **budesonide**
- **buspirone**
- **carbamazepine**
- calcium channel blockers such as **amlodipine**, **diltiazem**, nicardipine, **nifedipine**, and verapamil
- cancer medications such as bortezomib, busulfan, dasatinib, docetaxel, erlotinib, ixabepilone, lapatinib, nilotinib, paclitaxel, trimetrexate, vincristine, vinblastine, and vinorelbine
- ciclesonide
- cilostazol
- cinacalcet

- **colchicine**
- dexamethasone
- **digoxin**
- eletriptan
- **fentanyl**
- fesoterodine
- **fluticasone**
- **haloperidol**
- HIV medications such as darunavir, efavirenz, fosamprenavir, indinavir, maraviroc, nevirapine, ritonavir, and saquinavir
- immunosuppressants such as **cyclosporine**, everolimus, sirolimus, and **tacrolimus**
- **imatinib**
- erectile dysfunction medications such as **sildenafil**, **tadalafil**, and **vardeafil**
- indigestion, heartburn, or ulcer medications such as cimetidine, **famotidine**, **lansoprazole**, nizatidine, **omeprazole**, and **ranitidine**
- **methylprednisolone**
- nadolol
- **oxycodone**
- **phenytoin**
- praziquantel
- **quetiapine**
- **ramelteon**
- repaglinide
- **risperidone**
- **salmeterol**
- saxagliptin
- **solifenacin**
- **tamsulosin**
- telithromycin
- **tolterodine**
- tuberculosis medications such as isoniazid, rifabutin, and **rifampin**

Antacids containing aluminum, calcium, or magnesium or other acid-secretion suppressors or acid neutralizers should be taken at least one hour before or two hours after taking ketoconazole.

Food and other substances

Alcohol, including beer, wine, or alcohol-containing medications such as cough syrup, increase the risk of liver damage from ketoconazole and can cause side effects such as flushing, rash, nausea, headache, and swelling of the hands, feet, ankles, or lower legs.

Resources

PERIODICALS

Gupta, A. K., D. Daigle, and K. A. Foley. "Drug Safety Assessment of Oral Formulations of Ketoconazole." *Expert Opinion on Drug Safety* 14, no. 2 (2015): 325–34.

WEBSITES

"Ketoconazole Dosage." Drugs.com. <http://www.drugs.com/dosage/ketoconazole.html> (accessed February 14, 2015).

MedlinePlus. "Ketoconazole." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682816.html> (accessed February 14, 2015).

U.S. Food and Drug Administration. "FDA Drug Safety Podcast: FDA Limits Usage of Nizoral (Ketoconazole) Oral Tablets Due to Potentially Fatal Liver Injury and Risk of Drug Interactions and Adrenal Gland Problems." <http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm362820.htm> (accessed February 14, 2015).

U.S. Food and Drug Administration. "Nizoral (Ketoconazole) Tablets." <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm364157.htm> (accessed February 14, 2015).

ORGANIZATIONS

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

World Health Organization, Avenue Appia 20, Geneva 27, Switzerland 1211, +41 22 791 21 11, Fax: +41 22 791 31 11, info@who.int, <http://www.who.int/en>.

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Ketoprofen

Definition

Ketoprofen is a nonprescription painkiller (analgesic) that belongs to the family of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs).

Purpose

Ketoprofen is used to treat mild to moderately severe pain. It is particularly effective against osteoarthritis, rheumatoid arthritis, and menstrual pain.

Off-label uses

Ketoprofen has been used as a preventive drug against the onset of migraine headaches in susceptible individuals.



Ketoprofen. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

Adult-strength ketoprofen is available in capsule form in strengths of 50 and 75 milligrams (mg). An extended-release capsule form is also available in a 200 mg strength.

Children's-strength ketoprofen is available in scored, chewable tablets containing 100 mg of active drug. A liquid formulation is available in 50 mg per 1.25 milliliters (mL) for infants and 100 mg/5 mL for children.

U.S. brand names

Ketoprofen was initially sold in the United States under many brand names, including Orudis, Oruvail, Actron, and Orudis KT. It is currently only available as a generic.

Canadian brand names

In Canada, ketoprofen is sold only as a generic.

International brand names

Ketoprofen is sold under several hundred brand names internationally, including Advel (Germany), Altofen (Indonesia), Begsan (Estonia), Dolagis (Sweden), Epatec (Japan), Findol (Italy), Lolita (Thailand), and PowerGel (United Kingdom). In some countries, ketoprofen is only one component of the medication, and there are other medications included in

KEY TERMS

Analgesic—A drug used to control pain.

Ankylosing spondylitis—A type of arthritis in the spine that leads to the stiffening and fusion of the vertebral (spinal) bones.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Gout—A condition in which the deposition of uric acid crystals in the joints causes swelling and pain.

Migraine headache—A condition that causes episodes of severe headache, usually with light and sound sensitivity, visual changes, and nausea/vomiting.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Osteoarthritis—A type of arthritis marked by chronic degeneration of the cartilage of the joints, leading to pain and sometimes loss of function.

Pericarditis—Inflammation of the sac around the heart.

Rheumatoid arthritis—A joint disease of unknown origins that may begin at an early age, causing deformity and loss of function in the joints.

the formulation. In some locations, it is only available for veterinary, not human, use.

Recommended dosage

For the oral administration of ketoprofen in adults, recommended dosages are as follows:

- inflammatory diseases: 400–800 mg per dose, three to four times a day (maximum dose per 24 hours is 3.2 grams [g])
- general pain, fever, menstrual pain: 200–400 mg per dose every 4–6 hours (maximum dose per 24 hours is 1.2 g, unless supervised by a physician, who may prescribe a maximum daily dose of 2.4 g)

- migraine headache: 400 mg immediately at start of symptoms (maximum dose per 24 hours is 400 mg, unless otherwise directed by a physician)
- pericarditis: 400–800 mg per dose, three to four times a day (maximum dose per 24 hours is 3.2 grams)

Pediatric

For the oral administration of ketoprofen in pediatric patients, doses are determined based on weight. Recommended dosages are as follows.

For a fever in patients ages 6 months to 12 years:

- temperature less than 102.5°F (39°C): 5 mg per kilogram (kg, or 2.2 lb.) of body weight every 6–8 hours (maximum dose per 24 hours is 40 mg/kg)
- temperature greater than 102.5°F (39°C): 10 mg/kg every 6–8 hours (maximum dose per 24 hours is 40 mg/kg)

For juvenile idiopathic arthritis, the dose is 30–50 mg/kg divided into three doses, given every 8 hours, for a maximum of 2.4 g/day.

For pain relief, the dose is 4–10 mg/kg given every 6–8 hours.

Precautions

Ketoprofen carries a boxed warning that states:

- Individuals should be aware of an increased risk of life-threatening heart attack or stroke with the use of ketoprofen. Risk elevates over time and in the setting of other cardiovascular risk factors or conditions.
- Individuals should be aware of an increased risk of life-threatening gastrointestinal irritation, inflammation, ulceration, bleeding, or perforation. People with a history of these problems; the elderly; smokers; heavy alcohol drinkers; or those using **aspirin**, blood thinners, or steroid medications should use particular caution or take an alternate drug.
- Ketoprofen should not be given to patients who have had a recent coronary artery bypass graft (CABG) due to a greatly increased risk of heart attack or stroke.

Ketoprofen can cause vision problems, including blurring, decreased vision, blind spots, and problems discerning color. If these symptoms occur, patients should stop ketoprofen use and go to an eye doctor (ophthalmologist).

Ketoprofen increases bleeding time. Patients with clotting disorders or who are taking other medications, such as blood thinners or aspirin, should use particular caution and have regular monitoring for the development of anemia. Individuals who are scheduled to have dental

or surgical procedures should avoid the use of ketoprofen in the week prior to the procedure.

Ketoprofen can cause an increased blood level of potassium, especially in older people, individuals with kidney disease or diabetes, and individuals taking other drugs that can increase potassium.

Ketoprofen can cause skin reactions, including rashes, welts, hives, blisters, and separation/peeling of the skin layers. If this occurs, ketoprofen use should be immediately stopped.

Geriatric

The elderly are at particular risk of complications from ketoprofen use, especially bleeding, heart attack, and stroke. Ketoprofen should be used with extreme caution and close monitoring in this population.

Pregnant or breastfeeding

Ketoprofen is a pregnancy category C drug up to 30 weeks' gestation and a pregnancy category D drug after 30 weeks' gestation. Category C means that risk cannot be ruled out in pregnant individuals. If possible, use of this drug should be avoided. Category D means that studies have shown risk to the developing fetus. Ketoprofen should not be used by women in the last trimester of pregnancy.

Whether ketoprofen passes into breast milk is not known. It should be avoided by breastfeeding women.

Other conditions and allergies

Ketoprofen may exacerbate certain conditions and should be avoided in individuals with:

- systemic lupus erythematosus (may increase the risk of a form of noninfectious meningitis)
- asthma (may cause severe bronchospasm and wheezing)
- recent coronary artery bypass graft (CABG) surgery
- liver disorders (may cause hepatitis/liver failure)
- high blood pressure (may prompt the onset of high blood pressure or worsen preexisting high blood pressure)
- kidney impairment (may worsen preexisting kidney problems or prompt the onset of kidney problems in the elderly or individuals who are dehydrated, have heart or liver failure, or are taking diuretic medications or ACE inhibitors)

Ketoprofen should not be taken by individuals who are hypersensitive to ketoprofen or NSAIDs, or who have bronchial asthma, aspirin intolerance, and rhinitis.

Individuals who have experienced bronchospasm, asthma, rhinitis, or hives while taking aspirin or other NSAIDs should not take ketoprofen.

Side effects

The most common side effects of ketoprofen treatment include:

- upset stomach, nausea, or vomiting
- abdominal pain
- sensation of indigestion
- gas, flatulence
- constipation or diarrhea
- nervous feelings
- ringing in the ears
- itching, rash, or hives
- headache, dizziness, or drowsiness
- seizures
- blood test evidence of bone marrow suppression, including low white blood count, low platelets, or low hematocrit
- blood test evidence of liver damage
- blood test evidence of kidney damage
- blood in the urine
- yellow cast to the skin and/or the whites of the eyes

Rare but serious signs of a significant allergic reaction to ketoprofen should prompt the individual to seek immediate medical care. These include:

- difficulty breathing or swallowing
- hoarse voice
- wheezing, shortness of breath, or cough
- fever
- pain in the abdomen
- blue skin or lips
- yellow cast to the skin and/or the whites of the eyes
- headache
- stiff neck
- confusion
- seizures
- swollen face, lips, tongue, or throat
- rash, hives, blisters, or peeling skin
- dizziness

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Ketoprofen may increase the potential toxic effects of the following drugs:

- 5-ASA derivatives
- antiplatelet drugs
- aminoglycoside antibiotics
- anticoagulants
- bisphosphonate derivatives
- collagenase
- **cyclosporine**
- desmopressin
- **digoxin**
- **haloperidol**
- lithium
- **methotrexate**
- salicylates
- **tacrolimus**
- tenofovir
- vancomycin

The risk of potential adverse effects from ketoprofen may be increased if used at the same time as the following drugs:

- ACE inhibitors
- angiotensin II receptor blockers
- tricyclic antidepressants
- corticosteroids
- dexketoprofen
- **diclofenac**
- floctafenine
- **ketorolac**
- probenecid
- selective serotonin reuptake inhibitors (SSRIs)
- serotonin/norepinephrine reuptake inhibitors (SNRIs)
- treprostinil

The use of ketoprofen may hamper the effectiveness of the following drugs:

- aliskiren
- beta blockers
- eplerenone
- hydralazine
- loop diuretics
- potassium-sparing diuretics
- thiazide diuretics

Bile acid sequestrants may hamper the effectiveness of ketoprofen.

Food and other substances

Gastrointestinal risks may be decreased when taken with food.

Resources

BOOKS

- Aronson, J. K. *Meyler's Side Effects of Analgesics and Anti-inflammatory Drugs*. Oxford: Elsevier, 2010.
- Benzon, Honorio T. *Essentials of Pain Medicine*. 3rd ed. Philadelphia: Saunders, 2011.
- Smith, Howard S. *Current Therapy in Pain*. Philadelphia: Saunders, 2009.
- Waldman, Steven D. *Pain Management*. 2nd ed. Philadelphia: Saunders, 2011.

WEBSITES

- "Ketoprofen." Drugs.com. <http://www.drugs.com/mtm/ketoprofen.html> (accessed March 3, 2015).
- MedlinePlus. "Ketoprofen." <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a686014.html> (accessed March 3, 2015).
- U.S. National Library of Medicine. "LactMed: Ketoprofen." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+624> (accessed March 3, 2015).

ORGANIZATIONS

- American Chronic Pain Association, PO Box 850, Rocklin, CA 95677, (800) 533-3231, APAC@theacpa.org, <http://www.theacpa.org/>.
- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- National Pain Foundation, 14828 W 6 Avenue, Suite 16-B, Room 1, Golden, CO 80401-5000, (720) 541-6808, Fax: (720) 541-6809, <http://www.thenationalpainfoundation.org/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Ketorolac

Definition

Ketorolac is a medicine that is used to relieve moderately severe pain for a short time. It is a type of nonsteroidal anti-inflammatory drug (NSAID) that is available only by prescription.



Ketorolac tromethamine. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Some pain is more severe than over-the-counter pain medications can address. For example, the pain a person has right after surgery or an injury is worse than the pain once healing has begun, which can often be controlled with over-the-counter NSAIDs such as **ibuprofen** or acetaminophen. Ketorolac works by stopping production of substances in the body that lead to inflammation (or swelling), pain, and fever. As a result, the medication can help relieve pain after surgery on joints, the eyes, and other areas of the body, and it is used by athletes to relieve pain from injuries or by some people with allergies or severe pain from other causes.

Description

Ketorolac comes in several forms, including a tablet taken by mouth, a nasal spray, as eyedrops, and as a liquid solution that can be injected into a muscle or vein. All forms of ketorolac are intended for short-term use, usually for five days or less. The medication is not intended for long-term, chronic pain control or regular use.

U.S. brand names

In the United States, the tablet brand of ketorolac known as Toradol is no longer available. Ketorolac oral tablets and injections are available in generic forms. Ketorolac eyedrops are sold as the brand names Acular

and Acuvail. The nasal spray is sold as the brand name Sprix.

Recommended dosage

Dosage of ketorolac depends on the type of solution being used and the age of the patient.

For pain in adults younger than age 65, the recommended dosage of ketorolac is one of the following:

- One 10 milligram (mg) tablet by mouth up to four times a day as needed (no more than 40 mg a day).
- A single dose of 60 mg by intramuscular injection. Adults who weigh less than 50 kg (about 110 pounds) should only receive a single 30 mg dose.
- A single intravenous dose of 30 mg, or 15 mg in one dose for those who weigh less than 50 kg (about 110 pounds).
- One 15.75 mg dose of nasal spray into each nostril every six to eight hours, not to exceed 126 mg a day.

Pediatric

Children prescribed ketorolac are usually recommended one of the following dosages:

- A single dose by intramuscular injection of 1 mg of ketorolac per kilogram (kg, or 2.2 lb.) of the child's weight, or 0.5 mg per kg of weight by intravenous injection. The intramuscular injection should not exceed 30 mg, and the intravenous injection should not exceed 15 mg.
- Multiple doses of 0.5 mg per kg of body weight given by intramuscular or intravenous injection every six hours as needed for no more than five days.

Children older than 16 years old and 50 kg (about 110 pounds) in weight can usually have adult dosages.

Geriatric

For pain in adults older than age 65, doctors recommend one of the following dosages of ketorolac:

- One 10 mg tablet by mouth up to four times a day as needed (no more than 40 mg a day), but only as continued therapy after an injection, not as an initial dose.
- A single dose of 30 mg by intramuscular injection.
- A single intravenous dose of 15 mg.
- One 15.75 mg dose of nasal spray into only one nostril every six to eight hours, not to exceed 63 mg a day.

Precautions

In 2007, the U.S. Food and Drug Administration (FDA) issued a boxed warning for oral ketorolac:

- The drug should be used only for severe pain and for no more than five days.
- There is a risk of developing gastrointestinal (GI) problems such as bleeding and peptic ulcers.
- Use of oral ketorolac may carry the risk of problems such as heart attack and stroke leading to death, with increased risk the longer the medicine is used.
- Ketorolac should not be used in people who are at high risk for cardiovascular disease or who are about to have coronary artery bypass graft surgery.
- There are warnings against using oral ketorolac in people who have advanced kidney disease or who are at risk for kidney failure.
- There is a risk of bleeding in certain patients, and warnings against the drug's use before surgery.

In addition, some people have allergic reactions to ketorolac. Anyone who is preparing to undergo surgery, dental surgery, or childbirth should inform their doctor that they are taking ketorolac.

Pediatric

The oral tablet is not intended for use in children.

Geriatric

Older people who take ketorolac by mouth are at higher risk for serious GI problems from the medicine.

Pregnant or breastfeeding

Ketorolac should not be used by women undergoing labor and delivery. The drug should not be taken by women who are breastfeeding their infants. The eyedrops should be used with caution in women who are pregnant or nursing.

Other conditions and allergies

People who have current ulcers or a history of peptic ulcers should avoid oral ketorolac. The drug also is not recommended for anyone with kidney disease or problems with kidney function. Other people should use caution when taking the drug, including anyone with a history of heart and blood vessel disease or bleeding disorders.

Side effects

Ketorolac can cause side effects, including:

- dizziness and drowsiness

KEY TERMS

Intramuscular—Into the muscle, as when a drug is injected by needle into a person's muscle.

Intravenous—Into a vein, as when a drug is injected by needle into a person's vein.

Nonsteroidal anti-inflammatory drug—A type of medicine (also known as NSAID) that controls pain and inflammation. Many, such as ibuprofen and acetaminophen, are sold without a prescription, and others are prescribed by doctors.

- headache
- constipation and gas
- diarrhea
- sores in the mouth
- headache

Some side effects can be severe, and should be reported to a doctor immediately. These include any effects reported in the boxed warning and the following:

- nausea
- fever
- extreme fatigue and low energy
- yellow skin or eyes
- flulike symptoms
- pain in the upper right portion of the stomach
- rapid heartbeat
- changes in the appearance of urine or problems and pain when urinating
- back pain

In addition to the side effects of ketorolac use, having ketorolac injected can also cause:

- ringing in the ears
- pain at the injection site
- small dots on the skin that are red or purple
- pale skin

In addition to the side effects of ketorolac, use of the nasal spray can cause:

- pain or irritation in the nose
- increased tears
- throat irritation
- problems swallowing or breathing
- hoarseness
- itching or hives

Use of ketorolac eyedrops can cause the following side effects:

- stinging or burning in the eyes
- blurred vision
- infection around the eye, which should be reported to the doctor
- signs of an allergic reaction, such as red or swollen eyes, lips, or tongue, and a skin rash, along with problems breathing or swallowing.

Signs of an allergic reaction or any other worrying side effects should be reported to the treating physician.

Geriatric

Side effects of ketorolac can be increased in the elderly. The dose may be reduced to minimize effects.

Interactions

Anyone taking ketorolac should provide their doctor with a complete medical history and a list of all medications, herbal remedies and supplements being taken.

Drugs

Ketorolac can interact with several drugs. Some of the interactions are listed, but it is important to inform the doctor and pharmacist of all medications being taken before using ketorolac.

- Taking **aspirin** along with ketorolac increases the side effects of ketorolac.
- Ketorolac can affect kidney function and how well diuretics (water pills) work.
- Use of ketorolac eyedrops along with topical corticosteroids can increase the risk of delayed healing.
- Taking ketorolac along with probenecid (Probalan) for gout is not recommended.
- Patients who take the anticoagulant **warfarin** (Coumadin) and ketorolac have a higher risk of GI bleeding.
- Using ketorolac and selective serotonin reuptake inhibitors (SSRIs) for depression increases the risk of GI bleeding.

Food and other substances

Drinking alcohol while taking ketorolac can increase side effects such as dizziness and drowsiness.

Resources

PERIODICALS

“Ketorolac for Pain Management: A Review of the Clinical Evidence.” *Canadian Agency for Drugs and Technologies in Health Rapid Response Service* (2014): 1–15.

Sawyer, George A., et al. “Intramuscular Ketorolac Injections in the Athlete.” *Sports Health* 4, no. 4 (2012): 319–27.

Resources

WEBSITES

Allergan, Inc. “Acular LS.” Allergan.com. http://www.allergan.com/products/eye_care/acular.htm (accessed February 14, 2015).

Drugs.com. “Ketorolac.” Drugs.com. <http://www.drugs.com/cdi/ketorolac.html> (accessed February 14, 2015).

MedlinePlus. “Ketorolac.” National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a693001.html> (accessed February 14, 2015).

MedlinePlus. “Ketorolac Injection.” National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a614011.html> (accessed February 14, 2015).

MedlinePlus. “Ketorolac Nasal.” National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a611042.html> (accessed February 14, 2015).

MedlinePlus. “Ketorolac Ophthalmic.” National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601241.html> (accessed February 14, 2015).

ORGANIZATIONS

American Academy of Pain Medicine, 8735 West Higgins Road, Suite 300, Chicago, IL 60631-2738, (847) 375-4731, Fax: (847) 375-6477, info@painmed.org, <http://www.painmed.org/patientcenter/>.

American College of Sports Medicine, 401 West Michigan Street, Indianapolis, IN 46202-3233, (317) 637-9200, Fax: (317) 634-7817, <http://www.acsm.org/>.

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Klonopin see **Clonazepam**

Klor-Con see **Potassium chloride**



Lamictal see **Lamotrigine**

Lamisil see **Terbinafine**

Lamivudine/zidovudine

Definition

Lamivudine/zidovudine is a combination oral medication consisting of two antiretroviral drugs in a single pill for treating the human immunodeficiency virus type 1 (HIV-1), which causes acquired immune deficiency syndrome (AIDS). Lamivudine and zidovudine are both drugs in the class known as nucleoside reverse transcriptase inhibitors (NRTIs). Lamivudine/zidovudine is referred to as a fixed-dose combination antiviral medication.

Purpose

Lamivudine/zidovudine is approved by the U.S. Food and Drug Administration (FDA) for use, in combination with other antiretroviral agents, in treating HIV-1 infection in adults and children weighing more than 30 kg (66 lb.). It does not cure HIV infection, but it may reduce the risk of developing AIDS and HIV-related illnesses, including other serious infections and cancer. Along with safe sexual practices, lamivudine/zidovudine may reduce the risk of transmitting HIV to uninfected partners. Lamivudine/zidovudine is also used to help prevent HIV infection following exposure to HIV-positive blood.

Description

Lamivudine (3TC) and zidovudine (azidothymidine, AZT, or ZDV) are synthetic analogs of nucleosides—normal components of RNA and DNA genetic material—that inhibit the HIV enzyme called reverse transcriptase. Reverse transcriptase copies HIV RNA into DNA, which

is a necessary step for producing more viruses. When reverse transcriptase incorporates these drugs, the enzyme is inhibited, and the growing DNA chain terminates. This prevents HIV from multiplying and can reduce the amount of the virus in the body (the “viral load”). Lamivudine and zidovudine are believed to act synergistically, which means that they are more effective together than either drug is alone. They can also delay the emergence of HIV genetic mutations that confer resistance to antiretroviral drugs.

Each lamivudine/zidovudine oral tablet contains 150 milligrams (mg) of lamivudine and 300 mg of zidovudine. The modified capsule-shaped tablets are film-coated and white. They are labeled so that when broken in half, each half shows the code “GX” on one side and “FC3” on the other.

U.S. brand names

Combivir is the U.S. brand name for lamivudine/zidovudine. The U.S. brand name of lamivudine is Epivir and of zidovudine is Retrovir. Lamivudine/zidovudine may also be referred to as 3TC and ZDV, 3TC and AZT, or 3TC and azidothymidine.

Canadian brand names

Canadian brand names are Combivir and Teva-Lamivudine/Zidovudine.

International brand names

Combivir is the most common international brand name for lamivudine/zidovudine. Other brand names include:

- Biovir
- Cipladuovir
- Duovir
- Duovir-D
- Ganvirel Duo
- Lamuzid



Combivir (lamivudine/zidovudine, 150 mg/300 mg).
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- Viradul
- Zidomax
- Zovilam

Origins

Lamivudine/zidovudine was approved by the FDA in 1997 as the first combination pill for treating HIV. It followed the 1996 introduction of triple-drug highly active antiretroviral therapy (HAART). The introduction of HAART marked the first effective treatment for reducing illness and death from HIV/AIDS. Early HAART involved complicated regimens that required taking many pills at different times each day, with significant long-term side effects. Lamivudine/zidovudine, taken twice a day, was developed to simplify dosing, improve treatment compliance, and reduce side effects. It soon was followed by Truvada (tenofovir DF/emtricitabine), taken once daily along with a third or fourth drug. Subsequently, zidovudine/lamivudine/abacavir (Trizivir) was introduced as the first single-tablet, twice-daily HIV drug. As of 2015, the most commonly used drugs for initial treatment of HIV infection are once-daily, three- or four-drug combination pills.

Recommended dosage

The recommended adult dosage of lamivudine/zidovudine is one tablet twice daily, with or without food. It is always taken in combination with other HIV

medications. A missed dose should be taken as soon as possible unless it is almost time for the next dose, in which case the missed dose should be skipped and the regular schedule resumed. Lamivudine/zidovudine is stored tightly closed in the container it came in, at 36°F–86°F (2°C–30°C), away from excessive heat and moisture.

Pediatric

The recommended dosage for pediatric patients weighing at least 30 kg (66 lb.) is one tablet twice daily. Children who cannot reliably swallow tablets should be prescribed lamivudine oral solution and zidovudine syrup separately.

Geriatric

Elderly patients may need lower dosages due to the possibility of decreased liver, kidney, or heart function; other diseases or conditions; or other medications. For these reasons, lamivudine/zidovudine may not be appropriate for geriatric patients.

Pregnant or breastfeeding

No dose adjustments are necessary during pregnancy.

Other conditions and allergies

Because lamivudine/zidovudine is a fixed-dose combination tablet, the dosage cannot be adjusted. Therefore, it is not used in patients with reduced kidney function, mild to moderate impaired liver function or cirrhosis, or other dose-limiting conditions. Patients who require adjusted dosages are prescribed separate liquid or solid lamivudine and zidovudine.

Precautions

Lamivudine/zidovudine comes with a boxed warning:

- Zidovudine may cause blood toxicities, including low red blood cell and white blood cell production (anemia and neutropenia, respectively), especially in patients with advanced HIV-1 disease. Frequent blood counts are recommended.
- With prolonged use, zidovudine may cause muscle disorders.
- Lamivudine and zidovudine, alone or in combination with other antiretrovirals, may cause life-threatening liver damage and lactic acidosis (buildup of lactic acid in the blood). Zidovudine is a particular risk for lactic acidosis. Early signs are loss of appetite, stomach pain, nausea, and vomiting. Life-threatening signs include

KEY TERMS

Acquired immune deficiency syndrome (AIDS)—A disease caused by infection with the human immunodeficiency virus (HIV). In people with this disease, the immune system breaks down, increasing vulnerability to other infections and some types of cancer.

Anemia—A deficiency in red blood cells, in the hemoglobin component of red blood cells, or in total blood volume.

Antiretroviral agents—Drugs that prevent, limit, or treat infections with retroviruses such as HIV.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Hepatitis B virus (HBV)—A virus that attacks the liver.

Hepatitis C virus (HCV)—A single-stranded RNA virus that causes liver disease.

Highly active antiretroviral therapy (HAART)—An individualized combination or drug cocktail of three or more antiretroviral drugs for treating HIV/AIDS.

Human immunodeficiency virus (HIV)—The virus that causes acquired immune deficiency syndrome (AIDS).

Immune reconstitution inflammatory syndrome (IRIS)—The reactivation of infections or development of new diseases that may occur as the immune system improves with the start of antiretroviral therapy.

Lactic acidosis—Buildup of lactic acid in the blood, which can occur with zidovudine.

Neutropenia—Deficiency of white blood cells, primarily neutrophils.

Nucleoside reverse transcriptase inhibitor (NRTI)—An antiretroviral drug that interferes with the action of viral reverse transcriptase inside infected cells, preventing the virus from replicating.

Retrovirus—A single-stranded RNA virus, such as HIV, that transcribes its RNA into DNA and inserts the DNA into the genetic material of infected cells.

rapid heart rate, rapid breathing, jaundice, and muscle weakness.

- Lab tests are required to monitor responses to lamivudine/zidovudine.

Immune reconstitution inflammatory syndrome (IRIS) and redistribution/accumulation of body fat have been reported in patients using lamivudine/zidovudine and other combination antiretroviral therapies. IRIS is an inflammatory response to latent or residual infections or the development of a new disease, including autoimmune disorders, that may occur as the immune system improves in response to therapy. Body fat may increase or be redistributed to different areas, such as the breasts or upper back.

Pediatric

Lamivudine/zidovudine should be used with caution in children with a history of pancreatitis (inflammation of the pancreas) or significant risk factors for pancreatitis.

Pregnant or breastfeeding

Lamivudine/zidovudine is in the FDA pregnancy category C—there are no adequate studies of lamivudine/zidovudine use during pregnancy, but animal data indicate increased risk of birth defects and fetal death. In a clinical trial, there were no differences in adverse events between HIV-infected untreated women and women treated with zidovudine, but the effects of lamivudine are unknown. Studies have indicated that zidovudine significantly reduces maternal transmission of HIV-1 to the fetus, and combination treatment may reduce the risk further. However, lamivudine/zidovudine should be used during pregnancy only if potential benefits outweigh potential risks.

HIV-infected mothers should not breastfeed to avoid potential HIV-1 transmission to their babies. Lamivudine and zidovudine are present in breast milk.

Other conditions and allergies

Patients should tell their doctor and pharmacist if they are allergic to lamivudine (Epivir); zidovudine (Retrovir); the lamivudine, zidovudine, and abacavir combination (Trizivir); any components of lamivudine/zidovudine; or any other medications. The doctor should be informed if the patient has or has ever had kidney or liver disease or drinks or has ever drunk large amounts of alcohol. Lamivudine/zidovudine should be used with caution in patients with a history of pancreatitis, significant risk factors for pancreatitis, or low hemoglobin or granulocyte counts because of the risk of anemia or neutropenia.

Lamivudine/zidovudine has a higher dose of lamivudine than the drug combination used to treat infection with hepatitis B virus (HBV). The safety and effectiveness of lamivudine have not been established for patients coinfecting with HIV-1 and HBV. The emergence of lamivudine-resistant HBV has been reported in coinfecting patients treated with antiretroviral regimens. Coinfecting patients may be at risk for severe, acute hepatitis upon discontinuation of lamivudine. Such patients should have their liver function closely monitored.

Side effects

In lamivudine/zidovudine clinical trials of adult and pediatric HIV-1 patients, side effects occurring in at least 15% of subjects were:

- headache
- nausea
- malaise and fatigue
- nasal signs and symptoms
- diarrhea
- cough

The doctor should be consulted if any of the following symptoms are severe or persistent:

- headache
- upset stomach
- diarrhea
- constipation
- loss of appetite
- dizziness
- difficulty falling asleep or staying asleep
- excessive tiredness
- stuffy nose
- cough
- hair loss
- depression

Uncommon but serious side effects of lamivudine/zidovudine include IRIS, pancreatitis, and changes in body fat. Serious or life-threatening side effects are:

- lactic acidosis
- liver problems
- muscle weakness (myopathy)
- blood disorders such as anemia or neutropenia
- acute symptoms of HBV infection
- worsening anemia in patients co-infected with HIV-1 and hepatitis C virus (HCV) and treated with ribavirin
- liver failure in patients co-infected with HIV-1 and HCV

- hives, skin rash, or itching
- difficulty breathing or swallowing
- wheezing
- numbness, tingling, or burning in the fingers or toes
- fever
- seizures

Interactions

The doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. They should also be informed if the patient has been taking anti-HIV medications for a long period. Lamivudine/zidovudine may interact with other medications and supplements and affect how they or lamivudine/zidovudine work. Certain medications and products may cause serious or life-threatening side effects in combination with lamivudine/zidovudine.

Drugs

Drugs that should not be used when taking lamivudine/zidovudine include:

- other drugs containing lamivudine or zidovudine
- the antiretroviral agents zalcitabine or stavudine or nucleoside analogs that affect DNA replication such as ribavirin
- drugs containing emtricitabine
- doxorubicin (Adriamycin, Rubex)
- ganciclovir (Cytovene, Vitrasert), interferon alfa, ribavirin, and other bone-marrow suppressive or cytotoxic agents that may increase the blood toxicity of zidovudine
- interferon- and ribavirin-based regimens in patients co-infected with HCV

Other drugs that may interact with lamivudine/zidovudine and require dosage changes or monitoring for side effects include:

- acetaminophen (Tylenol)
- **acyclovir** (Zovirax)
- atovaquone (Mepron)
- cancer chemotherapy drugs
- cidofovir (Vistide)
- dapsone (Avlosulfon)
- didanosine (ddI, Videx)
- **fluconazole** (Diflucan)
- foscarnet (Foscavir)
- interferon beta 1b (Betaseron)
- **methadone**

- nelfinavir (Viracept)
- probenecid (Benemid, Probalan)
- rifabutin (Mycobutin)
- **rifampin** (Rifadin, Rimactane)
- ritonavir (Norvir)
- trimethoprim (Trimplex, Proloprim)
- trimethoprim and sulfamethoxazole (Bactrim, Septra)
- **valproic acid** (Depakene, Depakote)

Resources

PERIODICALS

Rooney, James F., Miller, Michael, and Andrew Cheng. "123 New HIV Therapies." *Journal of Acquired Immune Deficiency Syndromes* 65, suppl. 2 (2014): 50.

WEBSITES

AIDS Info Drug Database. "Lamivudine/Zidovudine (Patient Version)." U.S. National Institutes of Health. <http://aidsinfo.nih.gov/drugs/285/lamivudine—zidovudine/0/patient> (accessed February 15, 2015).

AIDS Info Drug Database. "Lamivudine/Zidovudine (Professional Version)." U.S. National Institutes of Health. <http://aidsinfo.nih.gov/drugs/285/lamivudine—zidovudine/0/professional> (accessed February 15, 2015).

"Combivir." Drugs.com. <http://www.drugs.com/combivir.html> (accessed February 15, 2015).

MedlinePlus. "Lamivudine and Zidovudine." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601066.html> (accessed February 15, 2015).

ORGANIZATIONS

AIDSinfo, PO Box 4780, Rockville, MD 20849-6303, (301) 315-2816, (800) HIV-0440 (448-0440), Fax: (301) 315-2818, TTY: (888) 480-3739, ContactUs@idsinfo.nih.gov, <http://aidsinfo.nih.gov/>.

amFAR (Foundation for AIDS Research), 120 Wall Street, 13th Floor, New York, NY 10005-3908, (212) 806-1600, Fax: (212) 806-1601, <http://www.amfar.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Lamotrigine

Definition

Lamotrigine is an anticonvulsant drug commonly used to prevent seizures.



Lamictal (lamotrigine), 100 mg. (© Cengage Learning®.)

Purpose

Lamotrigine is used to prevent seizures in individuals with seizure disorders. It is also used as a mood stabilizer in people with bipolar disorder.

Description

Lamotrigine is available as oral, oral dissolvable, and chewable tablets. The drug appears to suppress the activity of neurons (nerve cells) in the brain. By stabilizing neurons, lamotrigine prevents seizure activity and may also stabilize abnormal mood swings.

U.S. brand names

In the United States, lamotrigine is available under the trade name of Lamictal.

Origins

The U.S. Food and Drug Administration (FDA) approved Lamotrigine in 1994.

Recommended dosage

The dosage of lamotrigine varies depending upon the age and weight of the patient, other medications that the patient is taking, and whether the patient has heart, liver, or kidney disease. It is common for patients to start

KEY TERMS

Bipolar disorder—A mood disorder marked by alternating episodes of extremely low mood (depression) and exuberant highs (mania); formerly known as manic-depressive disorder.

Seizure—A sudden attack, spasm, or convulsion.

with a low dosage of lamotrigine. The dosage is then increased slowly over several weeks to help prevent side effects. The dosage may be adjusted frequently by the prescribing physician. When discontinuing this medication, patients should reduce the dosage over time under their physicians' supervision.

A common dose for an adult who takes no other medications and has no other diseases is 150–250 milligrams (mg) taken twice daily.

Precautions

A serious and permanently disfiguring rash may occur as a result of lamotrigine. The rash, which is symptom of a systemic reaction to the drug, may be fatal. If a rash occurs, a doctor should be contacted immediately, and the drug should be stopped. People who have experienced any kind of rash while taking lamotrigine should never take the drug again.

Lamotrigine should be used under physician supervision. Lamotrigine has also been associated with the risks of developing aseptic meningitis or blood disorders.

Other conditions and allergies

In persons with heart, kidney, or liver disease, lamotrigine should be used only if the patient and physician determine that the benefits outweigh the risks. The dosage is usually reduced in these individuals.

Side effects

Side effects that occur in more than 10% of people taking lamotrigine include headache, dizziness, unsteadiness while walking, blurred vision, double vision, nausea, cold-like symptoms such as runny noses or sore throats, and infections.

Although relatively rare, any rash that develops while taking lamotrigine should be evaluated by a healthcare professional, since life-threatening rashes may occur. The rash is most likely to develop in patients ages 2–16 within the first two to eight weeks after starting treatment, but it could happen to any patient at any time while taking the medication.

Other side effects include confusion, impaired memory, sleep disorders, nonspecific pain all over the body, suicidal thoughts or actions, and disruption of menstrual cycles.

Interactions

To avoid the risk of drug interactions, individuals should discuss all medications they are currently taking, including over-the-counter drugs and supplements, with their healthcare provider.

Drugs

Some drugs can decrease the levels of lamotrigine in the body. This may make the drug less effective; examples include carbamazepine, phenobarbital, primidone, **phenytoin**, and **valproic acid**. Valproic acid and its close relative divalproex sodium have also been reported to increase lamotrigine levels in some people, which could increase the side effects of the drug. When lamotrigine and valproic acid or divalproex sodium are used together, there is a greater chance that a serious rash may develop. Very specific dosage guidelines must be followed when these two drugs are used at the same time.

Hormonal birth control pills may decrease the levels of lamotrigine in the body, and dosage adjustments may be needed when starting or stopping contraceptive use, as well as during the “hormone-free” week.

Lamotrigine may increase the levels of **carbamazepine** in the body, increasing adverse effects associated with carbamazepine.

An increased risk of certain side effects may occur if lamotrigine is used with drugs, such as **methotrexate**, that inhibit folic acid synthesis.

Resources

PERIODICALS

Wang, X. Q., et al. “Risk of a Lamotrigine-Related Skin Rash: Current Meta-Analysis and Postmarketing Cohort Analysis.” *Seizure* 25 (February 2015): 52–61.

WEBSITES

- AHFS Consumer Medication Information. “Lamotrigine.” American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a695007.html> (accessed February 25, 2015).
- Epilepsy Foundation. “Lamotrigine.” <http://www.epilepsy.com/medications/lamotrigine> (accessed February 25, 2015).
- NYU Langone Comprehensive Epilepsy Center. “Lamotrigine (Lamictal).” <http://epilepsy.med.nyu.edu/treatment/medications/lamotrigine#sthash.EfewxbUS.dpbs> (accessed February 25, 2015).
- U.S. Food and Drug Administration. “Lamotrigine (Marketed as Lamictal) Information.” <http://www.fda.gov/Drugs/>

DrugSafety/PostmarketDrugSafetyInformationforPatient-sandProviders/ucm110460.htm (accessed February 25, 2015).

ORGANIZATIONS

Epilepsy Foundation, 8301 Professional Place East, Suite 200, Landover, MD 20785-2353, (800) 332-1000, ContactUs@efa.org, <http://www.epilepsy.com/>.

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Lanoxin see **Digoxin**

Lansoprazole

Definition

Lansoprazole is a medicine available by prescription or over the counter. The prescription drug is used to treat gastroesophageal reflux disease (GERD) and ulcers, and the over-the-counter formula is taken to relieve heartburn, one of the symptoms of GERD. Lansoprazole is in a class of medications called proton pump inhibitors (PPIs), which help decrease acid in the stomach.



Prevacid (lansoprazole), 30 mg. (© Cengage Learning®.)

Purpose

People who have GERD have symptoms such as pain near the breast bone that burns, especially when they lie down or bend over. The burning sensation is caused by acid created in the stomach to break down food. In GERD, some of the acid backs up into the esophagus, which is called reflux. The constant reflux of acid can eventually damage the thin lining of the esophagus and cause ulcers, or sores, in the lining. Lansoprazole is used to prevent or treat heartburn, other GERD symptoms, and ulcers in the stomach and intestine.

Description

Over-the-counter lansoprazole formulas come in delayed-release capsules. The medicine is released in the intestine so that it is not broken down by acids in the stomach. Prescription lansoprazole also comes in a tablet that dissolves when taken by mouth. The drug may be prescribed with other medicines to treat and prevent stomach ulcers that are caused by *H. pylori* bacteria.

U.S. brand names

In the United States, lansoprazole is sold under the brand names of Prevacid, Prevacid SoluTab, and Prevacid 24HR. A product that combines lansoprazole with antibiotics (**amoxicillin** and **clarithromycin**) is called Prevpac.

Recommended dosage

To treat the symptoms of GERD, the recommended adult dosage of lansoprazole is a 15-milligram (mg) capsule taken once a day until symptoms improve, usually for no more than eight weeks. To treat gastric (stomach) ulcers, patients usually take 30 mg of the medicine by mouth once day, making sure to take the capsule 30 minutes before eating. Stomach ulcer treatment with lansoprazole usually lasts four to eight weeks. Generally, adults are given 15 mg of lansoprazole once per day, 30 minutes before meals, to prevent ulcers.

To treat *H. pylori* infection, a 30 mg dose of lansoprazole is combined with amoxicillin and clarithromycin in a delayed-release capsule taken by mouth every 12 hours for either 10 or 14 days.

Pediatric

Children ages 1 to 17 may receive lansoprazole for treatment of GERD in doses based on weight. Generally, doctors recommend between 0.7 mg and 3 mg per kilogram (kg, or 2.2 lb.) of weight per day. The contents of the capsule can be sprinkled onto soft foods or into

KEY TERMS

Gastroesophageal reflux disease (GERD)—A condition in which stomach acid passes back into the esophagus through the small muscle that normally allows food to travel down from the esophagus into the stomach. GERD can cause heartburn and lead to ulcers in the esophagus.

Intravenous—Within a vein, usually referring to how a drug is placed, or administered, through a needle or catheter into a vein and therefore into the blood system.

Osteoporosis—A chronic and progressive disease that leads to bone weakening and brittleness.

Pregnancy category—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk but no human studies exist, or adverse effects have been seen in animals but not in well-controlled human studies. Category C: No adequate human or animal studies exist, or adverse fetal effects have occurred in animal studies but there is no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk, and risks outweigh any benefits.

Proton pump inhibitor (PPI)—These medicines reduce how much acid is made by glands that are located in the stomach's lining. When less acid is made, less makes its way back into the esophagus, and the symptoms of gastroesophageal reflux disease are eased.

Ulcer—A sore or break in the skin or lining of an organ.

certain juices. There also is a flavored dissolving tablet for older children. Some children may receive the medicine through a special syringe or nasal tube if they are unable to eat. Generally, treatment of children with lansoprazole should not last longer than 8 to 12 weeks.

Precautions

The safety of using lansoprazole for more than 12 months, even at low doses, has not been tested. Use of lansoprazole for a long period of time, especially several times a day, can increase risk of bone fractures associated

with osteoporosis. Use of lansoprazole and other proton pump inhibitors also increases risk of diarrhea from colitis, which is caused by stomach bacteria.

Pediatric

Studies have shown that lansoprazole is not effective at controlling GERD symptoms in infants less than one year old.

Pregnant or breastfeeding

Lansoprazole is a pregnancy category B drug, and no well-controlled studies have been conducted in pregnant women. The medication should be used during pregnancy only if clearly needed. It is not known whether the drug is passed to infants in breast milk, so mothers who use lansoprazole should discuss with their doctors whether to stop taking the medication or avoid breastfeeding their infants while on lansoprazole.

Other conditions and allergies

Individuals who have problems with liver function may need to take lower doses of lansoprazole than other people their age or weight.

Side effects

Side effects of lansoprazole may include:

- headache
- constipation
- diarrhea
- dizziness

Some side effects of lansoprazole use can be more severe and should be reported to a doctor right away. These include:

- peeling or blistering skin
- rash or hives
- swelling of the face, lips, tongue, throat, or eyes
- problems with breathing or swallowing
- rapid or irregular heartbeat
- extreme fatigue
- light-headedness
- seizures
- muscle spasms

Interactions

It is important for individuals to inform their doctor about any medications, herbal preparations, or vitamin supplements that they are taking before starting treatment with lansoprazole.

Drugs

Lansoprazole can interact with several drugs. Interactions may affect how well one of the drugs works or worsen side effects. In particular, patients should tell their doctor if they are taking penicillin-type antibiotics such as ampicillin or anticoagulants, also known as blood thinners. Lansoprazole may increase levels of **methotrexate** (Rheumatrex), which is used to treat severe psoriasis.

Herbs and supplements

Patients should tell their doctor if they are taking iron supplements before using lansoprazole.

Food and other substances

If planning on mixing lansoprazole granules with food or liquids, individuals should consult with their healthcare provider and the prescribing instructions for recommended foods and juices.

Resources

PERIODICALS

Boeckxstaens, Guy, et al. "Symptomatic Reflux Disease: The Present, the Past, and the Future." *Gut* 63, no. 7 (2014): 1185–93.

Lightdale, Jennifer R. "Gastroesophageal Reflux: Management Guidance for the Pediatrician." *American Academy of Pediatrics* 131, no. 5 (2013): e1684–95.

WEBSITES

AHFS Consumer Medication Information. "Lansoprazole." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a695020.html> (accessed February 7, 2015).

Micromedex. "Lansoprazole (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/lansoprazole-oral-route/proper-use/drg-20067214> (accessed February 10, 2015).

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). "Gastroesophageal Reflux (GER) and Gastroesophageal Reflux Disease (GERD) in Adults." National Institutes of Health. <http://www.niddk.nih.gov/health-information/health-topics/digestive-diseases/ger-and-gerd-in-adults/Pages/overview.aspx> (accessed February 10, 2015).

NHS. "Lansoprazole." <http://www.nhs.uk/medicine-guides/pages/MedicineOverview.aspx?condition=Gastro-oesophageal%20reflux%20disease&medicine=lansoprazole> (accessed February 10, 2015).

U.S. Food and Drug Administration. "Highlights of Prescribing Information: Prevacid." http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020406s078-021428s0251bl.pdf (accessed February 10, 2015).

ORGANIZATIONS

American Gastroenterological Association, 4930 Del Ray Avenue, Bethesda, MD 20814, (301) 654-2055, Fax: (301) 654-5920, <http://www.gastro.org/>.

International Foundation for Functional Gastrointestinal Disorders, 700 W. Virginia Street, #201, Milwaukee, WI 53204, (414) 964-1799, (888) 964-2001, Fax: (414) 964-7176, iffgd@iffgd.org, <http://www.aboutgerd.org/>.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 9000 Rockville Pike, Bethesda, MD 20892-2560, (301) 496-3583, <http://www.niddk.nih.gov/>.

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, 1501 Bethlehem Pike, Flourtown, PA 19031, (215) 233-0808, naspghan@naspghan.org, <http://www.naspghan.org/>.

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REVIEWED BY KEVIN GLAZA, RPh

Lantus see **Insulin glargine**

Lasix see **Furosemide**

Levalbuterol

Definition

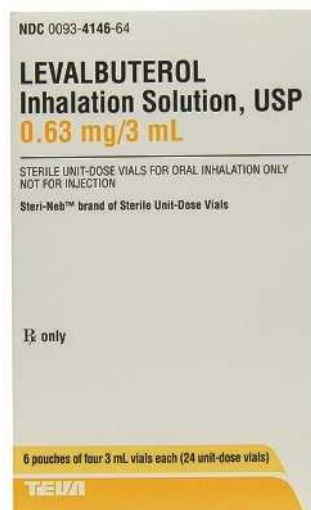
Levalbuterol is a type of drug known as a short-acting beta-agonist that relaxes the airways of people who have asthma or chronic obstructive pulmonary disease (COPD).

Purpose

When a person has trouble breathing because of asthma, the air passages, called the bronchi, can become tight and contract. Use of a bronchodilator such as levalbuterol helps to expand and relax those air passages, making it easier to breathe. Inhaling levalbuterol helps to prevent bronchospasm, or contraction of the muscles around the bronchi. Levalbuterol also is used by people who have chronic breathing problems, such as emphysema or chronic bronchitis. These progressive diseases are collectively known as COPD.

Description

An aerosol inhaler filled with a liquid solution of levalbuterol measures the dose and delivers it into the mouth of the person who has asthma and uses the inhaler to help prevent bronchospasm. A protective cap covers the canister to keep the mouthpiece clean. After shaking the canister and breathing out completely, the user places the canister's mouthpiece into the mouth and closes the mouth around it. The medication guide that comes with the prescription gives complete instructions explaining how to use the canister.



Levalbuterol solution. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

A nebulizer is a small machine, or compressor, that delivers a concentrated liquid mist of levalbuterol mixed with saline. Often called a breathing treatment, use of a nebulizer helps to deliver the levalbuterol deeper into the bronchi and lungs. The medication comes in a small foil pouch that the patient tears open one vial at a time to place inside the reservoir of the nebulizer and mix with the saline. The mist with the levalbuterol is delivered through a mouthpiece or face mask.

U.S. brand names

Levalbuterol for asthma inhalers is sold as Xopenex, Xopenex HFA, and Xopenex Concentrate.

Recommended dosage

Oral aerosol inhalation of levalbuterol is delivered in metered doses equivalent to 45 micrograms (mcg) of levalbuterol. To treat acute asthma, adults can have up to two inhalations every four to six hours as needed. Some adults need only one inhalation every four hours.

For adults using levalbuterol for maintenance or management of COPD in a nebulizer, the concentrated solution comes in a dose of 0.63 milligrams (mg) and can be used up to three times daily, or about every six to eight hours.

Pediatric

To treat acute asthma, children four years or older can have up to two inhalations every four to six hours or only one inhalation every four hours as needed.

Children older than 12 years who are using a nebulizer can have an adult dose, and those ages 6–12 can use the nebulizer as directed in a dose of 0.31 mg three times a day, or every six to eight hours.

Precautions

Despite its use in controlling bronchospasm, levalbuterol infrequently causes a condition called paradoxical bronchospasm, which is a potentially life-threatening tightening of the airways. When it does occur, the bronchospasm usually follows the first use of a new container of levalbuterol. It is important that people using levalbuterol not exceed the recommended dose.

People prescribed levalbuterol should inform their doctors of other medications they take, including supplements and vitamins, and of other diseases or conditions they have, especially heart disease.

Pediatric

Children should have an action plan that includes avoiding asthma triggers and having available rescue inhalers. Many children with asthma that is controllable rely only on short-acting beta-agonists such as levalbuterol to prevent attacks. Studies have found that children taking just these drugs have fewer hospitalizations and fewer complications than those who take long-acting beta-agonists, but some children have asthma that is more difficult to control.

Levalbuterol inhalation aerosol has been established as a safe medicine for children age four years and older when used as directed. No studies have shown that the drug is safe in children younger than age four.

Geriatric

Clinical trials have not included enough older patients to sufficiently test the effects of levalbuterol on the elderly, but it is recommended that people age 65 years and older begin levalbuterol treatment at the lowest possible dose. Many seniors take other medications that might interact with the drug, and as people age, they are more likely to have possible kidney, liver, or heart conditions that make them more likely to have serious side effects from levalbuterol.

Pregnant or breastfeeding

Levalbuterol is in pregnancy category C, which means that the drug has been tested only in animals, not humans. Some of the drug's effects were transferred to the fetus in these animal studies, so it is best for women who are pregnant to use levalbuterol only if the benefits outweigh any risks to an unborn child.

KEY TERMS

Bronchi—The tubes that serve as airways. There is a bronchus that leads from the trachea in the neck to each lung.

Bronchodilator—A medicine that relaxes the muscles around the airways, or bronchi, making it easier to breathe.

Nebulizer—A machine, usually run by a small compressor, that delivers a fine liquid mist with medicine through a mouth tube or face mask. The nebulizer is used as a breathing treatment for people who have respiratory, or lung, diseases.

Other conditions and allergies

In addition to heart problems such as irregular heartbeat, anyone who has seizures, diabetes, kidney disease, high blood pressure, or a problem with the thyroid gland should discuss these conditions with the doctor before using levalbuterol.

It is important to tell the doctor about any allergies to albuterol or other drugs before starting levalbuterol.

Side effects

Levalbuterol can cause several side effects. Some are minor, and others go away soon after use. Any severe or continuing symptoms should be reported to a doctor. Symptoms may include:

- dizziness
- headache
- vomiting and diarrhea
- nervousness and shaking
- heartburn
- coughing
- muscle pain or cramping
- fever

More serious side effects can include:

- rapid heartbeat
- chest pain
- trouble breathing
- hives or itchy rash

These symptoms should be reported to a doctor immediately.

Pediatric

The most common side effects in children age 4–11 years old that were observed in clinical trials of levalbuterol were vomiting, bronchitis, sore and swollen throat, and accidental injury.

Interactions

Several prescription medications cause major interactions when taken at the same time as levalbuterol.

Drugs

The following drugs are among those that interact with levalbuterol:

- diuretics (also known as water pills)
- beta-blockers for high blood pressure and other conditions, such as **propranolol**, **metoprolol**, **atenolol**, and others
- drugs used to lower eye pressure from glaucoma such as brimonidine
- current or recent use of certain antidepressant medicines, such as amitriptyline, clomipramine, and selegiline

Resources

PERIODICALS

- Schauer, S. G., et al. "Management of Acute Asthma in the Emergency Department." *Emergency Medical Practice* 15, no. 6 (2013): 1–28.
- Xia, Ying, et al. "Safety of Long-Acting Beta Agonists and Inhaled Corticosteroids in Children and Adolescents with Asthma." *Therapeutic Advances in Drug Safety* 4, no. 6 (2013): 254–63.

WEBSITES

- American Lung Association. "Understand Your Medication." Lung.org. <http://www.lung.org/lung-disease/asthma/taking-control-of-asthma/understand-your-medication.html> (accessed December 9, 2014).
- MedlinePlus. "Levalbuterol Oral Inhalation." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a603025.html> (accessed December 9, 2014).
- Micromedex. "Levalbuterol (Inhalation Route)." Mayo Clinic. <http://www.mayoclinic.org/drugs-supplements/levalbuterol-inhalation-route/description/DRG-20067232> (accessed December 10, 2014).
- Sunovian staff. "Xopenex HFA." Respiratory.com. <http://www.respiratory.com/aa/ast/treatments-xopenexhfa.html> (accessed December 9, 2014).

ORGANIZATIONS

- American Academy of Allergy Asthma & Immunology, 555 East Wells Street, Suite 1100, Milwaukee, WI 53202-3823, (414) 272-6071, <http://www.aaaai.org/home.aspx>.

American Lung Association, 55 West Wacker Drive, Chicago, IL 60601, Fax: (202) 452-1805, (800) 586-4872, <http://www.lung.org/>.

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Levaquin see **Levofloxacin**

Levemir see **Insulin detemir**

Levetiracetam

Definition

Levetiracetam is an antiepileptic drug (AED). It is often used in combination with other medications in the treatment of epilepsy, a neurological dysfunction in which excessive surges of electrical energy are emitted in the brain, causing seizures.

Purpose

While levetiracetam controls the partial seizures (focal seizures) associated with epilepsy, there is no known cure for the disorder. In partial epileptic seizures,



Keppra (levetiracetam), 500 mg. (© Cengage Learning®.)

neural disturbances are limited to a specific region of the brain, and the affected person usually remains conscious throughout the seizure. Although the precise mechanisms by which it works are unknown, levetiracetam is thought to exert its therapeutic effect by decreasing the abnormal activity and excitement within the brain area that may trigger partial seizures.

Description

Levetiracetam is taken by mouth in tablet form. It is available in regular or extended-release form. Levetiracetam lacks many of the usual side effects commonly associated with other AEDs. Levetiracetam has fewer negative interactions with other AEDs or anticonvulsants and may be used in combination with other AEDs in the treatment of epilepsy.

U.S. brand names

In the United States, levetiracetam is sold under the brand name Keppra.

Recommended dosage

As with many other AEDs, beginning a course of treatment that includes levetiracetam requires a gradual dose-increasing regimen. Adults and teenagers 16 years or older typically take 1,000 milligrams (mg) a day for the first two weeks. Daily dosages of levetiracetam may then be increased by as much as 1,000 mg every two weeks until reaching the maximum therapeutic dose (usually not more than 3,000 mg). It may take several weeks to realize the full benefits of levetiracetam.

Extended-release tablets are prescribed at 1,000 mg once daily, with gradual increases up to 3,000 mg per day as needed and tolerated and as prescribed by the doctor. Patients typically take divided doses (equal to one half of the total daily dose) twice daily.

It is important not to take a double dose of levetiracetam. If a dose is missed, it should be taken as soon as possible; however, if it is almost time for the next dose, then the missed dose should be skipped.

When ending treatment AEDs, including levetiracetam, physicians typically direct patients to gradually reduce their daily dosages over a period of several weeks. Stopping the medicine suddenly may cause seizures to return or occur more frequently.

Pediatric

The extended-release tablet dose for children 16 years of age and younger must be determined by the doctor.

For standard-release levetiracetam tablets, dosage is typically determined by weight:

- For children 4 to 15 years, the usual starting dose is 10 mg kilogram (kg, or 2.2 lb.) of body weight twice daily, with a maximum recommended dose of no more than 60 mg per kg of body weight per day.
- For children six months to 3 years, the usual starting dose is 10 mg per kg of body weight two times a day. The doctor may adjust the dose as needed and tolerated. However, the dose is usually not more than 50 mg per kg of body weight per day.
- For children one to five months, the usual starting dose is 7 mg per kg of body weight two times a day. The doctor may adjust the dose as needed and tolerated. However, the dose is usually not more than 42 mg per kg of body weight per day.
- In children younger than one month of age, the doctor must determine use and dose.

Precautions

Patients should consult a physician before taking levetiracetam with certain nonprescription (over-the-counter) medications. Patients should avoid alcohol and central nervous system (CNS) depressants (medications that make one drowsy or tired, such as antihistamines, sleep medications, and some pain medications) while taking levetiracetam, as the drug can exacerbate the side effects of alcohol and other medications. Before beginning treatment with levetiracetam, patients should notify their physician if they consume a large amount of alcohol or have a history of drug use.

Pediatric

Children younger than 16 years of age may use levetiracetam, but the extended-release tablets are not recommended. Studies on children younger than one month of age are inadequate to determine the effects of levetiracetam and dosing.

Geriatric

Elderly individuals are more likely to have age-related kidney problems requiring adjustments in dose or frequency of medication.

Pregnant or breastfeeding

Limited data is available regarding the effects of levetiracetam on women who are pregnant or breastfeeding. This medication is rated a category C drug for all trimesters of pregnancy, using the U.S. Food and Drug Administration (FDA) risk-factor designation. Patients taking levetiracetam with other AEDs or anticonvulsants should be aware that many AEDs and anticonvulsants have been shown to cause birth defects in animals. Safe use has not been established for

KEY TERMS

Anticonvulsant—A drug used or tending to control or to prevent convulsions (as in epilepsy).

Epilepsy—A brain disorder with symptoms that include seizures.

Seizure—Physical manifestations (as convulsions, sensory disturbances, or loss of consciousness) resulting from abnormal electrical discharges in the brain.

levetiracetam in pregnant or breastfeeding patients. Patients who become pregnant while taking any AED or anticonvulsants should contact their physician immediately.

Other conditions and allergies

Levetiracetam may not be suitable for persons with a history of kidney disease, depressed renal (kidney) function, or mental illness.

Side effects

Research indicates that levetiracetam is generally well tolerated and lacks many of the traditional side effects associated with AEDs; however, levetiracetam may cause a variety of usually mild side effects in some patients. Cough, dizziness, and muscle weakness are the most frequently reported side effects of levetiracetam. Because drowsiness and dizziness are occasional side effects, the full effects of levetiracetam should be known before driving or operating heavy machinery. Other possible side effects that do not usually require medical attention include:

- dryness or soreness of throat
- changes in mood or behavior
- fever
- asthenia (loss of strength)
- hoarseness or voice changes
- sleepiness or unusual drowsiness
- tender, swollen glands in neck
- numbness, prickling, “pins and needles,” or tingling feelings
- loss of appetite or weight loss

Many of these side effects disappear or occur less frequently during treatment as the body adjusts to the medication. If any symptoms persist or become too uncomfortable, consult the prescribing physician.

Other, uncommon side effects of levetiracetam can indicate a potentially serious condition. A patient taking

levetiracetam who experiences any of the following symptoms should immediately contact their physician:

- clumsiness or unsteadiness
- depression, paranoia, or other significant mood changes
- double vision
- problems with memory
- lower back or side pain
- painful or difficult urination
- shortness of breath, wheezing, or trouble breathing

Pediatric

Changes in mood or behavior may occur as a result of using levetiracetam. If anxiety, depression, getting angry or upset easily, or thoughts of harming oneself or others are noticed, the doctor should be notified immediately.

Interactions

Levetiracetam is often used with other seizure-prevention medications, as prescribed by a physician. No significant drug interactions have been identified. Unlike many other AEDs and anticonvulsants, levetiracetam does not decrease the effectiveness of **oral contraceptives** (birth control pills). Levetiracetam may alter the results of some lab tests.

Resources

BOOKS

- Aminoff, Michael J., ed. *Neurology and General Medicine*. 4th ed. New York: Churchill Livingstone, 2007.
- Brunton, Laurence, Bruce A. Chabner, and Bjorn Knollman. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill Professional, 2010.
- Devinsky, Orrin. *Epilepsy: Patient and Family Guide*. 3rd ed. New York: Demos Medical, 2007.
- George, Paulette. *Good Morning Beautiful: Winning the Battle over Seizures*. Greenville: Ambassador International, 2010.
- Kuzniecky, Ruben, editor. *Epilepsy 101: The Ultimate Guide for Patients and Families*. Leona: Medicus, 2009.
- Panayiotopoulos, C. P. *Antiepileptic Drugs, Pharmacopoeia*. New York: Springer, 2010.
- Patsalos, Philip N., and Blaise F. D. Bourgeois. *The Epilepsy Prescriber's Guide to Antiepileptic Drugs*. New York: Cambridge University Press, 2010.
- Shorvon, Simon. *Handbook of Epilepsy Treatment*. 3rd ed. New York: Wiley-Blackwell, 2010.
- Tatum, William O., Peter W. Kaplan, and Pierre Jallon. *Epilepsy A to Z: A Concise Encyclopedia*. 2nd ed. New York: Demos Medical, 2009.

PERIODICALS

- Abou-Khalil, Bassel. "Levetiracetam in the Treatment of Epilepsy." *Neuropsychiatric Disease and Treatment* 4, no. 3 (2008): 507–23.

- Alvarez, Vincent, et al. "Second-Line Status Epilepticus Treatment: Comparison of Phenytoin, Valproate, and Levetiracetam." *Epilepsia* 52, no. 7 (2011): 1292–96.
- Droz-Perroteau, C., et al. "The EULEV Cohort Study: Rates of and Factors Associated with Continuation of Levetiracetam after 1 Year." *British Journal of Clinical Pharmacology* 71, no. 1 (2011): 121–27.
- Fattore, C., et al. "A Multicenter, Randomized, Placebo-Controlled Trial of Levetiracetam in Children and Adolescents with Newly Diagnosed Absence Epilepsy." *Epilepsia* 52, no. 4 (2011): 802–9.
- Taylor, S., et al. "Levetiracetam Is Associated with Improved Cognitive Outcome for Patients with Intracranial Hemorrhage." *Neurocritical Care* 15, no. 1 (2011): 80–84.
- Verrotti, A., et al. "Levetiracetam in Childhood Epilepsy." *Pediatric Drugs* 12, no. 3 (2010): 177–86.

WEBSITES

- Epilepsy Foundation. "Seizure Medicines." http://www.epilepsy.com/EPILEPSY/SEIZURE_MEDICINES (accessed February 18, 2015).
- MedlinePlus. "Levetiracetam." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699059.html> (accessed February 18, 2015).
- Micromedex. "Levetiracetam." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/levetiracetam-oral-route/side-effects/drg-20068010> (accessed February 18, 2015).

ORGANIZATIONS

- American Academy of Neurology (AAN), 201 Chicago Avenue, Minneapolis, MN 55415, (612) 928-6000, Fax: (612) 454-2746, (800) 879-1960, memberservices@aan.com, <http://www.aan.com/>.
- American Academy of Physical Medicine and Rehabilitation, 9700 West Bryn Mawr Avenue, Suite 200, Rosemont, IL 60018-5701, (847) 737-6000, info@aapmr.org, <http://www.aapmr.org/>.
- American Epilepsy Society, 342 N Main Street, West Hartford, CT 06117-2507, (860) 586-7505, <http://www.aesnet.org/>.
- American Neurological Association, 1120 Route 73, Suite 200, Mount Laurel, NJ 08054, (856) 380-6892, info@myana.org, <http://myana.org/>.
- Epilepsy Foundation, 8301 Professional Place East, Suite 200, Landover, MD 20785-2353, (800) 332-1000, ContactUs@efa.org, <http://www.epilepsy.com/>.
- National Institute of Neurological Disorders and Stroke, NIH Neurological Institute, PO Box 5801, Bethesda, MD 20824, (301) 496-5751, (800) 496-5751, <http://www.ninds.nih.gov/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Laura Jean Cataldo, RN, Ed

Revised by Tracy Gardner Beno, RN

REVIEWED BY JAMES E. WAUN, MD, RPH

Levitra see **Vardenafil**

Levodopa/carbidopa see **Carbidopa/levodopa**

Levofloxacin

Definition

Levofloxacin is an antibiotic drug in the family of fluoroquinolone drugs.

Purpose

Levofloxacin treats a number of infections, including bronchitis and pneumonia, mastitis, anthrax exposure, and infections of the sinuses, skin, prostate, urinary tract, and kidney. Some of the organisms it is effective against include *Hemophilus influenzae*, *Hemophilus parainfluenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus* and *pyogenes*, *Enterococcus faecalis*, *Proteus mirabilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Yersinia pestis*, and *Mycobacterium avium*.



Levaquin (levofloxacin), 250 mg. (© Cengage Learning®.)

Description

Levofloxacin is available in tablet, liquid suspension, injectable (intravenous), and eyedrop forms. The medication is taken by mouth or through an intravenous line and must be prescribed by a physician. Levofloxacin is used internationally and is on the World Health Organization's list of essential medicines as a second-line treatment for multidrug-resistant tuberculosis. It is also occasionally used in veterinary medicine.

Levofloxacin is available in the following forms and strengths:

- Tablets are oval-shaped and may be pink or orange; they are available in 250, 500, or 750 milligram (mg) strengths. Imprint on tablets depends on manufacturer.
- A liquid suspension reconstitutes to a whitish-yellow or greenish-yellow strawberry-flavored suspension. Suspension strength is 25 mg per milliliter (mL).
- Eyedrops are available in 0.5% or 1.5% strengths.

U.S. brand names

Levofloxacin is sold under the brand name Levaquin. It is also manufactured as a generic by many different companies.

Canadian brand names

In Canada, levofloxacin is sold as Levaquin. It is also manufactured as a generic by many different companies.

International brand names

Levofloxacin is sold under a large variety of brand names internationally, including Avelar in Peru, Levoflox in Tunisia, Enatome in India, Bactifren in Argentina, Nevotek in Turkey, Tavalox in South Africa, and Wilovex in Phillipines. In some countries, levofloxacin is only one component of the medication, and there are other medications included in the formulation. In some locations, it is available only for veterinary, not human, use.

Recommended dosage

Recommended dosages are based on the amount of levofloxacin needed to treat the infection. It is important to read and follow the prescription instructions. Dosing schedules depend on the specific infection being treated. Levofloxacin is dosed once per day, and single doses are typically 250, 500, or 750 mg.

Eyedrops are administered every two to six hours, with one or two drops in the affected eye(s).

KEY TERMS

Anaphylaxis—A severe, systemic allergic reaction that can be potentially life threatening.

Peripheral neuropathy—Damage to the peripheral nerves (in the extremities of the body), causing numbness, tingling, or pain.

Pregnancy category—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk, but there are no human studies, or adverse effects have been seen in animals, but not in well-controlled human studies. Category C: No adequate human or animal studies exist, or adverse fetal effects have been seen in animal studies, but there is no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk. Risks outweigh any benefits.

QT interval—A segment of the EKG that represents the electrical conduction that occurs during the beating and relaxing of the ventricles (pumping chambers of the heart).

Pediatric

Pediatric dosing also depends on the infection being treated. In general, children are dosed by weight. Patients weighing less than 50 kilograms (kg, or 2.2 lb.) and over six months of age are dosed 8 mg per kg of body weight per day. The maximum daily dose is 250 mg. Treatment regimens with levofloxacin require only a single dose each day.

Eyedrops are administered every two to six hours, with one or two drops in the affected eye(s).

Precautions

The following precautions apply to all individuals:

- This drug should be taken for the entire length of the prescription. Failure to take a complete course of the medication can result in return of symptoms.
- Levofloxacin can be taken with or without food.
- Levofloxacin and other fluoroquinolones have been associated with tendinitis and tendon rupture. This risk is increased in individuals who are older than 60 years; who have had kidney, heart, or liver transplants; or who are taking steroid medications.
- Levofloxacin use has been associated with blood disorders.

- Levofloxacin increases the risk of heart arrhythmias, especially in individuals with known EKG abnormalities (particularly prolonged QT intervals), with low potassium levels, or on medications known to increase the EKG element called the QT interval.
- Levofloxacin can cause numbness, tingling, or pain in the extremities (peripheral neuropathy), which can become permanent if the drug is continued.
- Use over a long period of time can increase the risk of developing another fungal or bacterial infection.
- *C. difficile*—associated diarrhea and pseudomembranous colitis have both been associated with long-term use of levofloxacin, even months after the drug has been discontinued.
- Levofloxacin may make the skin more sensitive to sun exposure and tanning lights, resulting in more easily (and potentially severely) burned skin.

Geriatric

The risk of levofloxacin-induced heart, liver, and tendon side effects may be increased in the elderly.

Pregnant or breastfeeding

Levofloxacin has not been well studied in pregnant women. This drug is a pregnancy category C drug, meaning that there are potential adverse effects on the developing fetus. Women who are pregnant or breastfeeding should tell their doctor before taking levofloxacin. In most cases, an alternative drug will be utilized, unless the benefit is determined to outweigh the risk. This drug is believed to be safe for the lactating mother to use, although some practitioners recommend avoiding breastfeeding in the four to six hours directly following a dose.

Other conditions and allergies

Individuals with a history of kidney or liver problems or who are on dialysis should tell their doctor before taking this drug.

Individuals who have had seizures should take levofloxacin with great care, as the seizure threshold is lowered during its use. Individuals with myasthenia gravis may have worsened symptoms when taking levofloxacin.

Individuals should not take levofloxacin if they are allergic to levofloxacin or other fluoroquinolone-type drugs (e.g., **ciprofloxacin** or **moxifloxacin**) or have developed jaundice and liver problems when taking levofloxacin in the past. Individuals with a history of severe allergies, asthma, or prior reactions involving anaphylaxis, hives, or the severe swelling called

angioedema are at higher risk for serious reactions to levofloxacin.

Side effects

Serious and sometimes fatal reactions can occur in individuals who are allergic to fluoroquinolone drugs. Anyone who has had a severe reaction to any drug should alert the physician before taking this drug.

The most common adverse side effects of levofloxacin for all age groups tend to be mild. They include:

- upset stomach
- loose stools or diarrhea
- nausea and vomiting
- heartburn

These side effects should be brought to the doctor's attention if they do not go away within a few days.

Whitish vaginal discharge or white coating of the tongue and inside of the mouth should also be reported to the doctor.

A doctor should be notified immediately if any of these less common but more serious side effects occur:

- wheezing, difficulty breathing or swallowing; may indicate a severe allergic reaction and require immediate medical attention
- hoarse voice
- severe skin rash, itching, hives, or blistering or separating skin
- swelling
- yellowing of the skin or the whites of the eyes
- vaginal itching or discharge (females)
- seizures
- abdominal pain with fever
- sensation of an extra, skipped, or fast heartbeat
- dizziness, fainting
- confusion
- anxiety
- mood changes
- insomnia
- hallucinations (seeing or hearing things that are not present)
- thoughts of injuring yourself or others
- severe or bloody diarrhea, even if it occurs two months after ending levofloxacin treatment
- easy bruising or bleeding
- very dark urine
- severe muscle weakness or unusual loss of muscle control
- joint pain or any popping sensation in a joint

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herb, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Levofloxacin is known to interact with the following pharmaceutical drugs. Other interactions are possible. An individual who develops any unusual or unexpected symptoms should contact a physician.

- Due to increased risk of cardiovascular complications, avoid using levofloxacin in conjunction with all antiarrhythmic medications, such as amiodarone, dofetilide, procainamide, quinidine, and **sotalol**.
- Levofloxacin taken with the following drugs may increase the risk of serious cardiovascular side effects: arsenic, asenapine, bepridil, chloroquine, cisapride, **citalopram**, **clozapine**, crizotinib, dolasetron, droperidol, halofantrine, **haloperidol**, iloperidone, imidazoles (e.g., **fluconazole**, **ketoconazole**), macrolides (e.g., **erythromycin**), maprotiline, **methadone**, nilotinib, **ondansetron**, **pali-peridone**, pentamidine, phenothiazines (e.g., chlorpromazine), pimozide, **quetiapine**, romidepsin, **tacrolimus**, telithromycin, tetrabenazine, toremifene, tricyclic antidepressants (e.g., **nortriptyline**), tyrosine kinase inhibitors (e.g., sunitinib), vandetanib, or **ziprasidone**.
- Using levofloxacin while taking insulin or oral antidiabetic drugs may increase the risk of high or low blood sugar.
- Using levofloxacin while taking anticoagulant drugs may increase the risk of bleeding.
- Using levofloxacin while taking nonsteroidal anti-inflammatory drugs (NSAIDs) or theophylline may increase the risk of seizures and other severe adverse effects.
- Women taking **oral contraceptives** should ask their healthcare provider if they should use a second form of contraception while using levofloxacin, as this drug can interfere with the effectiveness of the birth control pill.

Resources

BOOKS

Bloom, Allyson K., and Edward T. Ryan. *Hunter's Tropical Medicine and Emerging Infectious Disease*. Philadelphia: Saunders, 2013.

- Cherry, J., et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Elsevier Saunders, 2014.
- Drug Information Handbook*. 23rd ed. Hudson, OH: Lexicomp Inc., 2014.
- Mandell, G. L., et al. *Douglas and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. London: Churchill Livingstone, 2015.
- Rang, H. P., et al. *Rang and Dale's Pharmacology*. 7th ed. London: Churchill Livingstone, 2012.

WEBSITES

- AHFS Consumer Medication Information. "Levofloxacin." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a697040.html> (accessed March 9, 2015).
- Micromedex. "Levofloxacin (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/levofloxacin-oral-route/description/drg-20064518> (accessed March 9, 2015).
- U.S. Food and Drug Administration. "Levofloxacin." <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=LEVOFLOXACIN> (accessed February 15, 2015).

ORGANIZATIONS

- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (800) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rosalyn Carson-DeWitt, MD
REVIEWED BY KEVIN GLAZA, RPH

Levonorgestrel

Definition

Levonorgestrel (pronounced LEE-voh-nor-JESS-trel) is a second-generation progestin (synthetic progestogen) used primarily as the active ingredient in emergency contraceptive medications, known as the "morning-after pill." The oral form of levonorgestrel is also used in some forms of birth control pills, both combined estrogen-progestin pills and progestin-only pills (so-called "mini-pills"). Levonorgestrel is also known as *l*-norgestrel.

Purpose

The primary purpose of the emergency contraceptive pill (ECP) is to prevent pregnancy after unprotected sex or



Plan B (levonorgestrel). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

the presumed failure of another method of contraception, most often condoms. Levonorgestrel is thought to prevent pregnancy by preventing ovulation, rather than by preventing the implantation of a fertilized ovum. It is not an abortifacient (drug intended to cause the termination of an existing pregnancy) and will not interrupt the development of a pregnancy. It is, however, classified as a U.S. Food and Drug Administration (FDA) pregnancy category X drug because of its potential to harm the fetus. Levonorgestrel should not be used as a regular method of birth control; in addition, it will not protect users against sexually transmitted diseases (STDs).

Description

Levonorgestrel ECPs are small, white tablets that come in two dosage strengths: 0.75 milligrams (mg) in the two-dose formulation and 1.5 mg in the single-dose formulation.

U.S. brand names

Levonorgestrel is sold in the United States under the brand names My Way, Plan B, Plan B One-Step, Take Action, and Next Choice. Next Choice and Take Action are generic formulations of Plan B.

Canadian brand names

Levonorgestrel is sold in Canada under the brand names Option 2, NorLevo, Plan B, and Next Choice.

International brand names

International brand names for levonorgestrel ECPs include Postinor, Postinor-2, Escapelle, Glanique, Norgest, NorLevo, Levonelle, and i-pill.

Origins

The use of levonorgestrel in emergency contraception goes back to the mid-1970s, when A. Albert Yuzpe, a Canadian gynecologist, devised what is known as the Yuzpe regimen for emergency contraception. The Yuzpe regimen consisted of two doses of a combination of estrogen and levonorgestrel 12 hours apart, taken within 72 hours of unprotected intercourse. It has been largely superseded by levonorgestrel-only ECPs.

Levonorgestrel-only ECPs were introduced as prescription-only medications in 1999; Plan B was the first prescription-only ECP to be approved by the FDA, in May 1999. This first formulation consisted of two levonorgestrel tablets to be taken 12 hours apart within 72 hours of unprotected intercourse or contraceptive failure. In the early 2000s, Barr Laboratories (the original manufacturer) went through various proposals with the FDA to make Plan B available as an over-the-counter (OTC) product for women 18 years and older but prescription only for those 17 years and younger. The FDA approved this proposal in August 2006.

In 2009, the one-step form of levonorgestrel ECPs was introduced by Teva Pharmaceuticals as Plan B One-Step and approved by the FDA in July 2009. It was subject to a slightly altered age restriction, being available OTC to women and men ages 17 and older. In 2013, a U.S. district judge ordered the FDA to make levonorgestrel ECPs available as OTC products without age restrictions. In June 2013, the FDA approved the unrestricted sale of Plan B One-Step as an OTC product. In February 2014, the FDA approved generic levonorgestrel one-step ECPs for unrestricted sale over the counter.

Recommended dosage

For emergency contraception, adults using the two-tablet formulation (Plan B, Next Choice) should take one 0.75 mg tablet by mouth as soon as possible within 72 hours of unprotected intercourse, then take the second tablet 12 hours later.

Adults using the one-tablet formulation (My Way, Plan B One-Step, Next Choice One Dose) should take the single 1.5 mg tablet as soon as possible within 72 hours of unprotected intercourse. Levonorgestrel ECPs are most effective when taken as soon as possible after intercourse.

KEY TERMS

Abortifacient—A drug or substance that will induce an abortion or miscarriage.

Ectopic pregnancy—A complication of pregnancy in which the embryo implants outside the uterus, most often in the fallopian tubes.

Progestins—Synthetic forms of progestogens, which are steroid hormones produced by the ovaries and placenta in women and which serve to maintain a pregnancy.

Yuzpe regimen—An older form of emergency contraception consisting of estrogen and levonorgestrel started within 72 hours after intercourse. It was developed in 1974 by A. Albert Yuzpe, a Canadian gynecologist, but is now considered obsolete.

Pediatric

The doses for adolescents past menarche are the same as for older women. If taking the two-tablet ECP, take one 0.75 mg tablet by mouth as soon as possible within 72 hours of unprotected intercourse, and take the second tablet 12 hours later.

Adolescents taking the one-tablet ECP should take the single 1.5 mg tablet as soon as possible within 72 hours of unprotected intercourse.

The two-tablet Plan B and two-tablet generic ECPs are available to adolescents without restrictions. Plan B One-Step, however, is not available in a generic formulation to adolescents younger than 17 years old because the manufacturer was granted exclusivity rights to market Plan B One-Step through April 2016.

Precautions

Levonorgestrel tablets should be stored away from heat, moisture, and light at temperatures between 68°F and 77°F (20–25°C). They should not be kept in the bathroom, and they should be kept out of the reach of children and pets.

Several studies done in Europe in 2013 indicated that levonorgestrel ECPs are less effective in women weighing more than 165 pounds. As of early 2015, the FDA was evaluating whether increased weight and a higher body mass index (BMI) reduce the effectiveness of emergency contraceptive pills containing levonorgestrel.

Pediatric

Levonorgestrel ECPs are not recommended for use in teenagers who have not begun to menstruate.

Pregnant or breastfeeding

Levonorgestrel carries the FDA pregnancy category X, meaning that studies in humans or animals have demonstrated the risk of harm to the fetus. In addition, the drug is known to pass into breast milk. Pregnancy and lactation are considered contraindications to the use of levonorgestrel for emergency contraception.

Other conditions and allergies

Women with any of the following conditions should not use levonorgestrel:

- pregnancy
- abnormal vaginal bleeding
- history of ectopic pregnancy
- known allergy to levonorgestrel or the other ingredients in the tablets
- history of stroke or bleeding in the brain, known or suspected breast cancer, or a blood-clotting disorder
- taking either **rifampin** (an antibiotic and antituberculo-sis drug) or nevirapine (an antiretroviral drug)

Women with diabetes should use levonorgestrel cautiously, as it may affect blood sugar levels, and they should monitor their blood sugar very carefully.

Levonorgestrel ECPs should not be used within four weeks of scheduled major surgery.

Side effects

The most common side effects of levonorgestrel ECPs are:

- headaches
- nausea
- fatigue
- dizziness (women are advised not to drive while taking levonorgestrel until they know how the drug affects them)
- lighter, heavier, or delayed menstrual periods
- diarrhea
- sore breasts
- stomach pain

These side effects usually resolve within 48 hours. Less common side effects include:

- acne
- hair loss

- migraine headache
- depression
- pelvic pain
- vaginal discharge

Women who have any of the following side effects should contact their healthcare provider at once:

- signs of a severe allergic reaction (hives; itching; sudden and unexplained swelling of the lips, mouth, or throat; difficulty breathing)
- vomiting within an hour after taking a levonorgestrel tablet (may indicate that the tablet was expelled)
- severe abdominal pain (may indicate an ectopic pregnancy)
- if the normal menstrual period is late by more than one week

The symptoms of a levonorgestrel overdose include severe nausea and vomiting and vaginal bleeding. A woman who thinks she may have taken an overdose of the drug should call the American Association of Poison Control Centers at (800) 222-1222, or the nearest hospital emergency room at once.

Interactions

Levonorgestrel is known to interact with various drugs, herbs, and other substances.

Drugs

Levonorgestrel is known to interact with the following medications:

- antiretroviral medications (e.g., indinavir, atazanavir, delavirdine, ritonavir, nelfinavir)
- antifungal medications (**fluconazole**, miconazole, ketoconazole, posaconazole)
- corticosteroids (cortisone, dexamethasone, hydrocortisone, fludrocortisone, **methylprednisolone**, **prednisone**, prednisolone, **triamcinolone**)
- **phenytoin**
- penicillin
- **tetracycline** antibiotics (tetracycline, **doxycycline**, **minocycline**)
- **valproic acid**
- **warfarin** and other blood thinners
- barbiturates (e.g., amobarbital, phenobarbital, secobarbital)
- beta-blockers (e.g., **sotalol**, **timolol**, **propranolol**, **atenolol**)
- **lamotrigine** (an antiepileptic drug)
- **tizanidine** (muscle relaxant)

- mycophenolate mofetil (an immunosuppressant used to prevent organ-transplant rejection)
- bosentan (a drug used to treat pulmonary artery hypertension)

Herbs and supplements

Women using levonorgestrel ECPs should avoid using herbal preparations containing St. John's wort, as this herb reduces the effectiveness of levonorgestrel.

Food and other substances

Women taking levonorgestrel should not smoke, as heavy smokers have an increased risk of heart disease if they use ECPs, particularly if they are over 35 years of age or smoke 15 or more cigarettes per day.

Women using levonorgestrel should consume alcohol only with caution, as it can increase the dizziness that may occur as a side effect of the drug.

Resources

BOOKS

- Foster, Angel M., and Lisa L. Wynn, eds. *Emergency Contraception: The Story of a Global Reproductive Health Technology*. New York: Palgrave Macmillan, 2012.
- Haussman, Melissa. *Reproductive Rights and the State: Getting the Birth Control, RU-486, Morning-After Pills and the Gardasil Vaccine to the U.S. Market*. Santa Barbara, CA: Praeger, 2013.
- Whitaker, Amy. *Contraception for Adolescent and Young Adult Women*. New York: Springer, 2014.

PERIODICALS

- Cleland, K., et al. "Emergency Contraception Review: Evidence-Based Recommendations for Clinicians." *Clinical Obstetrics and Gynecology* 57, no. 4 (2014): 741–50.
- Kapp, N., et al. "Effect of Body Weight and BMI on the Efficacy of Levonorgestrel Emergency Contraception." *Contraception* 91, no. 2 (2015): 97–104.
- Li, H. W., S. S. Lo, and P. C. Ho. "Emergency Contraception." *Best Practice and Research: Clinical Obstetrics and Gynaecology* 28, no. 6 (2014): 835–44.

WEBSITES

- "Levonorgestrel." Drugs.com. <http://www.drugs.com/cdi/levonorgestrel.html> (accessed February 16, 2015).
- "Levonorgestrel Oral (Rx, OTC)." Medscape.com. <http://reference.medscape.com/drug/plan-b-levonorgestrel-oral-342781> (accessed February 16, 2015).
- Micromedex. "Levonorgestrel (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/levonorgestrel-oral-route/description/drg-20074413> (accessed February 16, 2015).
- U.S. Food and Drug Administration. "FDA Approves Plan B One-Step Emergency Contraceptive for Use without a Prescription for All Women of Child-bearing Potential." <http://www.fda.gov/newsevents/newsroom/>

[pressannouncements/ucm358082.htm](http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm358082.htm) (accessed February 16, 2015).

ORGANIZATIONS

- American Congress of Obstetricians and Gynecologists (ACOG), PO Box 70620, Washington, DC 20024-9998, (202) 638-5577, (800) 673-8444, <http://www.acog.org/>.
- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rebecca J. Frey, PhD

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Levothyroxine

Definition

Levothyroxine sodium is a drug that treats hypothyroidism, a condition that occurs when the thyroid has been removed, injured, stops working, or is producing too little hormone for some other reason.



Synthroid (levothyroxine), 150 mcg. (© Cengage Learning®.)

Purpose

Levothyroxine is a hormone replacement drug. It replaces the hormone thyroxine, which is normally produced by the thyroid, a gland located in the lower part of the neck. The thyroid may not function correctly because it has been removed, damaged, is diseased, or has slowly lost function over time. In rare cases, individuals are born without a functioning thyroid. Thyroxine helps to regulate cellular metabolism, heart rate, blood pressure, body temperature, the rate at which food is converted into energy, and growth rate. Without enough thyroxine, children do not develop properly, and adults become fatigued, gain weight, and have difficulty paying attention. If hypothyroidism is not treated, it can progress to a life-threatening disease.

Description

Levothyroxine is a synthetic hormone that acts identically to the thyroxine produced by the body. For individuals whose thyroid does not produce enough thyroxine, treatment with levothyroxine can completely relieve the symptoms of hypothyroidism. Levothyroxine generally is taken for life, as the thyroid typically does not regain its function.

U.S. brand names

In the United States, the oral form of levothyroxine is sold under the brand names Unithroid, Levothroid, Synthroid, Levoxyl, and Tirosint. The injectable form of the drug is sold under the brand name Synthroid. The appearance and strength of the medication varies depending on the brand. Levothyroxine sodium refers to the generic form of the drug.

Canadian brand names

In Canada, levothyroxine is sold under the brand names Eltroxin, Levothyroxine, and Synthroid.

International brand names

Levothyroxine is sold under a variety of other brand names in other countries and as part of combination products with other drugs.

Recommended dosage

For oral levothyroxine, the recommended dosage depends on the severity of the hypothyroidism. A blood test can determine the amount of thyroid hormone in the blood. For mild hypothyroidism, an oral dose of 100–125 micrograms (mcg) taken once per day is generally recommended for adults under the age of 50 who do not have cardiovascular disease. For individuals with

KEY TERMS

Cardiovascular disease—A term for a variety of problems in which plaque has built up on the arteries and the blood cannot flow normally through the blood vessels and heart.

Hypothyroidism—A condition in which the thyroid gland does not produce enough thyroid hormone.

Osteoporosis—A condition found in older individuals in which bones decrease in density and become fragile and more likely to break. It can be caused by lack of vitamin D and/or calcium in the diet.

Trachea—Commonly called the windpipe, it is the air pathway that connects the nose and mouth to the lungs.

Type 2 diabetes—Formerly called adult-onset diabetes. In this form of diabetes, the pancreas either does not make enough insulin or cells become insulin resistant and do not use insulin efficiently.

cardiovascular disease or who are over the age of 50, the initial dose is generally 25–50 mcg daily. The initial dose may be increased by 12.5 to 25 mcg every few weeks until the levels of thyroxine in the blood are in the normal range as determined by a blood test. Even for individuals who are otherwise healthy, the dosage should not exceed 300 mcg per day unless coma or other severe illness is present.

Injectable levothyroxine is generally prescribed at between 50 and 100 mcg per day, injected in a single dose. If the injectable form is being used because of severe illness due to decreased thyroxine levels, larger doses may be administered.

Pediatric

For children, dosage depends on the weight of the child and the amount of thyroxine their thyroid is able to produce naturally.

Geriatric

Individuals over the age of 50 are generally started with an initial dose of 12.5 to 25 mcg per day. This dose can be slowly increased every few weeks until the amount of thyroxine in the blood reaches the desired levels. Dosing for the elderly is generally done conservatively, as reductions in liver and kidney function

that occur with age can impair the body's ability to break down medications.

Precautions

Levothyroxine should not be used for weight loss. Although it may cause some weight loss in individuals with abnormally low thyroxine levels, additional thyroxine will not cause weight loss in individuals whose thyroid is functioning normally. Overdoses of levothyroxine can be serious and even fatal.

Long-term use may increase the risk of osteoporosis, especially in women.

Pediatric

Studies have not found any specific issues in the use of levothyroxine in children.

Geriatric

Studies have not demonstrated any problems with levothyroxine specific to the elderly. However, because of age-related decreases in kidney function that can impair the body's ability to break down and eliminate drugs, elderly patients should be started with a conservative dose and monitored for side effects.

Pregnant or breastfeeding

Levothyroxine is a class A pregnancy drug, meaning that studies have shown it to be safe to use during pregnancy. Levothyroxine has not been found to pose any threat to infants through breast milk, so it is believed that breastfeeding mothers can take the drug safely.

Other conditions and allergies

Individuals who have cardiovascular disease or who have had a heart attack should be monitored closely when taking levothyroxine. The drug may also increase the severity of symptoms in individuals with type 2 diabetes.

Some brands, including Synthroid and Unithroid, contain lactose and should not be taken with individuals who are allergic to or intolerant of lactose.

Side effects

In rare cases, serious and sometimes life-threatening allergic reactions have been reported due to levothyroxine. Anyone experiencing swelling of the lips, face, throat, or tongue; difficulty swallowing or breathing; severe dizziness; rash or hives; fever; or other signs of allergic reaction should seek emergency medical attention immediately.

Anyone experiencing irregular heartbeat, pounding heart, chest pain, swelling of the limbs, or seizures may be experiencing an overdose of thyroxine and should get medical attention immediately.

Individuals who experience any of the following side effects after beginning levothyroxine should stop taking the drug and promptly call their healthcare provider:

- shortness of breath
- diarrhea
- uncontrolled shaking
- extreme nervousness
- sweating or hot flashes
- vomiting
- changes in menstrual periods

Common but less serious side effects include:

- hair loss
- decreased appetite
- increased appetite
- headache
- decreased bone density
- sensitivity to heat
- insomnia
- stomach cramps

Interactions

Individuals should tell both their doctor and pharmacist about any medications (over-the-counter and prescription), vitamins, herbs, or supplements that they are taking, because there are many substances and medications that can interact with levothyroxine. A patient's healthcare provider and pharmacist can help ensure that he or she can take levothyroxine as safely as possible.

Drugs

Levothyroxine is not recommended for individuals taking amifampridine, sodium iodide, or sucroferric oxyhydroxide as levothyroxine may pose serious interaction complications. Individuals who are taking clomipramine, **desipramine**, heparin, **warfarin**, or a variety of other drugs should not take levothyroxine if possible.

Individuals taking medications that contain calcium or iron (including supplements) should be monitored closely while taking levothyroxine.

Medications containing calcium carbonate, such as some over-the-counter antacids, should not be taken within four hours before or after taking levothyroxine.

This is not a complete list of drugs that may interact with levothyroxine. Individuals should check with their pharmacist for the most up-to-date information on drug interactions.

Food and other substances

Individuals who ingest a high amount of caffeine should be monitored closely while taking levothyroxine.

Resources

BOOKS

Hotze, Steven F. *Hypothyroidism, Health & Happiness*. Charleston, SC: Advantage, 2013.

O'Neill, Ashley, and Mason R. Quinn, eds. *Hypothyroidism: Diagnosis and Screening, Genetic Influences and Treatment Options*. New York: Nova Biomedical, 2013.

PERIODICALS

Lee, Sun Y., Lewis E. Braverman, and Elizabeth N. Pearce. "Changes in Body Weight after Treatment of Primary Hypothyroidism with Levothyroxine." *Endocrine Practice* 20, no. 11 (2014): 1122–28.

Samuels, Mary H., et al. "The Effects of Levothyroxine Replacement or Suppressive Therapy on Health Status, Mood, and Cognition." *Journal of Clinical Endocrinology & Metabolism* 99, no. 3 (2014): 843–51.

Souter, I., et al. "Are Levothyroxine-Treated Women with Hypothyroidism at Increased Risk for IVF Failure and Adverse Pregnancy Outcomes?" *Fertility and Sterility* 101, no. 2 suppl. (2014): e18–e19.

WEBSITES

"Levothyroxine." Drugs.com. <http://www.drugs.com/levothyroxine.html> (accessed February 18, 2015).

Mayo Clinic staff. "Levothyroxine (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/levothyroxine-oral-route/side-effects/drg-20072133> (accessed February 18, 2015).

MedlinePlus. "Levothyroxine." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682461.html> (accessed February 18, 2015).

ORGANIZATIONS

American Association of Clinical Endocrinologists (AACE), 245 Riverside Avenue, Suite 200, Jacksonville, FL 32202, (904) 353-7878, Fax: (904) 353-8185, <https://www.aace.com/>.

American Thyroid Association, 6066 Leesburg Pike, Suite 550, Falls Church, VA 22041, (703) 998-8890, Fax: (703) 998-8893, thyroid@thyroid.org, <http://www.thyroid.org/>.

Endocrine Society, 2055 L Street NW, Suite 600, Washington, DC 20036, (202) 971-3636, (888) 363-6274, Fax: (202) 736-9705, societyservices@endocrine.org, <http://www.endocrine.org/>.

National Endocrine and Metabolic Diseases Information Service, 6 Information Way, Bethesda, MD 20892-3569, (888) 828-0904, TTY: (866) 569-1162, Fax: (703) 738-

4929, endoandmeta@info.niddk.nih.gov, <http://www.endocrine.niddk.nih.gov/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Tish Davidson, AM

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Levsin see **Hyoscyamine**

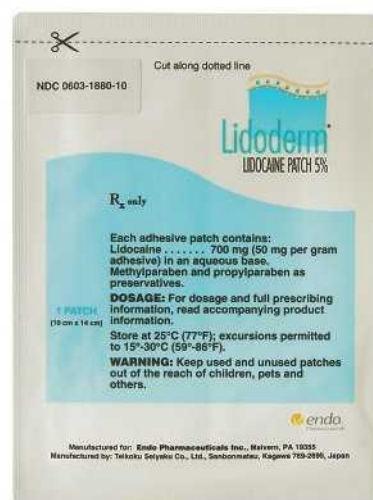
Lexapro see **Escitalopram**

Librium see **Chlordiazepoxide**

Lidocaine patch

Definition

Lidocaine belongs to a class of local and topical anesthetic medications. As lidocaine causes a temporary numbness or loss of sensation when injected in the tissues, it is used as a local anesthetic and in the treatment of pain. When given intravenously, lidocaine is also an antiarrhythmic agent, capable of correcting some instances of ventricular arrhythmia (irregular heartbeat). The lidocaine patch is a topical treatment that is especially helpful in the treatment of pain associated with postherpetic



Lidoderm (lidocaine patch). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

neuralgia, a condition that can occur after infection with the herpes varicella zoster (shingles) virus. Additionally, the lidocaine patch is sometimes used in the treatment of some chronic forms of nerve pain, such as the pain associated with fibromyalgia.

Purpose

The lidocaine patch relieves pain and discomfort by blocking signals sent to nerve endings in the skin. Almost 20% of the one million Americans who develop shingles yearly experience long-term pain after the infection has resolved. People over age 60 are especially prone to postherpetic neuralgia.

Description

The lidocaine patch is composed of an adhesive material containing 5% lidocaine that is applied to a polyester felt backing. When it is applied to the skin, lidocaine is released into the epidermal and dermal layers of the skin, reducing pain at the site of the dysfunctional nerves damaged by the prior herpes zoster infection. The lidocaine patch provides pain reduction without numbness of the affected skin.

U.S. brand names

In the United States, the lidocaine patch is sold under the name of Lidoderm.

Recommended dosage

The lidocaine patch is available in only one dose. Patches are applied directly to healthy, nonbroken skin that is close to the source of pain or discomfort. Patients may typically apply up to three patches at one time. However, patches should not be worn longer than 12 hours in a 24-hour period. Patches can be cut into smaller pieces before removing the release liner and applying to the skin. Clothing may be worn over the applied patch.

If a dose is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped. More patches than are instructed by the prescribing physician should never be applied.

Instructions for application include:

- Look at the skin where the lidocaine patch will be applied. If the skin is broken or blistered, the patch should not be applied to that area.
- Using scissors, remove the outer seal from the package and pull apart the zipper seal.
- Remove the prescribed number of patches from the package and press the zipper seal tightly together; the remaining patches will dry out if the zipper closure is not sealed.

KEY TERMS

Anesthetic—A substance or effect that causes a person to lose feeling and to feel no pain in part or all of the body.

Arrhythmia—A variation in the normal rhythm of the heartbeat. Ventricular arrhythmia starts in the lower chambers of the heart (the ventricles).

Dermis—The sensitive, vascular inner mesodermic layer of skin.

Epidermis—The outer layer of skin.

Fibromyalgia—A chronic disease syndrome characterized by fatigue, widespread muscular soreness, and pain at specific points on the body.

Nerve ending—The structure in which the distal end of the axon of a nerve fiber terminates.

Neuralgia—Acute pain that radiates along the course of one or more nerves, usually without a change in the nerve structure.

Postherpetic—Occurring after and especially as a result of herpes, which is the virus that causes shingles.

- Peel the transparent liner off the back of the patch.
- Press the patch firmly onto the skin. If the patch is to be applied to the facial area, use great care not to let the patch come in contact with the eyes. In the case of exposure to the eye, wash eye thoroughly with water or saline.
- Wash hands thoroughly after handling lidocaine patches, both the previously used, removed patches and the newly applied patches.
- Never reuse lidocaine patches.
- Dispose of all used patches by folding the patch onto itself and discarding where it is not accessible to children or pets. Used patches contain enough medication to seriously harm a child or pet.

Pediatric

This medication should be used with extreme caution in children under the age of three and only after other medicines have been considered or found to be ineffective. The healthcare provider should monitor the child carefully during therapy.

Geriatric

No specific information is available on the effect of this medicine in the elderly. This medication should be used only after other medicines have been considered or

found to be ineffective. Because of the potential for toxicity, the healthcare provider should monitor the patient carefully during therapy.

Precautions

Lidocaine may not be suitable for persons who have had a past reaction to any local anesthetic. Patients should discuss past adverse reactions to anesthetics with their physician before using the lidocaine patch. The lidocaine patch may also not be suitable for persons with a history of severe liver disease. Additionally, the lidocaine patch should be used with caution in persons receiving antiarrhythmic drugs.

Hand-washing is important after handling or applying the lidocaine patch. Contact with eyes should be avoided. The zipper pouch containing the lidocaine patches should be completely closed after opening, as the patches will lose potency if allowed to dry. Patches can be cut with scissors to the size and shape necessary to fit facial areas, but care should be used not to allow the material in the lidocaine patch to enter the eye. The lidocaine patch should never be chewed or ingested or used to relieve pain inside the mouth.

Side effects

As only minute amounts of lidocaine enter the bloodstream from the patch, side effects are few. Most patients tolerate normal use of the lidocaine patch well, but some patients may experience mild side effects. Localized tingling may occur. If a rash or burning sensation occurs after application, the patch should be removed and not reapplied until the irritation subsides. If any symptom becomes uncomfortable, patients should consult the prescribing physician.

Some patients may be allergic to topical lidocaine and the lidocaine patch. Medical treatment should be sought immediately if any of the following symptoms occur:

- cough
- difficulty breathing or swelling of the tongue
- dizziness, fainting, or loss of consciousness
- hives or swelling of the face
- trouble breathing

Other, less common side effects of the lidocaine patch may be serious, potentially indicating that too much medication is being absorbed into the body. A patient should seek medical treatment if experiencing:

- excessive, all-over numbness
- blurred or double vision
- ringing or buzzing in the ears

- uncontrollable nervousness, shaking
- slow heartbeat

Interactions

As the lidocaine patch is a topical treatment and only minute amounts of the drug are absorbed into the bloodstream, interactions with other drugs are few.

Drugs

The lidocaine patch may have rare negative interactions with digoxin (Lanoxin) or any medications for irregular heartbeat. Some antibiotics, antidepressants, and monoamine oxidase inhibitors (MAOIs) may adversely react with the lidocaine patch or lessen its effectiveness.

Resources

PERIODICALS

Bai, Y., et al. "Lidocaine Patch for Acute Pain Management: A Meta-Analysis of Prospective Controlled Trials." *Current Medical Research & Opinion* (January 28, 2015): e-pub ahead of print. <http://dx.doi.org/10.1185/03007995.2014.973484> (accessed February 17, 2015).

Derry, S., et al. "Topical Lidocaine for Neuropathic Pain in Adults." *Cochrane Database of Systematic Reviews* 7, art no. CD010958 (2014). <http://dx.doi.org/10.1002/14651858.CD010958.pub2> (accessed February 17, 2015).

To, D., I. Kossintseva, and G. de Gannes G. "Lidocaine Contact Allergy Is Becoming More Prevalent." *Dermatologic Surgery* 40, no. 12 (2014): 1367–72. <http://dx.doi.org/10.1097/DSS.0000000000000190> (accessed February 17, 2015).

WEBSITES

AHFS Consumer Medication Information. "Lidocaine Transdermal." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a603026.html> (accessed February 15, 2015).

Micromedex. "Lidocaine Topical." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/lidocaine-topical-application-route/description/drg-20072776> (accessed February 12, 2015).

Adrienne Wilmoth Lerner

Revised by Tracy Gardner Beno, RN

REVIEWED BY JAMES E. WAUN, MD, RPH

Lidoderm see **Lidocaine patch**

Linezolid

Definition

Linezolid is an antibiotic drug in the family of oxazolidinone drugs.



Zyvox (linezolid), 600 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Linezolid is used to treat severe or resistant bacterial infections primarily of the lungs (in particular, community-acquired pneumonia), skin, skin structures (for example, diabetic foot infections), and blood that are sensitive to oxazolidinone drugs. Resistant infections occur when the causative bacteria develop the ability to destroy antibiotics or block their actions.

Off-label use

Linezolid may be used off label in children to treat community-acquired pneumonia. It is also sometimes used to treat joint infections in artificial (prosthetic) joints, brain abscesses, and other brain infections.

Description

Linezolid is available in tablet, liquid suspension, and injectable forms. The medication is taken by mouth or administered through an intravenous (IV) line and must be prescribed by a physician.

Linezolid is available in the following forms and strengths:

- tablets, white, oval: available in 600 milligram (mg), imprinted with dosage and product name “ZYVOX”
- liquid suspension: reconstitutes to an orange-flavored suspension containing 100 mg of active drug per 5 milliliters (mL)

- injection (IV): contains either 200 mg of active drug per 100 mL of solution or 600 mg of active drug per 300 mL of solution

U.S. brand names

Linezolid is sold under the brand name Zyvox. A generic form is available for injection but not for oral use.

Canadian brand names

Linezolid is sold as Apo-Linezolid; Linezolid Injection; Sandoz-Linezolid; and Zyvoxam in Canada.

International brand names

Linezolid is sold under many different brand names internationally. For example, it is marketed in Kenya as Amizole 500, in India as Infulid, in Bangladesh as Linozid, in Bulgaria as Zolinid, and in Turkey as Zizolid. In some countries, linezolid is only one component of the medication, and there are other medications included in the formulation. In some locations, it is available only for veterinary, not human, use.

Recommended dosage

Recommended dosages are based on the amount of linezolid needed to treat the infection. In general, recommended adult dosages are 600 mg every 12 hours for 10–14 days. Other dosing formats may be followed for specific infections or circumstances. Duration of treatment is usually between 10 and 28 days.

Pediatric

Children under age 12 are dosed by weight. The IV dose is 10 mg per kilogram (kg, or 2.2 lb.) of body weight, or the oral dose may be taken every 8 hours for 10–14 days. Duration of treatment is usually between 10 and 28 days.

Children over the age of 12 are dosed as adults.

Precautions

Linezolid can cause a condition called serotonin syndrome in susceptible individuals. People at risk for this disorder include:

- individuals who are taking antidepressant medications, especially monoamine oxidase inhibitors (MAOIs) such as isocarboxazid, phenelzine, rasagiline, selegiline, and tranylcypromine, or who have taken any of these drugs within the two weeks prior to initiating linezolid treatment
- individuals who eat foods that contain large amounts of tyramine (found in aged cheeses, sauerkraut, broad beans, soy, beer, red wine, and cured meats like salami)

KEY TERMS

Abscess—A localized pocket of pus due to infection.

Anaphylaxis—A severe, systemic allergic reaction that can be potentially life threatening.

Carcinoid tumor—A slow-growing tumor that produces hormones. Often originates in the lungs or gastrointestinal system.

Community-acquired—Describing an infectious disease that is passed among individuals who have close contact with one another.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Pheochromocytoma—A tiny tumor within the adrenal gland, which produces the hormones epinephrine and norepinephrine, resulting in episodes of high blood pressure, shakiness, and headache.

Pregnancy category—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies

have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk, but there are no human studies, or adverse effects have been seen in animals but not in well-controlled human studies. Category C: No adequate human or animal studies exist, or adverse fetal effects have been seen in animal studies, but there is no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk. Risks outweigh any benefits.

Prosthetic joint—An artificial joint, implanted to take the place of a damaged or destroyed joint.

Resistance—A characteristic developed by some organisms that allows them to escape the effects of certain antibiotics or to destroy the antibiotic.

Secondary infection—An infection by a microbe that occurs because the body is weakened by a primary infection caused by a different kind of microbe; also called an opportunistic infection.

Serotonin syndrome—A cluster of symptoms due to too much of the neurotransmitter serotonin, resulting in a high heart rate, shivering and shaking, sweating, fever, overactive reflexes, diarrhea, confusion, hallucinations, agitation, and irritability.

- individuals with a carcinoid tumor (a type of lung or gastrointestinal tumor that produces serotonin-like chemicals)

This drug should be taken for the entire length of the prescription, even if symptoms subside. Failure to take a complete course of the medication can result in return of symptoms.

Use over a long period of time can increase the risk of developing another fungal or bacterial infection (secondary infection). *C. difficile*-associated diarrhea and pseudomembranous colitis have both been associated with long-term use of linezolid, even months after the drug has been discontinued.

Many antibiotics make the skin more sensitive to sun exposure and tanning lights, resulting in more easily (and potentially severely) burned skin.

Pregnant or breastfeeding

Linezolid has not been well studied in pregnant women. This drug is a pregnancy category C drug, meaning that the possibility of harm to a developing fetus

cannot be excluded. Women who are pregnant or breastfeeding should tell their doctor before taking linezolid, and it should be used only if the benefits clearly outweigh the risks. This drug can pass into breast milk and may cause diarrhea, yeast infection, or allergic reaction in the nursing child. Caution should be used in lactating women.

Other conditions and allergies

Individuals with a history of kidney problems or on dialysis should tell their doctor before taking this drug.

Caution should be taken in individuals with a history of high blood pressure, pheochromocytoma, blood disorders, hyperthyroidism, or seizures. People with diabetes who take this drug may have unpredictable drops in blood sugar. Individuals with phenylketonuria should be advised against using the suspension, because it contains aspartame, which converts into phenylalanine.

Individuals who are allergic to linezolid or any form of oxazolidinone drugs (such as Tedizolid) should not take linezolid. Individuals with a history of severe

allergies, asthma, or prior reactions involving anaphylaxis, hives, or the severe swelling called angioedema are at higher risk for serious reactions to linezolid.

Side effects

Serious and sometimes fatal reactions can occur in individuals who are allergic to oxazolidinone drugs. Anyone who has had a severe reaction to any drug should alert the physician before taking this drug.

The most common adverse side effects of linezolid for all age groups tend to be mild. They include:

- upset stomach
- loose stools or diarrhea
- nausea and vomiting
- headache
- dizziness
- difficulty sleeping

These side effects should be brought to the doctor's attention if they do not go away within a few days.

Whitish vaginal discharge or white coating of the tongue and inside of the mouth should also be reported to the doctor.

A doctor should be notified immediately if any of these less common but more serious side effects occur:

- wheezing, hoarseness, difficulty breathing or swallowing—may indicate a severe allergic reaction and require immediate medical attention
- severe skin rash, itching, hives, blistering or peeling of the skin
- fever
- swelling
- yellowing of the skin
- vaginal itching or discharge (females)
- seizures
- abdominal pain with fever
- confusion, problems with thinking, hallucinations, memory loss
- difficulty with coordination
- easy bruising or bleeding
- vision changes
- seizures

Signs of serotonin syndrome should also be immediately reported to the doctor, including:

- fast heart rate
- shivering and shaking
- sweating
- fever

- overactive reflexes
- diarrhea
- confusion
- hallucinations
- agitation
- irritability

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herb, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Linezolid is known to interact with the following pharmaceutical drugs. Other interactions are possible. An individual who develops any unusual or unexpected symptoms should contact a physician.

- Concomitant use of these agents increases risk of serotonin syndrome: anilidopiperidine opioids, antiemetics, antipsychotic agents, buprenorphine, **buspirone**, **carbamazepine**, catechol-O-methyltransferase (COMT) inhibitors, **cyclobenzaprine**, dapoxetine, **dexmethylphenidate**, meperidine, **metoclopramide**, **mirtazapine**, nefazodone, pholcodine, selective serotonin reuptake inhibitors (SSRIs), trazodone, or tricyclic antidepressants.
- Linezolid use may increase the risk of problematic side effects when administered with the following agents: apraclonidine, atomoxetine, bezafibrate, brimonidine, **clozapine**, dipyrrone, domperidone, hydrocodone, **hydromorphone**, hypoglycemic agents, isometheptene, levodopa, lithium, maprotiline, **methadone**, methyl-dopa, mianserin, **morphine**, oxycodone, oxymorphone, pizotifen, reserpine, **tramadol**, or tryptophan.
- Linezolid use may decrease the effects of bacillus Calmette–Guérin (BCG) and typhoid vaccines.
- Linezolid use may increase blood levels of betahistine.
- Linezolid use may increase the possibility of high blood pressure when used with **bupropion**, dexmethylphenidate, diethylpropion, levonordefrin, **methylphenidate**, sympathomimetics, or tetrahydrozoline.
- Women using **oral contraceptives** should ask their healthcare provider if they need to use a second form of contraception while using linezolid, as some antibiotics can interfere with the effectiveness of birth control pills.

produced by the pancreas that raises low blood glucose. One of the main advantages of liraglutide is that it stimulates insulin secretion only when blood glucose levels are higher than normal, which means that low blood sugar (hypoglycemia) and its related symptoms do not occur.

Liraglutide has been evaluated as a treatment for obesity in four clinical trials with over 5,000 patients. In 2014, the FDA approved liraglutide for managing chronic weight problems in people with high body mass index (BMI). Candidates for liraglutide have a BMI of 27 to 30 or higher, indicating overweight or obese status. To receive liraglutide, they must also have at least one weight-related condition, such as hypertension, high cholesterol, or type 2 diabetes. Liraglutide helps control weight gain by decreasing appetite and lowering the levels of circulating lipids called triglycerides. Liraglutide also promotes a feeling of fullness (satiety) while eating, which may help reduce the quantity of food consumed. Liraglutide has been evaluated for weight loss in women with polycystic ovary syndrome (PCOS), but additional studies are needed to confirm its effectiveness in this population.

For best results in managing weight in overweight and obese adults, liraglutide is recommended to be used in conjunction with a reduced-calorie diet and regular exercise.

U.S. brand names

The antidiabetic formula of liraglutide is sold in the United States under the brand name Victoza. As a treatment for obesity, it is sold under the brand name Saxenda.

Canadian brand names

In Canada, liraglutide is sold under the brand name Victoza.

International brand names

Internationally, liraglutide is sold under the brand name Victoza.

Recommended dosage

Liraglutide is formulated as an injectable drug and is prepared in a prefilled injection pen containing a 3 mL solution, equal to 18 mg of liraglutide. Subcutaneous injections are administered at home by the patient or by a caregiver, or by a healthcare professional if the patient is in a long-term care facility. The typical dosage for controlling blood glucose levels in type 2 diabetes mellitus is 1.2 mg once a day. Dosages at 1.8 mg or higher are not recommended. To ensure that blood glucose levels are controlled, the drug is often

KEY TERMS

Glucagon—A peptide hormone produced by the pancreas. It acts to increase low blood glucose levels.

Hyperglycemia—High blood glucose (blood sugar).

Hypoglycemia—Low blood glucose (blood sugar).

Incretins—Metabolic hormones that reduce blood glucose levels by increasing insulin secretion.

Satiety—A feeling of fullness or satisfaction after consuming a meal, which may reduce the amount of food consumed.

Sulfonylureas—Antidiabetic drugs that help manage type 2 diabetes mellitus by increasing the release of insulin from beta cells in the pancreas.

Thiazolidinediones—Medications used to treat type 2 diabetes mellitus; also known as glitazones. These drugs activate certain nuclear receptors, which increases transcription of specific genes and decreases transcription of other genes. This activity decreases insulin resistance and increases proteins involved in the metabolism of fats and glucose, ultimately decreasing lipid levels and free fatty acids in the blood.

given in combination with other antidiabetic drugs, such as **metformin**, and either a sulfonylurea or thiazolidinedione.

When used for weight control, the standard dosage of liraglutide is once-daily subcutaneous injections of 3 mg.

Precautions

Liraglutide should not be used by patients with insulin-dependent type 1 diabetes mellitus. Diabetic patients who are in a state of diabetic ketoacidosis, which requires insulin injection, should not take liraglutide.

Liraglutide is not recommended for patients who have glandular tumors (endocrine neoplasia type 2), who have a history of thyroid cancer, or who have been diagnosed with insulin-dependent diabetes. Patients should inform their physician about previous stomach or digestive problems, kidney or liver disease, high blood pressure, high triglycerides, pancreatitis, or gallstones. A history of alcoholism should also be reported.

Liraglutide has been found to cause thyroid C-cell tumors in animal studies using male and female rats and

PATIENT PROFILE

Liraglutide (Victoza) was prescribed for a 54-year-old woman who had been diagnosed with type 2 diabetes. Liraglutide is similar to a naturally occurring intestinal hormone involved in stimulating insulin secretion. It is formulated as an injectable drug and is used to help control blood glucose levels in patients with non-insulin-dependent diabetes. When liraglutide is injected, the normal rise in blood glucose levels that occurs after meals (hyperglycemia) is stopped by the increasing insulin secretion stimulated by the drug. Normal emptying of the stomach (gastric emptying) is also delayed, which stops secretion of glucagon, a peptide hormone that raises low blood glucose. Liraglutide is considered an ideal treatment for type 2 diabetes because it stimulates insulin secretion only when blood glucose levels are higher than normal, which successfully prevents the occurrence of low blood sugar (hypoglycemia) and its related symptoms. Although other drugs such as sulfonylureas help control type 2 diabetes by increasing insulin secretion, liraglutide is also able to promote a feeling of fullness (satiety) after eating, which also helps to reduce amounts of food consumed and reduce weight in diabetes patients.

The dosage of liraglutide for this patient was prescribed as 1.8 mg injected under the skin (subcutaneous injection) once a day using a prefilled injection pen. If she responded favorably to the drug, the doctor thought that blood glucose control could be maintained long-term without adding other antidiabetic drugs. The patient was advised that controlling blood glucose levels would also require adhering to a low-fat, low-carbohydrate diet, including nonstarchy vegetables, lean meat and fish, and

avoidance of carbonated sugary drinks and alcohol, as well as engaging in regular low-impact exercise like walking or swimming.

After the first four weeks of using liraglutide, the patient complained to her doctor of having persistent nausea and occasional vomiting and diarrhea. She expressed a strong desire to stop taking the drug and to restore her digestive condition to normal. Soon after, at a follow-up visit to her doctor's office, her laboratory tests indicated that she had achieved adequate glucose control, which was the goal of treatment. Nevertheless, since the patient was suffering from gastrointestinal problems that could possibly be dose related, the doctor reduced the dose of liraglutide to 1.2 mg per day. In addition, to ensure that blood glucose levels were still controlled at the lower dosage of liraglutide, the doctor recommended add-on therapy with metformin (Glumetza). Metformin is an oral antihyperglycemic drug that is often the first-line drug of choice for treating type 2 diabetes, and it also helps to reduce cholesterol levels. A sustained-release tablet of 500 mg was prescribed to be taken once a day. Again, four weeks later, the patient complained of continued digestive upsets with nausea and vomiting. At this point, her doctor discontinued liraglutide and substituted glimepiride (Amaryl), which was shown in studies to have a lower percentage of gastrointestinal upsets than liraglutide. The doctor prescribed glimepiride at 1 mg per day in combination with metformin. Within a few weeks, the patient had regained her digestive health and was able to maintain adequate glucose control over time.

mice. Tumor development is dependent on the dosage and duration of treatment. Although studies are under way, it is not yet known whether liraglutide causes thyroid C-cell tumors, such as medullary thyroid carcinoma, in humans. Patients are advised to consult their physician about associated risks, and patients already taking liraglutide should be aware of symptoms of thyroid tumors. Patients should inform their physicians about any personal or family history of thyroid cancer.

Pregnant or breastfeeding

Liraglutide carries the FDA pregnancy category C, meaning that animal studies have demonstrated risk to the fetus, but no controlled data from human studies exist. The medication should only be used in pregnant women if the benefits exceed potential risks to the fetus. Breastfeeding mothers should consult their physician before using this medication.

Other conditions and allergies

Before taking liraglutide, patients should inform their physician about any known allergies and any history of allergic reactions. Some patients may have allergic reactions to liraglutide. Signs of an allergic reaction may include hives; difficulty breathing; and swelling of the face, lips, tongue, or throat. Patients should stop taking liraglutide and report any signs or symptoms to the physician immediately.

Side effects

The delayed gastric emptying that supports the drug's effectiveness also produces some of its adverse effects. The most common side effects of liraglutide are headache; dizziness; upset stomach and loss of appetite; nausea and vomiting; diarrhea or constipation; and cold symptoms such as a stuffy nose, sore throat, sneezing,

and sinus pain. Patients may also feel tired, have back pain, or develop a mild skin rash or redness where the medication was injected. More serious side effects may include:

- swelling or a lump in the throat area
- hoarse voice, difficulty swallowing, or shortness of breath
- urinating more or less often than usual or significantly reduced urine
- weakness, confusion, increased thirst, fast or uneven heartbeats, or fluttering in the chest
- swelling, weight gain
- severe pain in upper abdomen, spreading to the back (pancreatitis)
- signs of infection such as fever, chills, sore throat, flu symptoms, and mouth sores
- easy bruising or bleeding (nosebleed or bleeding gums)

Allergic reactions to liraglutide may include signs such as hives; difficulty breathing; and swelling of the face, lips, tongue, or throat. All signs and symptoms that may represent side effects or possible allergic reactions should be reported to the physician as soon as they occur.

Interactions

Before taking liraglutide, patients should inform their physician about all medications being taken, including over-the-counter drugs and prescription drugs as well as vitamins, herbs, and supplements. Certain medications may need to be discontinued. This should be determined by the physician.

Drugs

Liraglutide may inhibit the activity of other oral drugs used for treating diabetes. Oral antidiabetic agents such as glipizide, glipizide/metformin (Metaglip), **glimepiride** (Amaryl), rosiglitazone (Avandaryl), **pioglitazone** (Duetact), glibenclamide (DiaBeta), glyburide (Micronase), glyburide/metformin (Glucovance), and others may lose their effectiveness if taken with liraglutide.

Resources

BOOKS

American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda, MD: ASHP, 2015.

WEBSITES

“Liraglutide.” Drugs.com. <http://www.drugs.com/mtm/liraglutide.html> (accessed February 28, 2015).

MedlinePlus. “Liraglutide Injection.” U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a611003.html> (accessed February 28, 2015).

.nih.gov/medlineplus/druginfo/meds/a611003.html (accessed February 28, 2015).

ORGANIZATIONS

American Society for Clinical Pharmacology and Therapeutics, 528 N Washington Street, Alexandria, VA 22314, (703) 836-6981, info@ascpt.org, <http://www.ascpt.org/>.

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

L. Lee Culvert

REVIEWED BY JAMES E. WAUN, MD, RPh

Lisdexamfetamine

Definition

Lisdexamfetamine is a medication used to treat attention deficit hyperactivity disorder (ADHD). It belongs to the class of drugs known as central nervous system (CNS) stimulants and acts on the neurological signaling chemicals norepinephrine and dopamine. Norepinephrine and dopamine are types of neurotransmitters involved in



Vyvanse (lisdexamfetamine), 70 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

normal brain function and have an effect on mood, concentration, and impulse control.

Purpose

Lisdexamfetamine is used to treat some of the symptoms of ADHD in both adults and children six years old and older. It is a CNS stimulant that improves memory, concentration, and impulse control. CNS stimulants remain the mainstay of ADHD therapy.

Description

Lisdexamfetamine acts as a prodrug, meaning that the chemical compound present in the swallowed pill is metabolized and altered to another, active drug once inside the body. After it is taken, lisdexamfetamine is converted to the active compound **dextroamphetamine** within the body, which has a therapeutic mechanism of action focused on the natural body chemicals norepinephrine and dopamine. Norepinephrine and dopamine are types of neurotransmitter in the nervous system, chemicals that neurons use to signal to one another for normal brain and body functioning. It is believed that a decrease in norepinephrine and dopamine levels contributes to ADHD. Dextroamphetamine increases the amounts of norepinephrine and dopamine left in the brain, which has an impact on the areas of the brain that involve attention span, judgment, response to external stimuli, memory, motor function, mental focus, and impulse control.

The prodrug compound is used in treatment because this formulation is thought to extend the period of time the drug is effective. The extended effective time mainly removes the need for re-dosing through the school day or workday. It is used for patients for whom this is a priority.

U.S. brand names

Lisdexamfetamine is sold under the brand name Vyvanse.

Recommended dosage

Lisdexamfetamine is given as an oral medication in pill form, taken once each morning. It is available in doses that range from 20 to 70 milligrams (mg). Patients are frequently reassessed for the need for treatment, as drugs for ADHD are avoided unless absolutely necessary. The dose chosen depends on individual patient response to the medication regarding its effectiveness and adverse effects. Patients are dosed at the lowest possible effective dose to avoid the development of adverse side effects. Slowly increasing the dose helps with minimizing side effects. The usual dose of

lisdexamfetamine in both adults and children six years old and older is 30 mg taken once a day. The dose is increased by 10 or 20 mg increments every week for a maximum of 70 mg a day as needed. Doses are lowered if side effects become intolerable.

Precautions

Lisdexamfetamine reactions vary from patient to patient, with some patients more sensitive to the medication and the development of side effects. Higher doses increase the risk of adverse events, so the lowest dose possible is used for treatment. Clinicians weigh the potential for benefit with lisdexamfetamine treatment against the potential undesirable outcomes when making treatment decisions.

Lisdexamfetamine has a high potential for abuse and should never be used for longer time periods or at higher doses than prescribed. Patients are often given “drug holidays”—for example, when school is over for the summer—during which they forgo medication to avoid the development of adverse effects. Caution is used in patients with a history of substance abuse and related disorders. Lisdexamfetamine causes withdrawal symptoms if stopped abruptly and needs to be tapered off.

There is an association between ADHD and Tourette syndrome. Patients with Tourette syndrome typically have involuntary movements or vocalizations known as tics. Patients who have Tourette syndrome with ADHD may find that the stimulant medications used to treat ADHD worsen their tics. Caution must be used in treating patients with motor tics, Tourette syndrome, or a family history of the disorder. Lisdexamfetamine may not be appropriate for use in these patients. Rare but serious reactions include severe elevations in blood pressure, heart arrhythmias, heart attack, stroke, seizures, toxic skin reactions, and sudden death. Some patients develop increased aggressiveness, psychosis, mania, or suicidality in the first weeks of use. Patients taking lisdexamfetamine are monitored closely for behavioral changes, especially when starting treatment or after dose changes. Cardiac function, heart rate, and blood pressure may also be monitored while taking lisdexamfetamine.

Pediatric

Children are especially at risk for behavioral side effects, and growth retardation may occur with prolonged use.

Pregnant or breastfeeding

Lisdexamfetamine is classified as category C for pregnancy, which means that either there are no adequate

KEY TERMS

Attention deficit hyperactivity disorder (ADHD)—A condition characterized by lack of concentration, impulsive or inappropriate behavior (relative to age level), and hyperactivity.

Bipolar disorder—Psychiatric mood disorder characterized by periods of manic behavior that may alternate with periods of depression, also known as manic depressive disorder.

Dopamine—A type of neurotransmitter involved in regulation of concentration, impulse control, judgment, mood, attention span, psychostimulation, and disease states such as addiction, ADHD, and depression.

Mania—Physiological state of hyperactivity experienced by patients with certain psychiatric illnesses involving inappropriate elevated mood, pressured speech, poor judgment, and sometimes psychotic episodes superimposed on the state of mania.

Monoamine oxidase inhibitors (MAOIs)—Type of antidepressant medication that affects various kinds of neurotransmitters, including serotonin.

Neurotransmitter—One of a group of chemicals secreted by a nerve cell (neuron) to carry a chemical message to another nerve cell, often as a way of

transmitting a nerve impulse. Examples of neurotransmitters include acetylcholine, dopamine, serotonin, and norepinephrine.

Norepinephrine—A type of neurotransmitter involved in regulation of concentration, impulse control, judgment, mood, attention span, psychostimulation, and disease states such as ADHD and depression.

Prodrug—The inactive form of a drug that is metabolized into an active compound inside the body.

Tic—Involuntary movements (such as twitching or facial grimacing) or vocalizations (such as throat clearing or barking) associated with Tourette syndrome.

Tourette syndrome—An inherited neuropsychiatric disorder characterized by the development of both motor and vocal tics. The tics are preceded by a feeling of tension or urgency in the affected individual until the tic behavior is performed and relieves the perceived feeling of tension.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

human or animal studies, or that adverse fetal effects were found in animal studies, but there is no available human data. The decision whether to use category C drugs in pregnancy is generally based on weighing the critical needs of the mother against the risk to the fetus. Other, lower-category agents are used whenever possible. There are data that suggest lisdexamfetamine is considered unsafe for use during breastfeeding.

Other conditions and allergies

Lisdexamfetamine may be contraindicated or may require caution in use in patients with high blood pressure, blood vessel disease, heart rhythm abnormalities, heart conditions or structural abnormalities, certain thyroid disorders, liver function impairment or liver disease, kidney function impairment, or glaucoma. Lisdexamfetamine may lower seizure threshold in some patients and may not be appropriate for use in patients with seizure disorder. Lisdexamfetamine is discouraged from use in patients with bipolar disorder, as it is more likely to induce a state of mania in these individuals than in those without bipolar disorder.

Side effects

Lisdexamfetamine has many side effects in addition to the intended treatment effect. Sensitivity to lisdexamfetamine varies among patients, and some patients may find that even lower doses are more than their body system can tolerate. Common reactions include rash, fever, sweating, dizziness, insomnia, anxiety, restlessness, mood swings, abdominal pain, nausea and vomiting, decreased appetite, weight loss, changes in blood pressure, tremor, dry mouth, diarrhea, tic exacerbation, shortness of breath, and visual disturbances.

Interactions

Patients should make their doctor aware of all medications and supplements they are taking before using lisdexamfetamine.

Drugs

Patients taking drugs that affect the liver may alter the metabolism of lisdexamfetamine, resulting in too little or too much of the drug in the body. Other drugs may also cause serious effects when used in combination

with lisdexamfetamine, such as serious heart rhythm abnormalities, excess nervous system stimulation, or blood pressure changes. Such medications and substances include the obesity drug sibutramine, some migraine medications such as ergotamines, and decongestants such as phenylephrine.

Use of the antipsychotic pimozide with lisdexamfetamine increases the risk of motor tics as a side effect of medication. Use of certain other antipsychotics, such as fluphenazine, increases the risk of psychosis. Antacids and the glaucoma and diuretic drug acetazolamide decrease the excretion of lisdexamfetamine and may cause toxic levels. Many antidepressants interact with lisdexamfetamine, as well. The antidepressant **bupropion** increases the risk of seizures when used with lisdexamfetamine, and **venlafaxine** may cause greater than expected weight loss when used with lisdexamfetamine.

A class of antidepressants known as monoamine oxidase inhibitors (MAOIs) increase the amount of norepinephrine and dopamine released into the brain and should not be used concurrently with lisdexamfetamine or its metabolites, as the combination may cause overstimulation of the central nervous system and toxicity. A patient switching from an MAOI to lisdexamfetamine will need to stop taking the MAOI for at least two weeks before starting treatment with lisdexamfetamine (and vice versa).

Herbs and supplements

Many herbal supplements also interact with lisdexamfetamine and may cause toxicity, including green tea and ginseng.

Food and other substances

Using alcohol while taking lisdexamfetamine may create toxic reactions in the body and should be avoided. Caffeine and marijuana derivatives may cause excessive stimulation, resulting in abnormal heart rhythm and blood pressure changes.

Resources

BOOKS

Brunton, Laurence L., et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill Medical, 2011.

Stargrove, Mitchell Bebel, et al. *Herb, Nutrient, and Drug Interactions: Clinical Implications and Therapeutic Strategies*. St. Louis: Mosby, 2007.

PERIODICALS

Dittmann, R. W., et al. "Treatment Response and Remission in a Double-Blind, Randomized, Head-to-Head Study of

Lisdexamfetamine Dimesylate and Atomoxetine in Children and Adolescents with Attention-Deficit Hyperactivity Disorder." *CNS Drugs* 28, no. 11 (2014): 1059–69.

Maneeton, N., et al. "Exploratory Meta-Analysis on Lisdexamfetamine versus Placebo in Adult ADHD." *Drug Design, Development, and Therapy* 8 (October 3, 2014): 1685–93.

McElroy, S. L., et al. "Adjunctive Lisdexamfetamine in Bipolar Depression: A Preliminary Randomized, Placebo-Controlled Trial." *International Clinical Psychopharmacology* 30, no. 1 (2015): 6–13.

McElroy, S. L., et al. "Efficacy and Safety of Lisdexamfetamine for Treatment of Adults with Moderate to Severe Binge-Eating Disorder: A Randomized Clinical Trial." *JAMA Psychiatry* (January 14, 2015): e-pub ahead of print. <http://dx.doi.org/10.1001/jamapsychiatry.2014.2162> (accessed February 25, 2015).

Weisler, R. H., et al. "Relationship of ADHD Symptoms and Global Illness Severity in Adults Treated with Lisdexamfetamine Dimesylate." *Postgraduate Medicine* 126, no. 5 (2014): 31–41.

WEBSITES

AHFS Consumer Medication Information. "Lisdexamfetamine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a607047.html> (accessed February 25, 2015).

U.S. Food and Drug Administration. "Vyvanse (Lisdexamfetamine Dimesylate) Capsules." <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm234015.htm> (accessed February 25, 2015).

ORGANIZATIONS

Children and Adults with Attention-Deficit/Hyperactivity Disorder, 4601 Presidents Drive, Suite 300, Lanham, MD 20706, (301) 306-7070, (800) 233-4050, Fax: (301) 306-7090, <http://www.chadd.org/>.

Mental Health America, 2000 N. Beauregard Street, 6th Floor, Alexandria, VA 22311, (703) 684-7722, (800) 969-6642, Fax: (703) 684-5968, <http://www1.nmha.org/>.

Maria Eve Basile, PhD

REVIEWED BY GREGORY A. PRATT, RPH

Lisinopril

Definition

Lisinopril is an oral, long-lasting medication for treating high blood pressure (hypertension). It is in the drug class known as angiotensin-converting enzyme (ACE) inhibitors.



Lisinopril, 30 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Lisinopril is approved by the U.S. Food and Drug Administration (FDA) for:

- treating hypertension in adults and children ages six and older
- treating acute myocardial infarction (heart attack)
- as adjunct therapy for heart failure

Hypertension causes more heart attacks and strokes than any other condition. It also increases the risk of heart failure, kidney failure, and dementia and is a major cause of death. Although people with slightly high blood pressure can sometimes control it with lifestyle changes—diet, exercise, weight control, limiting alcohol, and quitting smoking—or with a diuretic such as **hydrochlorothiazide** or chlorthalidone, hypertension can be hard to control. ACE inhibitors such as lisinopril are used by approximately 40 million people in the United States. Millions more people are unaware of their high blood pressure and are not receiving treatment.

Lisinopril is used alone or in combination with other medications for treating high blood pressure and in combination with other drugs for heart failure. It is also used to improve survival after a heart attack and to help prevent further heart attacks. Along with angiotensin-receptor blockers (ARBs), ACE inhibitors are the first-line treatment for lowering blood pressure in people with diabetes. ACE inhibitors lower the risk of heart failure by easing strain on the heart and slow the progression of

kidney disease in patients with and without diabetes. However, lisinopril does not cure hypertension or heart failure. Lisinopril is sometimes prescribed for other purposes.

Description

Lisinopril is a synthetic peptide (protein) derivative that inhibits ACE, an enzyme in the renin-angiotensin-aldosterone system (RAAS)—a signaling pathway that controls blood pressure. Low blood pressure and certain nerve impulses stimulate the kidneys to release renin, an enzyme that converts angiotensinogen to angiotensin I. ACE then converts angiotensin I to active angiotensin II. Angiotensin II is a peptide hormone and powerful vasoconstrictor that narrows blood vessels throughout the body and especially in the kidneys, thereby raising blood pressure. By inhibiting ACE, lisinopril reduces the amount of active angiotensin, enabling blood vessels to relax and dilate, thus lowering blood pressure. This allows the blood to flow more easily and the heart to work more efficiently and with less strain. Angiotensin II also stimulates the secretion of aldosterone, adrenaline (**epinephrine**), and noradrenaline (norepinephrine) by the adrenal gland and the water-retaining hormone vasopressin in the pituitary gland. Aldosterone causes the kidneys to retain more water and sodium and to excrete more potassium, increasing total blood volume and blood pressure. Although the effects of lisinopril on hypertension and heart failure are believed to result primarily from inhibition of RAAS, lisinopril also lowers blood pressure in people with low-renin hypertension, although the blood pressure–lowering response to lisinopril is reduced in people of African ancestry, who usually have low-renin hypertension. Coadministration of lisinopril and hydrochlorothiazide lowers blood pressure further and eliminates any racial response differences. Hydrochlorothiazide is a diuretic (“water pill”) that helps the kidneys remove excess salt and water in the urine.

Lisinopril may be used alone, but it is often used along with other blood pressure–lowering drugs, including diuretics, beta-blockers, calcium channel blockers, or ARBs. Lisinopril is similar to other ACE inhibitors in its indications, contraindications, and side effects. It differs from other ACE inhibitors in that it is not metabolized by the liver and has a longer half-life (the length of time it stays in the body) and greater tissue penetration. People often try different ACE inhibitors to find the one that is most effective for them.

Lisinopril is supplied as 2.5, 5, 10, 20, 30, and 40 milligram (mg) oral tablets. It is also available as a combination drug with hydrochlorothiazide (Prinzide,

Zestoretic). Lisinopril should be stored at room temperature, in the tightly closed container it is supplied in, away from excess heat and moisture (not in the bathroom).

U.S. and Canadian brand names

The U.S. and Canadian brand names for lisinopril are Prinivil, developed and marketed by Merck, and Zestril, marketed by AstraZeneca.

International brand names

There are many international lisinopril brand names and generics, of which the most common are Prinivil and Zestril. Other brand names include Lisdene, Irumed, and Lisigamma.

Origins

Lisinopril was the third FDA-approved ACE inhibitor, after captopril (Capoten) and **enalapril** (Vasotec). Prinivil was approved in 1987 and Zestril in 1988. Generic lisinopril has been available in the United States since 2002.

Recommended dosage

The recommended dosage depends on the condition being treated.

- For hypertension, the initial dose is usually 10 mg once daily or 5 mg for patients taking diuretics. Depending on the blood pressure response, lisinopril may be gradually increased up to 40 mg daily. However, side effects are minimized with the lowest possible dose.
- For heart failure, the initial dose is 5 mg once daily, increased up to 40 mg daily if tolerated.
- For myocardial infarction, 5 mg is given within 24 hours of the attack, followed by 5 mg after 24 hours, and then 10 mg once daily.

It is best to take lisinopril at about the same time every day. A missed dose should be taken as soon as possible, unless it is almost time for the next dose, in which case the missed dose should be skipped and the regular dosing schedule resumed.

Pediatric

The initial lisinopril dose for children aged six and older is 0.07 mg per kilogram (kg, or 2.2 lb.) of body weight, up to a maximum of 5 mg once daily.

Other conditions and allergies

Dosage adjustments are needed in some patients with kidney disease, depending on their creatinine

KEY TERMS

Aldosterone—A hormone produced in the cortex of the adrenal gland that increases the reabsorption of sodium and water and the release of potassium in the kidneys.

Angioedema—Severe, painful, allergic swelling of the skin and sometimes other organs, including the mouth and throat; a rare side effect of lisinopril.

Angiotensin—A peptide hormone that narrows blood vessels (vasoconstriction), especially in the kidneys, and raises blood pressure.

Angiotensin-converting enzyme (ACE)—The enzyme that converts angiotensin I to active angiotensin II; inhibited by lisinopril.

Angiotensin-receptor blocker (ARB)—A blood-pressure-lowering drug that may be an alternative to an angiotensin-converting enzyme inhibitor such as lisinopril.

Diuretic—“Water pill”; a medication that increases urine excretion and removes water and salt from the body, which helps lower blood pressure.

Hydrochlorothiazide—A diuretic that is often used in combination with lisinopril.

Hyperkalemia—Excess potassium in the blood.

Hypertension—High blood pressure.

Hypotension—Low blood pressure.

Myocardial infarction—Heart attack; damage or death to heart muscle due to an insufficient blood supply.

Renin—An enzyme produced in the kidneys that controls the activation of the hormone angiotensin, which stimulates the adrenal glands to produce aldosterone.

Renin-angiotensin-aldosterone system (RAAS)—A signaling pathway that regulates blood pressure and is disrupted by lisinopril.

clearance rates. Creatinine is a waste material that is filtered out of the body by the kidneys; measuring the amount of creatinine in a patient's urine helps determine kidney function. For patients with kidney impairment and creatinine clearance of 10–30 milliliters (mL) per minute, the lisinopril dose is half the usual initial dose. The initial dose is 2.5 mg for patients within creatinine clearance less than 10 mL per minute or on hemodialysis.

Precautions

The following precautions should be taken while using lisinopril:

- Blood pressure should be checked regularly to monitor responses to lisinopril. Lab tests may also be ordered.
- Patients should tell their doctors and dentists that they are taking lisinopril before having any type of surgery.
- Patients should not stop taking lisinopril without consulting their doctor.
- Diarrhea, vomiting, not drinking sufficient fluids, profuse sweating, or lisinopril overdose can cause a drop in blood pressure, which may result in light-headedness and fainting.

Pediatric

The safety and effectiveness of lisinopril for hypertension in children aged 6 to 16 years old have been established, and no differences in adverse reactions have been identified between children and adults. Safety and effectiveness have not been established in children under age 6 or with poor kidney function.

Geriatric

No dosage adjustment is necessary in elderly patients. In one study, slightly more patients aged 75 years and older discontinued lisinopril because of kidney dysfunction compared with younger patients. No other differences in safety and effectiveness have been observed between younger and elderly patients, although some older individuals may be more sensitive to lisinopril.

Pregnant or breastfeeding

Lisinopril is in the FDA pregnancy category D—it may cause fetal injury or death. Lisinopril and other drugs that affect RAAS reduce fetal renal (kidney) function during the second and third trimesters and increase fetal and newborn injury and death. Lisinopril should be discontinued as soon as possible in women who become pregnant. Although it is not known whether lisinopril is excreted in human milk, because of the potential for serious adverse effects on the infant, women should either discontinue nursing or discontinue lisinopril.

Other conditions and allergies

Patients with a history of angioedema (an allergic condition that causes painful swelling and difficulty swallowing or breathing) or hypersensitivity reactions and patients with diabetes who are taking aliskiren should not take lisinopril. Patients should tell their doctor

and pharmacist if they are allergic to lisinopril, enalapril, benazepril (Lotensin), **captopril**, **fosinopril** (Monopril), moexipril (Univasc), perindopril (Aceon), **quinapril** (Accupril), **ramipril** (Altace), trandolapril (Mavik), or any other medications. Patients should tell their doctors if they have or have ever had heart or kidney disease, diabetes, lupus, or scleroderma. Patients with kidney impairment should have their renal function periodically monitored while taking lisinopril. Patients with high serum potassium (hyperkalemia) should have periodic serum potassium monitoring, since lisinopril can increase potassium in the body.

Side effects

The most common side effect of lisinopril is a dry, irritating cough. Like other blood pressure-lowering drugs, lisinopril can sometimes cause light-headedness or dizziness. Angioedema, a potentially dangerous reaction, occurs in fewer than 1% of patients, but it is five times more likely in people of African descent than in people of other racial groups. Angioedema is also more common in women, smokers, and patients with oral allergy syndrome. Common side effects occurring in at least 2% of patients, according to their condition, are:

- headache, dizziness, and cough in patients taking lisinopril for hypertension
- hypotension (low blood pressure) and chest pain in patients taking lisinopril for heart failure
- hypotension in patients taking lisinopril for acute myocardial infarction

Patients should consult their doctor if any of the following symptoms are severe or persistent:

- cough
- dizziness
- headache
- excessive tiredness
- nausea
- diarrhea
- weakness
- sneezing
- runny nose
- rash
- decreased sexual ability

The doctor should be called immediately if any of the following uncommon but serious side effects occur:

- swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs
- hoarseness
- difficulty breathing or swallowing

- fever, sore throat, chills, and other signs of infection
- yellowing of the skin or eyes
- light-headedness
- fainting
- chest pain
- hallucinations
- depressive symptoms or other mood alterations

Geriatric

Angioedema is somewhat more likely in people over age 65.

Interactions

It is very important that the doctor and pharmacist be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used or planning to be used by the patient, as well as any medications that the patient stops using while taking lisinopril. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Drugs

Drugs that may interact with lisinopril and require changing dosages or careful monitoring for side effects include:

- **aspirin** and other nonsteroidal anti-inflammatory drugs (NSAIDs) such as **indomethacin** (Indocin), which increase the risk of kidney impairment and loss of blood pressure-lowering effects
- diuretics, which may cause an excessive drop in blood pressure
- lithium (Eskalith, Lithobid), which may cause symptoms of lithium toxicity
- other drugs that inhibit the renin-angiotensin system, which may increase the risk of renal impairment, hypotension, and hyperkalemia
- gold-containing medications

Herbs and supplements

Potassium supplements can increase the risk of hyperkalemia.

Food and other substances

A low-salt or low-sodium diet may be prescribed. Patients should consult their doctor before using salt substitutes containing potassium.

Resources

OTHER

U.S. Food and Drug Administration. "Full Prescribing Information." http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019777s057lbl.pdf (accessed February 15, 2015).

WEBSITES

American Heart Association. "Types of Blood Pressure Medications." http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/PreventionTreatmentofHighBloodPressure/Types-of-Blood-Pressure-Medications_UCM_303247_Article.jsp (accessed February 15, 2015).

Bayer Health Care. "The Renin-Angiotensin-Aldosterone System (RAAS)." <http://www.bayerpharma.com/en/research-and-development/research-focus/cardiovascular/raas/index.php> (accessed February 15, 2015).

MedlinePlus. "Lisinopril." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a692051.html> (accessed February 15, 2015).

"Treating High Blood Pressure: Is an ACE Inhibitor Drug Right for You?" *Consumer Reports*. http://www.consumerreports.org/health/resources/pdf/best-buy-drugs/2pager_ACEIs.pdf (accessed February 15, 2015).

U.S. Food and Drug Administration. "Zestril (Lisinopril) Tablets." <http://www.fda.gov/safety/medwatch/safetyinformation/ucm165413.htm> (accessed February 15, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY JAMES E. WAUN, MD, RPh

Lithium

Definition

Lithium is a naturally occurring element that is classified as an antimanic drug.

Purpose

Lithium is commonly used to treat mania and bipolar depression (manic depression). Less commonly, lithium is used to treat certain mood disorders, such as schizoaffective disorder and aggressive behavior and



Lithium, 300 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

emotional instability in adults and children. Lithium is rarely used to treat depression in the absence of mania. When this is the case, it is usually taken in addition to other antidepressant medications.

Description

The way lithium works in the body is unclear, but its therapeutic benefits are probably related to its effects on electrolytes such as sodium, potassium, magnesium, and calcium. The drug is available in 300 milligram (mg) tablets and capsules, 300 mg and 450 mg sustained-release tablets, and a syrup containing approximately 300 mg per teaspoonful.

The therapeutic effects of lithium may appear slowly. Maximum benefit is often not evident for at least two weeks after starting the drug. People taking lithium should be aware of this and should continue taking the drug as directed even if they do not see immediate changes in mood.

U.S. brand names

Lithium is available in the United States under the brand name Lithobid. It is primarily sold under its generic name.

Origins

Lithium was first noted as a possible treatment for depression in the 1880s, and in the 1950s it was seen to improve the symptoms of bipolar disease.

Recommended dosage

Depending on the patient's medical needs, age, weight, and kidney function, doses of lithium can range from 600 to 2,400 mg per day, although most patients will be stabilized on 600 to 1,200 mg per day. Patients who require large amounts of lithium often benefit from the addition of another antimanic drug, which may allow the dose of lithium to be lowered.

Generally, lithium is taken two or three times daily. However, the entire dose may be taken at once if the physician believes that a single-dose program will increase patient compliance. The single-dose schedule is especially helpful for people who are forgetful and may skip doses on a multiple-dose schedule. Additionally, evidence indicates that once-daily doses are associated with fewer side effects.

More than with any other drugs used in the treatment of mental disorders, it is essential to maintain lithium blood levels within a certain narrow range to derive the maximum therapeutic benefit while minimizing serious negative side effects. It is important that patients have their blood levels of lithium measured at regular intervals.

Lithium may be taken with meals to help decrease any stomach upset. Extended-release tablets must be swallowed whole and should not be crushed or chewed.

Precautions

Because lithium intoxication may be serious and even life-threatening, blood concentrations of lithium should be measured weekly during the first four weeks of therapy and less often after that.

Patients taking lithium should have their thyroid function monitored and should maintain an adequate sodium (salt) and water balance. Dosage reduction or complete discontinuation may be necessary during infection, diarrhea, vomiting, or a prolonged fast.

Lithium should be discontinued 24 hours before major surgery, but it may be continued normally for minor surgical procedures.

Geriatric

Individuals over age 60 should discuss the risks and benefits of lithium treatment with their doctors before beginning therapy.

Pregnant or breastfeeding

Lithium is in pregnancy category D, meaning that it has known adverse effects on a fetus. It is also present in breast milk and can pass on to the infant. Still, the drug

KEY TERMS

Bipolar depression—Depression with the presence of at least one manic episode.

Mania—An elevated or euphoric mood or irritable state that is characteristic of bipolar disorder. Mania is characterized by mental and physical hyperactivity, disorganization of behavior, and inappropriate elevation of mood.

Tremor—Involuntary shaking.

may need to be used in some cases where the benefits outweigh the risks.

Other conditions and allergies

Lithium should not be used, or should be used only with very close physician supervision, in patients with kidney impairment, heart disease, and other conditions that affect sodium balance.

Side effects

Tremor is the most common neurological side effect. Lithium tremor is an irregular, nonrhythmic twitching of the arms and legs that is variable in both intensity and frequency. Lithium-induced tremors occur in approximately half of people taking this medication. The chance of tremors decreases if the dose is reduced. Acute lithium toxicity (poisoning) can result in neurological side effects, ranging from confusion and coordination impairment, to coma, seizures, and death. Other neurological side effects associated with lithium therapy include lethargy, memory impairment, difficulty finding words, and loss of creativity.

About 30%–35% of patients experience excessive thirst and urination, usually due to the inability of the kidneys to retain water and sodium. However, lithium is not known to cause kidney damage.

Lithium inhibits the synthesis of thyroid hormone. About 10%–20% of patients treated with lithium develop some degree of thyroid insufficiency, but they usually do not require supplementation with thyroid hormone tablets.

Gastrointestinal side effects include loss of appetite, nausea, vomiting, diarrhea, and stomach pain. Weight gain is another common side effect for patients receiving long-term treatment. Changes in saliva flow and enlargement of the salivary glands may occur. An increase in tooth cavities and the need for dental care among patients taking lithium has been reported.

Skin reactions to lithium are common but usually can be managed without discontinuing lithium therapy. Lithium may worsen folliculitis (inflammation of hair follicles), psoriasis, and acne. Thinning of the hair may occur, and, less commonly, hair loss may be experienced. Swollen feet are an uncommon side effect that responds to dose reduction.

Electrocardiographic abnormalities may occur with lithium therapy, but significant cardiovascular effects are uncommon except as the result of deliberate or accidental overdose.

A mild to moderate increase in the number of white blood cells is a frequent side effect of lithium use. Conversely, lithium may slow the formation of red blood cells and cause anemia.

Interactions

Patients taking lithium should always be concerned that other medications they are taking may adversely interact with the drug and should consult their physician or pharmacists about potential interactions.

Drugs

The following list represents just some of the medications that lithium may interact with to either (a) increase or decrease the effectiveness of the lithium or (b) increase or decrease the effectiveness of the other drug:

- amiodarone, an antiarrhythmic drug
- angiotensin-converting enzyme (ACE) inhibitors such as captopril, **lisinopril**, or **enalapril**
- antacids containing sodium bicarbonate
- anticonvulsants such as **phenytoin** and **carbamazepine**
- antidepressants
- antidiabetic therapy
- asthma drugs such as theophylline and aminophylline
- calcium channel blockers such as verapamil or **diltiazem**
- diuretics (water pills) such as **hydrochlorothiazide**, **furosemide**, or ethacrynic acid
- **metronidazole**, a commonly prescribed antibiotic used to treat infections
- muscle relaxants such as **methocarbamol**, **carisoprodol**, and **cyclobenzaprine**
- nonsteroidal anti-inflammatory drugs (NSAIDs) such as **ibuprofen** or naproxen

Resources

BOOKS

American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda: American Society of Health-System Pharmacists, 2015.

Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger Publications, 2013.

PERIODICALS

Aida, M. "Lithium in the Treatment of Bipolar Disorder: Pharmacology and Pharmacogenetics." *Molecular Psychiatry* (February 17, 2015): e-pub ahead of print. <http://dx.doi.org/10.1038/mp.2015.4> (accessed February 25, 2015).

Armstrong, Carrie. "ACOG Guidelines on Psychiatric Medication Use During Pregnancy and Lactation." *American Family Physician* 15, no. 78 (2008): 772–78.

WEBSITES

Micromedex. "Lithium." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/lithium-oral-route/description/drg-20064603> (accessed February 25, 2015).

National Alliance on Mental Illness. "Lithium." <http://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Lithium> (accessed February 25, 2015).

ORGANIZATIONS

Mental Health America, 2000 N. Beauregard Street, 6th Floor, Alexandria, VA 22311, (703) 684-7722, (800) 969-6642, Fax: (703) 684-5968, <http://www1.nmha.org/>.

National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.

National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

Jack H. Raber, PharmD

Revised by Ruth A. Wienclaw, PhD

REVIEWED BY GREGORY A. PRATT, RPh

Lodine see **Etodolac**

Lofibra see **Fenofibrate**



Loperamide, 2 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Patients take loperamide to treat diarrhea, which is technically described as three or more loose or watery bowel movements each day, usually lasting for a period of two or three days. Loperamide may be used to control and relieve the symptoms of acute nonspecific diarrhea (the infrequent diarrhea that is not associated with an intestinal disorder) and of chronic diarrhea that is associated with Crohn's disease, ulcerative colitis, and other inflammatory bowel diseases.

Loperamide is also used in patients who have had ileostomy surgery. An ileostomy is an opening in the abdominal wall for the purpose of removing fecal matter, which is then collected in a bag (known as a colostomy bag or pouch) on the outside of the body. Ileostomy is necessary when the last section of an individual's intestine (the large intestine) is not functioning properly. In this circumstance, loperamide is used to reduce the volume of the fecal matter before it is removed.

Description

Loperamide modifies intestinal processes and tones the anal sphincter to ultimately treat diarrhea. This drug is an opioid-receptor agonist, which means that it interferes with the action of certain receptors. Receptors are sites on a cell membrane that respond to particular substances. When substances bind to receptors, they can affect the

Loperamide

Definition

Loperamide, also known as loperamide hydrochloride, is an over-the-counter and by-prescription antidiarrheal drug.

function of the cell. In the case of loperamide, the drug interferes with the normal binding of receptors in the cells of the myenteric plexus, which is a collection of nerve fibers that help control muscles in the intestinal walls and regulate the movement of intestinal contents—the digesting food, or fecal matter—through the intestines. By doing so, loperamide slows that movement, which is otherwise known as intestinal motility. This retains fecal matter in the intestines longer, and during this extended time additional water is removed, allowing the fecal matter to become more solid.

In addition, loperamide lessens the urge to defecate and tones and improves the function of the anal sphincter (the ring of muscle that controls the exit of feces from the body). These actions further assist in lengthening the time that fecal matter remains within the intestines.

Loperamide hydrochloride is sold as 2 milligram (mg) capsules or chewable tablets and as a liquid formulation of 1 mg loperamide hydrochloride per 7.5 milliliters (mL). All formulations are taken by mouth.

U.S. brand names

Loperamide is available in the United States under the brand names Imodium, Imodium A-D, Imodium A-D EZ CHEWS, Imodium A-D Liquid for Use in Children, and Imodium Multi-Symptom Relief. The latter includes simethicone, which is a compound that reduces symptoms of excess gas, such as bloating and discomfort.

Canadian brand names

Loperamide is sold in Canada under the brand names Imodium, APC-Loperamide, Apo-Loperamide, and Riva-Loperamide, and Sandoz Loperamide.

International brand names

Loperamide is available internationally as Imodium and a variety of other brand names, including:

- Chemists' Own Diarrhoea Relief
- Diarstop
- Elissan
- Fortasec
- Gastro-Stop
- Harmonise
- Imomed
- Indiaral
- Lexadium
- Lomotil
- Lopedium

- Lopemic
- Loperam
- Loperamid
- Salvacolina
- Seldiar
- Stoperan
- Vacontil

Origins

Janssen Pharmaceuticals initially developed loperamide in 1969. Choosing the brand name Imodium, the company applied for and received a patent in 1973 for the drug. The U.S. Food and Drug Administration (FDA) granted approval for the drug in December 1976.

Recommended dosage

The typical adult dosage for use in treating chronic diarrhea is:

- In capsule or tablet form, the initial dosage is 4 mg followed by 2 mg after the passage of loose or watery stool until the diarrhea is controlled. Once controlled, the dosage is reduced to meet individual requirements. The maximum daily dose is 16 mg.
- In capsule or tablet form, the maintenance dosage is typically 4–8 mg per day, with a daily maximum of 16 mg.

Patients who do not see improvement in two days should consult a physician.

Pediatric

Children younger than 2 years old should not use loperamide. Dosages for children aged 2–12 years vary by age and the weight of the child. Children older than 12 years of age use the adult dosages.

To treat acute diarrhea, the dosages are:

- For children aged 2–5 years old and 28–44 lb. (13–20 kg), the first-day dosage is 1 mg three times a day. After the first day, subsequent doses of 1 mg per 22 lb. (10 kg) of body weight are administered after the passage of a loose stool, with a maximum daily dosage of 3 mg. Children in this age group should use only the liquid formulation.
- For children aged 6–8 years old and 44–66 lb. (20–30 kg), the first-day dosage is 2 mg two times a day. After the first day, subsequent doses of 1 mg per 22 lb. (10 kg) of body weight are administered after the passage of a loose stool, with a maximum daily dosage of 4 mg. Children in this age group may use either the liquid or capsule formulation.

KEY TERMS

Abdominal distention—The swelling or expansion of the abdomen.

Colon—The last part of the human intestine, located between the small intestine and the rectum. It is often called the large intestine, although the large intestine technically includes the cecum, rectum, and anus as well as the colon.

Diarrhea—Technically described as three or more loose or watery bowel movements each day, usually lasting for a period of two or three days.

Ileostomy—An opening in the abdominal wall for the removal of fecal matter from the intestine.

Ileus—A blockage of the intestines due to a lack of the normal abdominal muscle contractions known as peristalsis.

- For children aged 8–12 years old and more than 66 lb. (30 kg), the first-day dosage is 2 mg three times a day. After the first day, subsequent doses of 1 mg per 22 lb. (10 kg) of body weight are administered after the passage of a loose stool, with a maximum daily dosage of 6 mg. Children in this age group may use either the liquid or capsule formulation.

Parents should consult a doctor before using loperamide to treat chronic diarrhea in children, as dosage has not been established for this age group.

Geriatric

Dosage recommendations are the same for older adults as they are for younger adults.

Precautions

Patients who do not see improvement within 48 hours of beginning a regimen of loperamide or who experience bloody stools or a fever should consult the doctor. Patients who experience constipation, distension (swelling or expansion) of the abdomen, or ileus (a blockage of the intestines due to a lack of the normal abdominal muscle contractions known as peristalsis) should stop taking loperamide and consult the doctor.

Although extremely rare, allergic reactions including anaphylaxis and anaphylactic shock have been reported with the use of loperamide.

Patients who have diarrhea often require replenishment of fluids and electrolytes. Loperamide does not

replenish fluids or electrolytes, so additional measures should be taken to do so.

Pregnant or breastfeeding

Loperamide carries the FDA pregnancy category C, which indicates that animal studies have shown a risk to the fetus. A pregnant woman may wish to consult with a doctor to determine whether the benefits of loperamide outweigh the risks. It is further recommended that women do not take the drug while they are nursing, because small amounts of loperamide may transfer to breast milk.

Other conditions and allergies

Patients with liver (hepatic) disease or dysfunction should consult a doctor about the use of loperamide and, if they use the drug, should be monitored for potential toxicity. This drug is not recommended for patients who have ileus, megacolon (abnormal dilation of the colon), or toxic megacolon (megacolon with abdominal distension). AIDS patients should stop taking loperamide if they experience abdominal distention, as this represents a potentially dangerous side effect.

Side effects

Most patients tolerate loperamide well. Some rare side effects, however, do occur. They include:

- abdominal distension
- constipation
- loss of appetite
- severe stomach pain accompanied by nausea or vomiting
- skin rash
- dizziness or drowsiness that may affect the ability to drive a vehicle or operate heavy machinery
- dryness of the mouth

Interactions

Interactions with loperamide have been noted.

Drugs

The use of loperamide with certain other medications, including **diphenhydramine** (Benadryl) and **duloxetine** (Cymbalta), may cause dizziness, difficulty concentrating, or drowsiness, which may affect the alertness necessary for driving a vehicle or operating machinery. Patients should avoid these activities until they know how this combination of medications affects them.

PATIENT PROFILE

A 30-year-old man with a history of opioid and alcohol abuse had been self-medicating with an over-the-counter (OTC) antidiarrheal drug, loperamide (Imodium) 2 mg, to stop persistent diarrhea after traveling to South America on business. The diarrhea had continued for about ten days after his trip, usually after meals. At first, one 2 mg loperamide dose after experiencing diarrhea relieved abdominal cramping and the diarrhea effectively for a few hours, but it recurred after the next meal. When taking one or two tablets after experiencing diarrhea was no longer sufficient, he started taking more each time, sometimes hourly throughout a single day. The diarrhea was becoming chronic, and the man sought the advice of his family physician, who had treated him for many years and was familiar with his prior substance abuse and rehab treatment.

After hearing the patient's complaints of abdominal cramping and diarrhea, the doctor prescribed loperamide as 2 mg oral capsules to be taken as two to four capsules a day and one additional capsule after each occurrence of unformed stool, but no more than 16 capsules (32 mg) per day. The doctor was confident in prescribing loperamide for this patient, even with his prior addictive behavior, since the drug has low abuse potential. Although its chemical structure is similar to meperidine (Demerol) and diphenoxylate (Lomotil), which are opiate agonists that work by stimulating opiate receptors in the central nervous system, loperamide does not produce euphoric effects at normal therapeutic dosages.

Within two weeks after his visit with the doctor, the patient had refilled the prescription twice. Three weeks later he called his doctor's office asking for renewal of the prescription, explaining that he was still having chronic diarrhea. The office nurse called in the prescription and noted it on the patient's chart, which would be reviewed by the doctor. Knowing that each

prescription was for 30 capsules of loperamide, each with three refills, the doctor was concerned about the duration of the diarrhea and the apparent escalation of daily dosage. He felt that consultation with the patient at the four-week juncture was needed to evaluate the patient's condition and question the amount of loperamide he was taking.

At his follow-up visit, the patient admitted to buying OTC loperamide every few days from different retail sources and taking 10 to 12 of the 2 mg capsules hourly in his waking hours, or up to 240 mg a day. The doctor considered this dosage to be consistent with physical dependence, unrelated to controlling diarrhea. When asked, the patient denied that the drug had any euphoric effects, yet he still could not explain why he continued to take it, since he no longer had diarrhea and was sometimes even constipated. The doctor explained that he had become physically dependent on the drug and that discontinuation was necessary to protect his health and restore proper gastrointestinal and nervous system function. He urged the patient to discontinue the drug by cutting the dosage in half each day until he was no longer taking loperamide. However, within days, the patient reported that his attempt to stop the drug had resulted in sudden, acute withdrawal symptoms, including shortness of breath, chest pain, chills, abdominal discomfort, nausea, and vomiting. The doctor immediately admitted the patient to the local hospital and prescribed short-term treatment with methadone to relieve the patient's symptoms. Inpatient treatment consisting of a slow tapering of the methadone dose was able to treat the patient's physical dependence on loperamide successfully. Although gastrointestinal side effects and dizziness are fairly common with loperamide use, the type of physical dependence experienced by this patient is an exceptionally rare side effect of loperamide that may occur only when normal dosage is markedly exceeded.

Herbs and supplements

No specific interactions are noted, but patients should still inform their doctors about any herbs or supplements they are taking.

Foods and other substances

Alcohol consumption can exacerbate the drowsiness and dizziness that some patients experience when taking loperamide, especially when combined with certain drugs (e.g., diphenhydramine and duloxetine), so alcohol use should be avoided or at least limited.

Resources

BOOKS

- Dlugosz, Cynthia Knapp. "Diarrhea." In *The Practitioner's Quick Reference to Nonprescription Drugs*. 2nd ed. Washington, DC: American Pharmacists Association, 2012.
- Krinsky, Daniel L., et al, editors. *Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care*. 18th ed. Washington, DC: American Pharmacists Association, 2014.
- Lacy, Brian E. "Treatment Options for IBS with Diarrhea." In *Making Sense of IBS: A Physician Answers Your Questions about Irritable Bowel Syndrome*. 2nd ed. Baltimore, MD: Johns Hopkins University Press, 2013.

WEBSITES

"Imodium." RxList.com. <http://www.rxlist.com/imodium-drug.htm> (accessed March 6, 2015).

"Loperamide." Drugs.com. <http://www.drugs.com/cdi/loperamide.html> (accessed March 6, 2015).

MedlinePlus. "Loperamide." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682280.html> (accessed March 6, 2015).

Micromedex. "Loperamide (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/loperamide-oral-route/description/drg-20064573> (accessed March 6, 2015).

UK Department of Health. "Loperamide Hydrochloride (Loperamide 2mg Capsules)." NHS Choices. <http://www.nhs.uk/medicine-guides/pages/MedicineOverview.aspx?condition=Diarrhoea&medicine=Loperamide%20hydrochloride&preparationLoperamide%202mg%20capsules> (accessed March 6, 2015).

ORGANIZATIONS

American Gastroenterological Association, 4930 Del Ray Avenue, Bethesda, MD 20814, (301) 654-2055, (301) 654-5920, <http://www.gastro.org/>.

National Digestive Diseases Information Clearinghouse, 2 Information Way, Bethesda, MD 20892, (800) 891-5389, <http://www.digestive.niddk.nih.gov/>.

National Institute of Diabetes and Digestive and Kidney Diseases, 9000 Rockville Pike, Bethesda, MD 20892-2560, (301) 496-3583, <http://www.niddk.nih.gov/>.

Leslie A Mertz, PhD

REVIEWED BY GREGORY A. PRATT, RPH

Lopid see **Gemfibrozil**

Lopressor see **Metoprolol**

Lorazepam

Definition

Lorazepam, a mild tranquilizer in the class of drugs known as benzodiazepines.

Purpose

Lorazepam is used for management of anxiety, nausea and vomiting, insomnia, and seizures (the injectable form). It is also used prior to surgery to produce sedation, sleepiness, drowsiness, relief of anxiety, and a decreased ability to recall the events surrounding the surgery.



Lorazepam, 1 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

Lorazepam is a member of the benzodiazepine family. Benzodiazepines primarily work by enhancing the function of a certain naturally occurring brain chemical called gamma-aminobutyric acid (GABA), which is responsible for inhibiting the transmission of nervous impulses in the brain and spinal cord. At the same time, the enhancement of GABA in the brain decreases symptoms associated with anxiety. Lorazepam differs from drugs such as **diazepam** (Valium) and **chlordiazepoxide** (Librium) in that it is shorter acting and does not accumulate in the body after repeated doses.

Lorazepam is available in 0.5, 1, and 2 milligram (mg) tablets and in an injectable form.

U.S. brand names

Lorazepam is sold in the United States under the brand name Ativan. It is also available generically.

Recommended dosage

Lorazepam is taken several times daily by mouth (or injected) to treat anxiety. Dosage ranges from 1 to 2 mg taken every 8 to 12 hours. The maximum daily total dosage for anxiety is 10 mg given in two or three divided doses. For help with sleep, patients may take from 2 to 4 mg at bedtime. Doses taken before surgery range from 2.5 to 5 mg.

KEY TERMS

Anterograde amnesia—The inability to form new memories.

Benzodiazepines—A class of drugs that have a hypnotic and sedative action, used mainly as tranquilizers to control symptoms of anxiety.

Dependence—A state in which a person requires a steady concentration of a particular substance in order to avoid withdrawal symptoms.

Gamma-aminobutyric acid (GABA)—A neurotransmitter that helps to lower or reduce the level of excitement in the nerves, leading to muscle relaxation, calmness, sleep, and the prevention of seizures.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

Between 0.5 mg and 1 mg of lorazepam may be taken every 6 to 8 hours to help control treatment-related nausea and vomiting (nausea and vomiting that occur as a side effect of a drug or medical treatment). Two milligrams (mg) of lorazepam are often given half an hour before treatment to help prevent stomach upset. An additional 2 mg may be taken every four hours as needed.

The usual dose to treat seizures is 4 mg given intravenously (through a vein). This dose may be increased to 8 mg in patients who do not respond to the 4 mg dose.

Precautions

Lorazepam, like other drugs of this type, can cause physical and psychological dependence. Patients should not increase the dosage or frequency of this drug on their own, nor should they suddenly stop taking this medication. When stopping the drug, the dosage should gradually be decreased and then discontinued. If the drug is stopped abruptly, patients may experience agitation, irritability, difficulty sleeping, convulsions, and other withdrawal symptoms.

Drowsiness and sleepiness are common and expected effects of lorazepam. Patients should not drive, operate machinery, or perform hazardous activities that require mental alertness until they have a sense of how lorazepam will affect their alertness. The effects of an injection may impair performance and driving ability for 24–48 hours. The impairment may last longer in older patients and those taking other central nervous system depressants, such as some pain medications.

Lorazepam has been associated with the risk of developing anterograde amnesia.

Pediatric

Children under age 12 should not take lorazepam. Children between the ages of 12 and 18 may take the drug by mouth but not intravenously.

Geriatric

Patients over age 50 may experience deeper and longer sedation after taking lorazepam. These effects may subside with continued use or dosage reduction.

Pregnant or breastfeeding

Pregnant women and those trying to become pregnant should not take lorazepam. This drug has been associated with damage to the developing fetus when taken during the first three months of pregnancy. Similarly, women taking this drug should avoid breastfeeding.

Other conditions and allergies

Patients who are allergic to benzodiazepines should not take lorazepam. Those with narrow-angle glaucoma, pre-existing depression of the central nervous system, severe uncontrolled pain, or severe low blood pressure should not take lorazepam. This drug should be used with caution in patients with a history of drug abuse.

Side effects

Lorazepam may make patients feel dizzy, weak, unsteady, or clumsy. Less frequently, individuals may feel depressed, disoriented, nauseous, or agitated while taking this drug. Other side effects include headache, difficulty sleeping, rash, yellowing eyes, vision changes, and hallucinations. Redness and pain may occur at the injection site.

Patients may experience high or low blood pressure and difficulty breathing after an injection of lorazepam. Nausea, vomiting, dry mouth, and constipation may also occur. The patient's sex drive may decrease, but this side effect is reversible once the drug is stopped. Patients should alert their physician to any confusion, depression, excitation, nightmares, impaired coordination, changes in personality, changes in urinary pattern, chest pain, heart palpitations, or other side effects.

Interactions

Individuals should consult with their healthcare provider about potential drug interactions with lorazepam,

including interactions with over-the-counter drugs and supplements.

Drugs

Other central nervous system depressants can increase the drowsiness associated with this drug. Some over-the-counter medications depress the central nervous system. Patients should check with their doctors before starting any new medications while taking lorazepam.

Herbs and supplements

The herbal remedies kava kava and valerian may increase the effects of lorazepam.

Food and other substances

People should not drink alcoholic beverages when taking lorazepam and for 24–48 hours before receiving an injection prior to surgery.

Resources

BOOKS

Lacy, Charles F. *Drug Information Handbook with International Trade Names Index*. Hudson, OH: Lexi-Comp, Inc. 2011.

Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger Publications, 2013.

PERIODICALS

Chamberlain, J. M., et al. "Lorazepam vs. Diazepam for Pediatric Status Epilepticus: A Randomized Clinical Trial." *JAMA* 311, no. 16 (2014): 1652–60.

Huang, Y. C., et al. "Rapid Relief of Catatonia in Mood Disorder by Lorazepam and Diazepam." *Biomedical Journal* 36, no. 1 (2013): 35–39.

Izaute, M., and E. Bacon. "Effects of the Amnesic Drug Lorazepam on Complete and Partial Information Retrieval and Monitoring Accuracy." *Psychopharmacology* 188, no. 4 (November 2006): 472–81.

Verster, Joris C., Dieuwke S. Veldhuijzen, and Edmund R. Volkerts. "Is It Safe to Drive a Car When Treated with Anxiolytics? Evidence from On-the-Road Driving Studies During Normal Traffic." *Current Psychiatry Reviews* 1, no. 2 (June 2005): 215–25.

WEBSITES

National Alliance on Mental Illness. "Lorazepam (Ativan)." [http://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Lorazepam-\(Ativan\)](http://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Lorazepam-(Ativan)) (accessed February 25, 2015).

National Institute of Mental Health. "Anxiety Disorders." National Institutes of Health. <http://www.nimh.nih.gov/health/topics/anxiety-disorders/index.shtml> (accessed February 25, 2015).

U.S. National Library of Medicine. "Lorazepam (By Mouth)." Pubmed Health. <http://www.ncbi.nlm.nih.gov/pubmed-health/PMHT0010988> (accessed February 25, 2015).

U.S. National Library of Medicine. "Lorazepam—Lorazepam Tablet." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=24f766c1-f92b-4e48-b2f1-9d88b1b1be0c> (accessed February 25, 2015).

ORGANIZATIONS

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.

National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.

National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051 nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

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Losartan

Definition

Losartan potassium is an oral drug used for treating hypertension (high blood pressure) and kidney disease from type 2 diabetes (diabetic nephropathy). It is in the drug class of angiotensin II receptor blockers (ARBs) or angiotensin II receptor antagonists.

Purpose

Losartan is used alone or in combination with other drugs to treat hypertension and to treat kidney disease in individuals who have both type 2 diabetes and hypertension. Diabetic nephropathy is a major cause of illness and death in individuals with diabetes, and it is the leading cause of end-stage renal (kidney) disease worldwide. Losartan can control high blood pressure but does not cure it. Losartan is also used to decrease the risk of stroke in individuals who have both hypertension and left ventricular hypertrophy (LVH), a heart condition in which the walls on the left side of the heart become enlarged. Results from clinical trials in 2014 showed that losartan did not reduce LVH or fibrosis in such patients, and losartan may not decrease stroke risk in African Americans. Based on results from clinical trials,



Cozaar (losartan), 100 mg. (© Cengage Learning®.)

international guidelines recommend an ARB such as losartan following acute myocardial infarction (heart attack) in patients who cannot tolerate another common class of antihypertensive drugs—angiotensin-converting enzyme (ACE) inhibitors.

Off-label use

Losartan is used for other purposes. It may be used to treat Alport syndrome, an inherited disorder that damages small blood vessels in the kidneys. It is also sometimes used to treat congestive heart failure, in which the heart is unable to pump sufficient blood to the rest of the body. Initial studies suggested that losartan might slow enlargement of the aorta and help prevent aortic aneurysms in children and young adults with Marfan syndrome, an inherited disorder that leads to unchecked aortic growth and possible rupture, as well as other severe heart problems. However, a large clinical trial reported in 2014 that losartan was no more effective in slowing aortic growth than the standard treatment with **atenolol**, a beta-blocker that lowers blood pressure and slows the heart rate.

Description

Losartan is a selective, competitive ARB or angiotensin II receptor antagonist. Angiotensin II is a peptide hormone that is a powerful vasoconstrictor for narrowing

blood vessels throughout the body and especially in the kidneys, thereby raising blood pressure. Angiotensin II also stimulates the secretion of aldosterone by the adrenal gland. Aldosterone causes the kidneys to retain more water and sodium and to excrete more potassium, increasing total blood volume and blood pressure. Losartan blocks the binding of angiotensin II to angiotensin II receptor type 1 (AT1) and prevents the vasoconstricting and aldosterone-secreting effects of angiotensin II, thereby lowering blood pressure. Losartan and other ARBs interfere with the renin-angiotensin-aldosterone system (RAAS)—a signaling pathway that controls blood pressure.

Losartan enables the blood to flow more easily and the heart to work more efficiently, and its effects are relatively long lasting. Losartan also has diuretic effects that increase urine flow rate and the excretion of sodium, potassium, chloride, magnesium, uric acid, calcium, and phosphate. ARBs such as losartan may inhibit RAAS more completely than another class of drugs used for treating hypertension known as ACE inhibitors. ARBs may also be less likely to cause side effects such as cough, a severe allergic reaction called angioedema, and liver toxicity.

Losartan is available in film-coated tablets with 25, 50, and 100 milligram (mg) strengths. Losartan is also available in generic formulations and as an orphan drug for treating Marfan syndrome.

Losartan potassium tablets are taken by mouth, usually once or twice a day, with or without food, at about the same time each day. The tablets are stored at room temperature, away from excess heat, light, and moisture (not in the bathroom). Losartan liquid suspensions may be stored in the refrigerator for up to four weeks.

U.S. brand names

Losartan is sold under the brand name Cozaar in the United States.

Canadian brand names

Losartan is sold under the brand name Cozaar in Canada.

International brand names

Losartan is sold under a wide variety of brand names internationally; Cozaar is the most common international brand name.

Origins

Losartan potassium is one of eight ARBs approved by the U.S. Food and Drug Administration (FDA). Cozaar was originally approved in 1995.

KEY TERMS

Aldosterone—A steroid hormone produced by the adrenal cortex that regulates salt and water balance in the body.

Angioedema—Severe, painful, allergic swelling of the skin and sometimes other organs, including the mouth and throat.

Angiotensin II—A peptide hormone that narrows blood vessels (vasoconstriction), especially in the kidneys, and raises blood pressure.

Angiotensin II receptor blocker (ARB)—Angiotensin II receptor antagonist; a blood pressure-lowering drug, such as losartan, that blocks angiotensin II binding to its receptor.

Angiotensin-converting enzyme (ACE) inhibitor—A blood pressure-lowering drug that inhibits the enzyme that converts angiotensin I to active angiotensin II.

Antagonist—A drug, such as losartan, that blocks the action of a substance by binding to its receptor.

Beta-blocker—A drug that slows heart rate and lowers blood pressure by blocking beta-receptors for the hormones epinephrine (adrenaline) and norepinephrine.

Boxed warning—A warning label required by the U.S. Food and Drug Administration (FDA) for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Diuretic—“Water pill”; a medication that increases urine excretion and removes water and salt from the body, which helps lower blood pressure.

Hyperkalemia—Excess potassium in the blood.

Hypertension—High blood pressure.

Hypotension—Low blood pressure.

Left ventricular hypertrophy (LVH)—A heart condition in which the walls of the left side of the heart are enlarged.

Marfan syndrome—An inherited connective tissue disorder that leads to severe heart problems, including unchecked growth of the aorta, which can cause aortic rupture and death.

Nephropathy—Kidney impairment secondary to another condition, such as diabetes.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the FDA. It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Orphan drug—A drug that treats a rare disease.

Receptor—A molecule, usually a protein, inside or on the surface of a cell that binds a specific substance to initiate a series of events.

Renal—Referring to the kidneys.

Renin-angiotensin-aldosterone system (RAAS)—A signaling pathway that regulates blood pressure and is disrupted by losartan.

Stroke—The obstruction (ischemic) or rupture (hemorrhagic) of a blood vessel in the brain.

Type 2 diabetes—Sometimes called adult-onset diabetes, this disease prevents the body from properly using glucose (sugar) but can often be controlled with diet and exercise.

Vasoconstriction—Narrowing of blood vessels to increase blood pressure.

Recommended dosage

Losartan is usually initiated at 50 mg once daily and may be gradually increased based on blood pressure response. In general, the dose is adjusted monthly, with higher doses for high-risk patients:

- for hypertension, 25–100 mg in one or two daily doses
- for diabetic nephropathy in patients with type 2 diabetes and hypertension, 50–100 mg once daily
- for stroke reduction in patients with LVH and hypertension, 50 mg once daily, which may be increased to

100 mg once daily, possibly in combination with a thiazide diuretic

A missed dose should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the regular dosing schedule resumed.

Pediatric

For hypertension in children ages 6 through 16, the usual initial dose is 0.7 mg per kilogram (kg, or 2.2 lb.) of body weight once daily, with a maximum dose of 50 mg per day. The dose can be adjusted according to

the response, up to a maximum of 1.4 mg/kg or 100 mg per day. The pharmacist can prepare a liquid suspension for children who are unable to swallow tablets. Losartan is not recommended for children with kidney impairment.

Other conditions and allergies

No dose adjustment is necessary for adults with kidney impairment. The initial dose for patients with liver impairment or blood volume depletion or who are taking diuretics for hypertension is 25 mg per day.

Precautions

Losartan should be taken exactly as directed—no more or less—and should not be stopped without consulting the treating physician. Blood pressure should be checked regularly to monitor response. Although blood pressure may decrease during the first week of treatment with losartan, it can take three to six weeks to obtain the full benefit.

Additional precautions include:

- Losartan increases the risk of low blood pressure (hypotension) and high blood potassium (hyperkalemia).
- Losartan can cause dizziness, light-headedness, or fainting when rising quickly from a lying position, especially when first taking the drug, so it is important to get out of bed slowly and rest the feet on the floor for a few minutes before standing.
- Diarrhea, vomiting, sweating profusely, or not drinking sufficient liquids can cause a drop in blood pressure and light-headedness or fainting.
- Symptoms of losartan overdose can include dizziness, fainting, and fast or slow heartbeat.

Pediatric

The safety and effectiveness of losartan have not been established in children under age six.

Pregnant or breastfeeding

Losartan comes with a boxed warning against use during pregnancy. It is in the FDA pregnancy category D, which means that there is evidence of risk to the fetus. Drugs affecting the RAAS may cause malformations or fetal or newborn injury or death if taken during the second or third trimesters of pregnancy. Women who become pregnant while taking losartan should stop taking the drug immediately and call their healthcare provider. It is not known whether losartan passes into breast milk, but taking the drug while breastfeeding is not recommended.

Other conditions and allergies

Patients should tell their doctor and pharmacist if they are allergic to losartan, any ingredients in losartan tablets, or any other medications. Individuals with diabetes who are taking aliskiren (Tekturna, in Amturnide, Tekamlo, Tekturna HCT) should not take losartan. Caution is advised in patients who have or have ever had:

- angioedema or anaphylactic (severe allergic) reactions
- severe congestive heart failure
- kidney or liver disease
- low blood volume (volume depletion)
- renal artery stenosis (narrowing)

Losartan can worsen renal failure. Patients with atherosclerosis, heart failure, or diabetes with end-organ damage who use two RAAS-interfering drugs, such as an ARB and an ACE inhibitor, are at increased risk for hypotension, fainting, hyperkalemia, and impaired kidney function, including acute renal failure.

Side effects

Common side effects occurring in more than 10% of patients are:

- fatigue
- hypoglycemia (low blood sugar)
- weakness
- diarrhea
- anemia (low red blood cell counts)
- urinary tract infection
- chest pain
- cough, especially in patients who experienced cough with ACE inhibitor treatment

Less common side effects, occurring in 1%–10% of patients, are:

- upper respiratory infection
- hypotension
- dizziness
- cellulitis (connective tissue inflammation)
- gastritis (stomach-lining inflammation)
- nausea

Other possible side effects include:

- angioedema
- edema (swelling)
- headache
- malaise
- abdominal pain
- hyperkalemia

- back pain

Patients should contact their healthcare provider if any of the following symptoms are severe or persistent:

- dizziness
- leg, knee, or back pain
- muscle cramps or weakness
- diarrhea
- heartburn
- decreased sensitivity to touch

Other conditions and allergies

Serious allergic and other symptoms that require calling the doctor immediately are:

- swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs
- hoarseness
- difficulty breathing or swallowing
- chest pain

Interactions

It is very important that the doctor and pharmacist be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements that the patient is using or planning to use. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Drugs

Losartan should never be coadministered with aliskiren. Other drugs that can have potentially serious or life-threatening interactions with losartan and require close monitoring include:

- other RAAS-blocking drugs such as ACE inhibitors, including **benazepril**, **captopril**, **enalapril**, **fosinopril**, **lisinopril**, moexipril, perindopril, **quinapril**, **ramipril**, and trandolapril
- beta-blockers
- idelalisib and ivacaftor, which inhibit the metabolism of losartan
- lithium (Eskalith CR, Eskalith, Lithobid), because losartan's effects increase lithium's toxicity
- intravenous potassium phosphates, which increase potassium levels

Some 142 drugs can significantly interact with losartan and require close monitoring. Another 29 drugs are known to have minor interactions. Use of the

following common drugs with losartan may require changing dosages or monitoring carefully for side effects:

- **aspirin** and other nonsteroidal anti-inflammatory drugs (NSAIDs) such as **ibuprofen** (Advil, Motrin) and naproxen (Aleve, Naprosyn)
- selective COX-2 inhibitors such as **celecoxib** (Celebrex)
- diuretics, including potassium-sparing diuretics such as amiloride (Midamor), **spironolactone** (Aldactone), and triamterene (Dyrenium)
- **fluconazole** (Diflucan)
- phenobarbital
- **rifampin** (Rifadin, Rimactane)

Herbs and supplements

St. John's wort may decrease losartan levels. Patients should avoid:

- dong quai, which has estrogenic activity
- ephedra, yohimbe, and ginseng, which may worsen hypertension
- garlic, which may have an increased antihypertensive effect
- potassium supplements

Food and other substances

Patients may be prescribed a low-salt or low-sodium diet. Salt substitutes containing potassium should not be used without consulting a healthcare provider.

Resources

PERIODICALS

"Drugs to Treat Hypertension." *Journal of Psychosocial Nursing & Mental Health Services* 52, no. 2 (2014): 11–12.

Hara, Masahiko, et al. "Comparison of 5-Year Survival after Acute Myocardial Infarction Using Angiotensin-Converting Enzyme Inhibitor Versus Angiotensin II Receptor Blocker." *American Journal of Cardiology* 114, no. 1 (2014): 1–8.

Kolata, Gina. "Heart Drug Falls Short of Promise in a Study." *New York Times* (November 19, 2014): A14.

WEBSITES

"Losartan (Rx)—Cozaar." Medscape.com. <http://reference.medscape.com/drug/cozaar-losartan-342323#0> (accessed February 19, 2015).

MedlinePlus. "Losartan." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a695008.html> (accessed February 19, 2015).

University of Maryland Baltimore Washington Medical Center. "Losartan." Health Library, <http://www.mybwmc.org/library/41/077659> (accessed February 19, 2015).

U.S. Food and Drug Administration. "High Blood Pressure—Medicines to Help You." <http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118594.htm> (accessed February 19, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

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Losartan/hydrochlorothiazide

Definition

Losartan/hydrochlorothiazide is an oral combination drug for treating hypertension (high blood pressure) and hypertension with left ventricular hypertrophy (LVH), a heart condition in which the



Hyzaar (losartan/hydrochlorothiazide, 100 mg/25 mg).
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walls on the left side of the heart are enlarged. **Losartan** potassium is in the drug class of angiotensin II receptor blockers (ARBs) or angiotensin II receptor antagonists. **Hydrochlorothiazide** (HCTZ) is a diuretic. The combination drug is in the class known as ARB/HCTZ combos.

Purpose

Losartan/HCTZ is used to treat hypertension to help prevent strokes, heart attacks, and kidney problems. It is also used to lower the risk of stroke in patients with hypertension and an enlarged heart. It can help control high blood pressure but does not cure it, and it may not reduce stroke risk in African Americans. Lifestyle changes—including eating a diet low in fat and salt, maintaining a healthy weight, exercising at least 30 minutes on most days, limiting alcohol, and quitting smoking—can increase the benefits of losartan/HCTZ.

Off-label uses

Losartan/HCTZ is also used off label—without specific approval by the U.S. Food and Drug Administration (FDA)—to treat heart failure.

Description

Losartan is a selective, competitive ARB or angiotensin II receptor antagonist. Angiotensin II is a peptide hormone that narrows blood vessels throughout the body (vasoconstriction) and especially in the kidneys, thereby raising blood pressure. Angiotensin II also stimulates the secretion of aldosterone by the adrenal gland. Aldosterone causes the kidneys to retain more water and sodium and to excrete more potassium, thereby increasing total blood volume and blood pressure. By blocking the binding of angiotensin II to its type 1 receptors, losartan blocks the vasoconstriction and aldosterone-secreting effects of angiotensin II to relax blood vessels and lower blood pressure. By preventing angiotensin II-stimulated blood-vessel constriction and aldosterone secretion, losartan enables the blood to flow more readily and the heart to work more efficiently. Losartan interacts reversibly with both angiotensin II type 1 and type 2 (AT1 and AT2) receptors in many tissues, but it has 1,000 times more affinity for the AT1 receptor. It has relatively long-lasting effects.

HCTZ is a sulfonamide diuretic, or "water pill," that increases urine production and helps the kidneys rid the body of extra water and salt, which also lowers blood pressure.

Losartan potassium/HCTZ is supplied as oral tablets of various shapes and colors, composed of:

- 12.5 milligrams (mg) HCTZ and 50 mg losartan potassium
- 12.5 mg HCTZ and 100 mg losartan potassium
- 25 mg HCTZ and 100 mg losartan potassium

The tablets are stored at room temperature, away from light and moisture (not in the bathroom).

U.S. brand names

The U.S. brand name for losartan potassium/hydrochlorothiazide is Hyzaar.

Canadian brand names

Canadian brand names for losartan potassium/hydrochlorothiazide include:

- Hyzaar
- Hyzaar DS
- ACT Losartan/HCT
- Apo-Losartan/HCTZ
- Auro-Losartan HCT
- JAMP-Losartan HCTZ
- Losartan-HCT
- Losartan-HCTZ
- Mint-Losartan/HCTZ
- Mint-Losartan/HCTZ DS
- Mylan-Losartan/HCTZ
- PMS-Losartan/HCTZ
- Sandoz-Losartan HCT
- Sandoz-Losartan HCT DS
- Teva-Losartan/HCTZ

Origins

Hyzaar was originally approved by the FDA in 1995. There are multiple generic versions.

Recommended dosage

Dosages are based on the condition being treated and response to the medication. For replacement therapy in patients who have been taking losartan and HCTZ individually, the combination medication can be substituted for the individual dosages of each drug. The initial recommended dosage of losartan/HCTZ for hypertension is 12.5 mg HCTZ and 50 mg losartan once a day. This may be increased to a maximum of 25 mg/100 mg once per day or 12.5 mg/50 mg every 12 hours. Losartan/HCTZ can be taken with or without food. If the drug causes frequent urination, it should be taken at least four hours before bedtime to avoid having to urinate during the night. A missed dose should be taken as soon as possible, unless it is almost time for the next dose, in

which case the dose should be skipped and the regular dosing schedule resumed.

Other conditions and allergies

For patients with low blood volume (volume depletion), the initial losartan dose should be reduced to 25 mg once per day. Patients with kidney impairment and a creatinine clearance below 30 milliliters (mL) per minute should not take HCTZ or other thiazide-containing products and should instead take a loop diuretic. Creatinine is a waste material that is filtered out of the body by the kidneys. Measuring the amount of creatinine in a patient's urine helps determine kidney function.

Precautions

Precautions for losartan/HCTZ include:

- Losartan/HCTZ should be taken regularly, at about the same time each day, to obtain the most benefit.
- Patients should check their blood pressure regularly and notify their healthcare provider if blood pressure readings worsen or do not improve.
- Losartan/HCTZ may cause dizziness, so patients should not drive, operate machinery, or perform activities that require alertness until they know how the drug affects them.
- Losartan and HCTZ both can cause dizziness, light-headedness, or fainting when rising quickly from lying down, especially when first taking the drug. It is important to get out of bed slowly and rest the feet on the floor for a few minutes before standing. Alcohol increases these side effects.
- Severe sweating, diarrhea, or vomiting can increase the risk of light-headedness or dehydration (excess water loss). Patients should drink plenty of fluids, unless directed otherwise by their healthcare provider, and should contact their doctor if they have prolonged diarrhea or vomiting.
- Patients should be monitored for signs of fluid or electrolyte imbalances, including low blood levels of sodium (hyponatremia), chloride (hypochloremia), or potassium (hypokalemia) and increased alkalinity of the blood (alkalosis).
- HCTZ can increase sun sensitivity. Patients should avoid unnecessary or prolonged sun exposure, tanning booths, and sunlamps and wear protective clothing, sunglasses, and sunscreen outdoors.
- Laboratory and medical tests, such as kidney function and potassium levels, should be performed periodically to monitor drug responses and side effects.
- Doctors and laboratory personnel should be informed of losartan/HCTZ use before performing certain

KEY TERMS

Aldosterone—A steroid hormone produced by the adrenal cortex that regulates salt and water balance in the body.

Angiotensin II—A peptide hormone that narrows blood vessels (vasoconstriction), especially in the kidneys, and raises blood pressure.

Angiotensin II receptor blocker (ARB)—Angiotensin II receptor antagonist; a blood pressure–lowering drug, such as losartan, that blocks angiotensin II binding to its receptors.

Angiotensin-converting enzyme (ACE) inhibitor—A blood pressure–lowering drug that inhibits the enzyme that converts angiotensin I to active angiotensin II.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Dehydration—Abnormal depletion of body fluids, as from vomiting, diarrhea, or a diuretic.

Diuretic—“Water pill”; a medication, such as hydrochlorothiazide, that increases urine excretion and removes water and salt from the body, which helps lower blood pressure.

Electrolytes—Ions, such as potassium, calcium, sodium, and chloride, that are dissolved in bodily fluids such as blood and that regulate or affect most metabolic processes.

Hydrochlorothiazide (HCTZ)—A sulfonamide diuretic that is combined with losartan in a blood pressure combination drug.

Hyperkalemia—High blood potassium.

Hypertension—High blood pressure.

Hypokalemia—Low blood potassium.

Hypotension—Low blood pressure.

Left ventricular hypertrophy (LVH)—A heart condition in which the walls of the left side of the heart are enlarged.

Receptor—A molecule, usually a protein, inside or on the surface of a cell, that binds a specific substance, such as angiotensin II, to initiate a series of events.

Stroke—The obstruction (ischemic) or rupture (hemorrhagic) of a blood vessel in the brain.

Sulfonamides—Common drugs including hydrochlorothiazide and sulfa drugs.

Vasoconstriction—Constriction of a blood vessel.

laboratory tests, such as tests of parathyroid function, because the drug can cause false results.

- Patients should inform their primary physician and dentist about losartan/HCTZ use (and all other prescription and nonprescription drugs and herbal products) before having any type of surgery.

Pediatric

The safety and effectiveness of losartan potassium/HCTZ have not been established in pediatric patients.

Pregnant or breastfeeding

Losartan comes with a boxed warning against use during pregnancy. It is in the FDA pregnancy category D, which means that there is evidence of risk to the fetus. Losartan and drugs with similar mechanisms of action may cause fetal malformations or injury or death if taken during the second or third trimesters of pregnancy. Women who become pregnant while taking losartan should stop taking it immediately and call their

healthcare provider. Although it is not known whether losartan passes into breast milk, taking losartan while breastfeeding is not recommended. HCTZ passes into breast milk but is unlikely to harm the nursing infant.

Other conditions and allergies

Patients with certain conditions may need to use caution when taking losartan/HCTZ:

- Before taking losartan/HCTZ, patients should tell their doctor or pharmacist if they are allergic to losartan, HCTZ, sulfonamide antibiotics, or penicillin, or if they have any other allergies, including allergies to inactive ingredients in losartan/HCTZ.
- Vision problems known as acute transient myopia and acute angle-closure glaucoma have been reported with losartan/HCTZ, especially in patients with a history of sulfonamide or penicillin allergies.
- Patients should not take losartan/HCTZ if they have liver impairment, kidney impairment with creatinine

clearance below 30 mL per minute, or defective urination (anuria).

- Losartan/HCTZ should not be coadministered with aliskiren (Tekturna, in Amturnide, Tekamlo, Tekturna HCT) in patients with diabetes.
- Losartan/HCTZ can affect blood sugar levels in patients with diabetes. Blood sugar levels should be checked regularly, and diabetes medications, exercise programs, and diet may need adjustment.
- Patients should tell their healthcare provider if they have ever had gout, kidney or liver disease, lupus, asthma, high cholesterol, or dehydration.
- Blood-volume depletion should be corrected before administering losartan/HCTZ.
- Serum lithium levels should be monitored in patients receiving both lithium and HCTZ.
- Patients with atherosclerosis, heart failure, or diabetes with end-organ damage who use two drugs with a similar mechanism of action to losartan (such as an ARB together with an angiotensin-converting enzyme [ACE] inhibitor) are at increased risk for hypotension (low blood pressure), fainting, high blood potassium (hyperkalemia), and impaired kidney function, including acute renal failure. Patients taking losartan and in combination with a similar drug should be closely monitored for blood pressure, renal function, and electrolytes.

Side effects

Dizziness or light-headedness may occur when first taking losartan/HCTZ. Rising slowly from sitting or lying down reduces the risk. The treating physician should be notified promptly if these effects persist or worsen. Losartan/HCTZ also can cause dehydration or depletion of salts and minerals (electrolytes). The physician should be notified immediately if any of the following symptoms occur:

- extreme thirst
- very dry mouth
- decreased urination
- muscle cramps or weakness
- fast, slow, or irregular heartbeat
- confusion

Rare but serious side effects of losartan/HCTZ that require immediate healthcare provider notification include:

- fainting
- decreased vision
- eye pain

- symptoms of hyperkalemia, such as muscle weakness or slow or irregular heartbeat
- unusual change in the amount of urine (other than the normal increase from initiating a diuretic)

Side effects occurring in more than 10% of patients taking losartan are:

- fatigue
- hypoglycemia (low blood sugar)
- chest pain
- cough, especially in patients who developed a cough when taking an ACE inhibitor

Side effects occurring in 1%–10% of patients taking losartan are:

- diarrhea
- urinary tract infection
- hypotension
- nausea

Side effects of HCTZ include:

- hypotension
- anorexia (prolonged loss of appetite)
- stomach pain
- hypokalemia
- skin damage from the sun
- decreased blood platelets (thrombocytopenia)

Geriatric

Older adults may be more sensitive to side effects from losartan/HCTZ, especially dizziness and changes in urine amounts due to kidney problems.

Other conditions and allergies

Serious allergic reactions to losartan/HCTZ are rare. Patients should seek emergency medical attention if they experience severe allergic symptoms, including:

- rash
- itching or swelling, especially of the face, tongue, or throat
- severe dizziness
- difficulty breathing

Interactions

It is very important that the healthcare provider and pharmacist be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements that the patient is using or planning to use. Patients should bring a list of all

medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

- Losartan is not to be coadministered with aliskiren in patients with diabetes.
- Patients taking bile-acid-binding resins to lower cholesterol—such as cholestyramine or colestipol—should take losartan/HCTZ at least four hours before or at least four to six hours after taking these drugs.
- Taking corticosteroids, adrenocorticotrophic hormone, or glycyrrhizin (in licorice) with losartan/HCTZ may increase electrolyte depletion, especially hypokalemia.
- All medication labels—including those on cough and cold medications, diet aids, and nonsteroidal anti-inflammatory drugs (NSAIDs) such as **ibuprofen** and naproxen—should be checked for ingredients that can increase blood pressure or worsen heart failure.

At least 22 drugs should not be used in combination with losartan or HCTZ or require very close monitoring because of potentially serious or life-threatening interactions. These include:

- amisulpride
- **benazepril**
- **captopril**
- **carbamazepine**
- cisapride
- **cyclosporine**
- dofetilide
- **enalapril**
- **fosinopril**
- idelalisib
- isocarboxazid
- ivacaftor
- **lisinopril**
- lithium
- moexipril
- perindopril
- intravenous potassium phosphates
- **quinapril**
- **ramipril**
- squill
- trandolapril
- tretinoin

In addition to the ACE inhibitors listed, oral contraceptives containing drospirenone may increase the levels of potassium in the blood. At least 214 other drugs have significant interactions with losartan/HCTZ

and require close monitoring. Another 160 drugs have minor interactions.

Herbs and supplements

Patients taking losartan/HCTZ should avoid:

- St. John's wort, which may decrease losartan levels
- dong quai, which has estrogenic activity
- ephedra, yohimbe, and ginseng, which may worsen hypertension
- garlic, which may have an increased antihypertensive effect
- potassium supplements

Food and other substances

Patients may be prescribed a low-salt or low-sodium diet or told to eat increased amounts of potassium-rich foods, such as bananas, prunes, raisins, and orange juice. Potassium supplements or salt substitutes containing potassium should not be used without consulting the treating physician. Patients should limit alcoholic beverages.

Resources

PERIODICALS

- "Drugs to Treat Hypertension." *Journal of Psychosocial Nursing & Mental Health Services* 52, no. 2 (2014): 11–12.
- Suh, Soon Yong, et al. "Efficacy and Tolerability of Amlodipine Camsylate/Losartan 5/100-mg Versus Losartan/Hydrochlorothiazide 100/12.5-mg Fixed-Dose Combination in Hypertensive Patients Nonresponsive to Losartan 100-mg Monotherapy." *Clinical Therapeutics* 36, no. 10 (2014): 1402–11.

WEBSITES

- "Losartan and Hydrochlorothiazide." Memorial Sloan Kettering Cancer Center. <http://www.mskcc.org/cancer-care/patient-education/resources/losartan-and-hydrochlorothiazide> (accessed February 18, 2015).
- "Losartan/Hydrochlorothiazide (Rx)—Hyzaar." Medscape.com. <http://reference.medscape.com/drug/hyzaar-losartan-hydrochlorothiazide-342340> (accessed February 18, 2015).
- MedlinePlus. "Hydrochlorothiazide." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682571.html> (accessed February 18, 2015).
- MedlinePlus. "Losartan." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a695008.html> (accessed February 18, 2015).

ORGANIZATIONS

National Heart, Lung, and Blood Institute (NHLBI), PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbiinfo@nhlbi.org, <http://www.nhlbi.nih.gov/>

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Lotensin see **Benazepril**

Lotensin HCT see **Benazepril/hydrochlorothiazide**

Lotrisone see **Clotrimazole/betamethasone**

Lovastatin

Definition

Lovastatin is a member of the class of statins, drugs that are used to reduce high blood cholesterol levels and lower the risk of cardiovascular disease. Statins are also known as HMG-CoA reductase inhibitors because they inhibit the action of an enzyme called HMG-CoA reductase, which plays an important role in the liver's production of cholesterol.

Purpose

Lovastatin is used to lower the level of cholesterol and triglycerides in the blood in adult patients for whom

exercise and dietary modifications are insufficient to lower their risk of heart disease. It is also used to lower the risk of stroke, heart attack, and other cardiovascular complications in people with diabetes, coronary heart disease, or other risk factors, and to slow the progression of atherosclerosis in patients already diagnosed with coronary heart disease. It works best in patients who combine a cholesterol-lowering diet with use of the medication.

Lovastatin is used in children over the age of 10 to treat a condition known as familial heterozygous hypercholesterolemia, a genetic disorder in which people have one abnormal copy of the *LDLR* gene on chromosome 19, which encodes a protein that removes low-density lipoprotein (LDL) cholesterol from the blood. These patients typically develop premature heart disease by age 30 or 40.

Off-label use

Lovastatin has been used experimentally in the treatment of squamous cell carcinoma.

Description

Lovastatin in its pure form is a white crystalline powder that cannot be dissolved in water and is only barely soluble in alcohol. The drug is available only as tablets, in either an immediate-release or an extended-release form. The immediate-release form is available as 10 milligram (mg), 20 mg, and 40 mg tablets; the extended-release form is dispensed as 20 mg, 40 mg, and 60 mg tablets.

Generic immediate-release lovastatin tablets are round but come in a wide variety of colors (white, pale green, chartreuse, light blue, bright turquoise, peach, pink, light orange, light yellow, and bright orange), depending on the dosage and the manufacturer.

The extended-release tablets are round, varying in color from beige to peach to orange depending on the dose, and bear the Merck logo on one side.

U.S. brand names

Lovastatin is sold by Merck in the United States under the brand names Mevacor for the immediate-release form and Altoprev for the extended-release form. The immediate-release form of lovastatin went off patent in 2001. Generic versions of the immediate-release form are sold as lovastatin tablets by such companies as Teva Pharmaceuticals, Genpharm, Lupin Pharmaceuticals, Mylan Pharmaceuticals, Actavis, Sandoz, and Apotex. The extended-release form is still protected by patent.

Origins

Lovastatin was the first statin drug developed and approved for use in treating high blood cholesterol levels.



Lovastatin, 40 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

It is closely related to a naturally occurring compound found in such foods as oyster mushrooms (*Pleurotus ostreatus*) and red yeast rice (fermented rice cultivated together with the mold *Monascus purpureus*). In 1982, lovastatin was isolated from the fungus *Aspergillus terreus* and originally called mevinolin. Clinical trials indicated that it had an excellent safety profile as well as effectiveness in lowering triglyceride and LDL cholesterol levels as well as slightly raising high-density lipoprotein (HDL) cholesterol levels. The U.S. Food and Drug Administration (FDA) approved lovastatin in August 1987, with the extended-release form (Altoprev) approved in 2002.

Lovastatin has been largely superseded by such later statins as **simvastatin** (also produced by Merck), **atorvastatin**, and **rosuvastatin**; it is prescribed much less often than other statins as of 2015. It is still of interest, however, to researchers in the fields of cancer and bone diseases.

Recommended dosage

Adults with high blood cholesterol levels may take 20 mg of immediate-release lovastatin once a day with the evening meal. The dose may be adjusted every four weeks if required, but it must not exceed 80 mg per day. Immediate-release tablets must be taken with food. Extended-release lovastatin is dosed as 10–60 mg by mouth per day at bedtime. The extended-release form is taken without food.

Lovastatin tablets should be stored away from heat, light, and moisture, at temperatures between 68°F and 77°F (20°C–25°C); they should not be kept in the bathroom. The drug should be stored in a safe place inaccessible to children and pets.

Pediatric

Children and adolescents older than age ten with heterozygous familial hypercholesterolemia may take 20–40 mg by mouth once per day, with the total dosage not to exceed 40 mg per day.

Other conditions and allergies

The dosage of lovastatin may require adjustment in the following groups of adult patients:

- Patients taking **diltiazem** or verapamil (calcium channel blockers) or danazol (drug used to treat endometriosis in women): dose of lovastatin should not exceed 20 mg per day.
- Patients taking amiodarone (drug given to treat heart arrhythmias): dose of lovastatin should not exceed 40 mg per day.

KEY TERMS

Atherosclerosis—Thickening and hardening of the walls of an artery as the result of accumulations of white blood cells, cholesterol, and triglycerides (fats).

Familial hypercholesterolemia (FH)—A genetic disorder characterized by high levels of LDL cholesterol in the blood and cardiovascular disease early in life. The heterozygous form is more common and can be treated with statins; the homozygous form is very rare (about one case in every million live births) and may respond only to liver transplantation.

HMG-CoA reductase—An enzyme that affects the production of cholesterol in the liver. Lovastatin and other statins lower blood cholesterol levels by inhibiting the activity of this enzyme.

Rhabdomyolysis—A condition in which damaged skeletal muscle undergoes rapid breakdown. It is a rare but potentially serious effect of taking statins.

- Patients with severe kidney or liver impairment should be given dosages above 20 mg per day only with great caution, and their liver function should be periodically monitored.

Precautions

Patients should tell their doctor if they have any of the following disorders or conditions before taking lovastatin:

- known allergies to foods, dyes, or other medications
- history of alcohol abuse, liver disorders, or muscle problems
- low blood pressure, kidney problems, poorly controlled diabetes, low thyroid function, metabolic disorders other than diabetes, hormonal problems, or electrolyte disturbances
- recent history of an organ transplant, use of immunosuppressant drugs, major surgery, or serious injury
- diagnosis of homozygous familial hypercholesterolemia, a rare genetic disorder characterized by abnormally high blood cholesterol levels at an early age

Pediatric

Lovastatin is not recommended for use in children below the age of ten. Teenage girls taking lovastatin should be counseled to use birth control to prevent pregnancy.

Pregnant or breastfeeding

Lovastatin is a pregnancy category X drug, which indicates that it is not to be used by pregnant women because the risk of harm to the fetus outweighs any possible benefit of the drug. It may cause such birth defects as skeletal malformations or learning disabilities. Lovastatin is also contraindicated for use by nursing mothers.

Other conditions and allergies

Lovastatin should be used with great caution in patients with liver and kidney disorders.

Side effects

The most common side effects of lovastatin include:

- body aches or mild muscle pain
- headache
- diarrhea
- flatulence (intestinal gas)
- stomach pain
- dizziness
- unexplained skin rash
- constipation
- weakness

Less common side effects of lovastatin include:

- hair loss
- dry mouth
- leg pain
- vomiting
- insomnia
- memory loss or confusion (should be reported to the doctor if it persists or gets worse)

The following side effects may indicate a serious condition and should be reported to the doctor at once:

- signs of a severe allergic reaction such as hives; itching; sudden and unexplained swelling of the lips, mouth, or throat; difficulty breathing
- jaundice, dark-colored urine, pain in the upper abdomen, or other signs of a liver disorder
- unexplained changes in urine output
- severe upper abdominal pain accompanied by nausea and vomiting, which may indicate pancreatitis
- signs of high blood sugar, such as increased thirst, urination, and hunger; dry mouth; fruity breath odor; drowsiness; weight loss; blurred vision

- severe muscle pain or tenderness accompanied by fever, which may indicate rhabdomyolysis (sudden breakdown of muscle tissue)
- persistent or severe memory loss
- flulike symptoms

Interactions

Drugs

Lovastatin interacts with the following medications:

- immunosuppressants used to prevent organ rejection (sirolimus, **tacrolimus**)
- macrolide antibiotics (**erythromycin**, **clarithromycin**, telithromycin)
- other statin medications (**pravastatin**, simvastatin, atorvastatin, etc.)
- **colchicine** (gout medication), which increases toxicity of lovastatin
- barbiturates (phenobarbital, pentobarbital, secobarbital, butabarbital, etc.), which decrease effectiveness of lovastatin
- corticosteroids (methylprednisolone, hydrocortisone, **prednisone**, prednisolone, etc.), which lower the effectiveness of lovastatin
- **ketoconazole** and other azole antifungal drugs
- **cyclosporine**
- fibrates (**gemfibrozil**, **fenofibrate**), which increase the risk of rhabdomyolysis
- niacin
- antiretroviral medications (indinavir, atazanavir, boceprevir, delavirdine, ritonavir, nelfinavir, etc.)
- **spironolactone**
- **warfarin**

Herbs and supplements

Patients who are prescribed lovastatin should not use herbal preparations containing St. John's wort, as this herb may increase the side effects of lovastatin.

Food and other substances

Patients taking lovastatin should not drink alcoholic beverages while taking the drug because of increased risk of liver damage. Alcohol can also raise the patient's triglyceride levels.

Patients also should not smoke or consume marijuana because this recreational drug magnifies the effects of lovastatin and may produce a life-threatening interaction.

Patients taking lovastatin should not eat red yeast rice, a dietary supplement that contains a natural compound nearly identical to lovastatin. They should also avoid grapefruit and grapefruit juice, which increase the risks of side effects during lovastatin therapy.

Resources

BOOKS

- La Grua, Benedetta, and Alessandro Molinelli, editors. *Statins: Pharmacology, Clinical Implications, and Adverse Effects*. New York: Nova Biomedical/Nova Science Publishers, 2012.
- Travers, Eric R., editor. *Statins: Medical Uses, Mechanisms of Action and Clinical Outcomes*. Hauppauge, NY: Nova Science Publishers, 2014.

PERIODICALS

- Chauvin, B., et al. "Drug-Drug Interactions between HMG-CoA Reductase Inhibitors (Statins) and Antiviral Protease Inhibitors." *Clinical Pharmacokinetics* 52, no. 10 (2013): 815–31.
- Finks, S. W., and J. D. Campbell. "Avoiding Patient Morbidity: Updated Statin Drug Interactions and Risks for Patient Harm." *Nurse Practitioner* 39, no. 11 (2014): 45–51.
- Patel, A. M., et al. "Statin Toxicity from Macrolide Antibiotic Coprescription: A Population-based Cohort Study." *Annals of Internal Medicine* 158, no. 12 (2013): 869–76.

WEBSITES

- eMedTV. "Lovastatin." Cholesterol.emedtv.com. <http://cholesterol.emedtv.com/lovastatin/lovastatin.html> (accessed February 15, 2015).
- "Lovastatin." Drugs.com <http://www.drugs.com/cdi/lovastatin.html> (accessed February 15, 2015).
- Mayo Clinic staff. "Lovastatin (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/>

lovastatin-oral-route/description/drg-20069029 (accessed February 15, 2015).

Medscape. "Lovastatin (Rx)." Reference.medscape.com. <http://reference.medscape.com/drug/mevacor-altoprev-lovastatin-342458> (accessed February 15, 2015).

ORGANIZATIONS

- American College of Cardiology (ACC), Heart House, 2400 N Street NW, Washington, DC 20037, (202) 375-6000, ext. 5603, Fax: (202) 375-7000, (800) 253-4636, ext. 5603, resource@acc.org, <http://www.cardiosource.org/>.
- American Heart Association (AHA), 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.
- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://connect.ashp.org/contactus>, <http://www.ashp.org/>.
- Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/AboutFDA/ContactFDA/default.htm>, <http://www.fda.gov/>.

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Lovenox see **Enoxaparin**

Lucentis see **Ranibizumab**

Lunesta see **Eszopiclone**

Luvox see **Fluvoxamine**

Lyrica see **Pregabalin**

Lysteda see **Tranexamic acid**



Macrobid see **Nitrofurantoin**

Maxalt see **Rizatriptan**

Mebendazole

Definition

Mebendazole is an anthelmintic drug used to treat infections with parasites, such as worms. It is considered a broad-spectrum agent, meaning that it has activity against a wide variety of parasites.

Purpose

Mebendazole is used to treat infections with many types of worms, including:

- roundworms (*Ascaris lumbricoides*)
- hookworms (*Ancylostoma duodenale* and *Necator americanus*)
- pinworms (*Enterobius vermicularis*)
- whipworms (*Trichuris trichiura*)
- tapeworms (*Taenia solium*)

Mebendazole can also treat infections with more than one type of a worm at a time.

Description

Mebendazole is a flat, round, orange tablet that is 10 millimeters (mm) in size. It is imprinted on one side with the numbers 93 and 107. Each pill contains 100 milligrams (mg) of active drug. The medication is taken by mouth and must be prescribed by a physician.

Mebendazole is on the World Health Organization's list of essential medicines. It is also frequently used in veterinary medicine.

U.S. brand names

Mebendazole is no longer available in the United States.

Canadian brand names

Mebendazole is sold under the brand name Vermox in Canada.

International brand names

Mebendazole is sold in many countries worldwide under a variety of names, including Wormex (South Africa), Versid (Turkey), Vermicide (Taiwan), Tesical (Argentina), Sufil (Spain), and Ovex (United Kingdom). In some countries, mebendazole is only one component of the medication, and there are other medications included in the formulation. In some locations, it is only available for veterinary, not human, use.

Recommended dosage

For roundworm, hookworm, whipworm, or tapeworm, the recommended dosage for adults who are treated with mebendazole is 100 mg twice daily for three days. If the infestation is not cured, then this regimen should be repeated in three weeks.

For pinworm, the recommended dosage for adults who are treated with mebendazole is a single 100 mg dose. This should be repeated after two weeks and again after four weeks. Family members who have close contact with the patient should also be treated with the same regimen.

Mebendazole is taken by mouth and may be taken whole, crushed, or chewed. It may be taken with or between meals.

Pediatric

For children over the age of two, the adult dosage recommendations may be used.



Ovex (mebendazole), 100 mg. (Finnbarr Webster/Alamy)

Precautions

Mebendazole should be taken for the entire length of the prescription.

Mebendazole can lead to bone marrow suppression when used at high doses or for long periods of treatment.

Pediatric

The safety and effectiveness of mebendazole in children under the age of two have not been established. Seizures have been reported when mebendazole is used in infants under a year old.

Pregnant or breastfeeding

Mebendazole carries the FDA pregnancy category C, meaning that risk to the fetus cannot be ruled out in pregnant individuals. If possible, use of this drug should be delayed until the third trimester.

Small amounts of mebendazole may pass into breast milk but are unlikely to affect the nursing infant.

Other conditions and allergies

Mebendazole should not be taken by individuals who are hypersensitive to mebendazole, benzimidazoles, or any other ingredient of the preparation.

Individuals with a history of liver problems should inform their healthcare provider prior to starting the medication, and care should be taken while taking the prescription.

Side effects

Side effects of mebendazole treatment include:

- upset stomach or abdominal pain, sensation of indigestion, nausea, vomiting, diarrhea
- hair loss
- itching, rash, hives

KEY TERMS

Anthelmintic—A drug that is used to treat an infection with parasitic worms.

Parasite—A type of organism that survives within another living host and nourishes itself by using that host's energy stores without providing the host with any benefit.

Roundworm—A type of worm with a long body that lives in the intestines of mammals.

Tapeworm—A type of flatworm that has many segments and lives within the intestines of its hosts, which can include humans and other animals that have backbones (vertebrates).

- headache, dizziness, drowsiness
- seizures
- blood test evidence of bone marrow suppression, including low white blood count, low platelets, or low hematocrit
- blood test evidence of liver damage
- blood test evidence of kidney damage
- blood in the urine
- yellow cast to skin and/or whites of eyes

Rare but serious signs of a significant allergic reaction to mebendazole should prompt the individual to seek immediate medical care. These include:

- difficulty breathing
- wheezing
- fever
- cough
- blue skin or lips
- seizures
- swollen face, lips, tongue, or throat

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients should tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Drugs that may decrease the amount of mebendazole in the bloodstream include antimalarial drugs such as

aminoquinolines, carbamazepine, fosphenytoin, and **phenytoin**. Cimetidine may increase the amount of mebendazole in the bloodstream. Close monitoring is recommended when these drugs are used together.

Using mebendazole and **metronidazole** at the same time can increase the risk of severe toxic effects from the metronidazole. It is recommended to avoid using these drugs at the same time.

Resources

BOOKS

- Bennett, John E., Raphael Dolin, and Martin J. Blaser. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia: Saunders, 2014.
- Cherry, James, et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Saunders, 2014.
- Lexicomp. *Drug Information Handbook*. 23rd ed. Hudson, OH: Lexicomp Inc., 2014.
- Magill, Alan, et al. *Hunter's Tropical Medicine and Emerging Infectious Diseases*. Philadelphia: Saunders, 2013.
- Rang, Humphrey, et al. *Rang and Dale's Pharmacology*. 7th ed. London: Churchill Livingstone, 2012.

Resources

WEBSITES

- "Mebendazole." Drugs.com. <http://www.drugs.com/mtm/mebendazole.html> (accessed February 19, 2015).
- MedlinePlus. "Mebendazole." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682315.html> (accessed February 19, 2015).
- U.S. National Library of Medicine. "LactMed: Mebendazole." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+465> (accessed February 19, 2015).

ORGANIZATIONS

- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Meclizine

Definition

Meclizine is an antihistamine commonly used to control nausea, vomiting, and dizziness.



Meclizine, 12.5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Meclizine may be given to help control nausea and vomiting that often occurs with cancer treatment, other medical conditions, or motion sickness. It is also used as part of palliative care for patients with terminal cancer.

Description

Meclizine acts as a central nervous system depressant. It is believed its therapeutic actions occur due to the drug's drying effects and its ability to depress conduction of nerve messages in the inner ear. Meclizine begins working about one hour after ingestion. It continues being effective for 8 to 24 hours.

U.S. brand names

In the United States, the prescription brand name of meclizine is Antivert. It is also sold over the counter as Bonine.

Recommended dosage

When used to manage dizziness, such as the dizziness that occurs with vertigo, patients generally take 25–100 milligrams (mg) daily in divided doses. The dosage to control nausea and vomiting associated with cancer treatment is 25–50 mg, every 8 to 12 hours. Patients should not double up on this medication if a dose is missed.

KEY TERMS

Antihistamine—Agent that blocks or counteracts the action of histamine, which is released during an allergic reaction.

Central nervous system depressant—Any drug that lowers the level of stimulation or excitement in the central nervous system.

Palliative—Referring to treatments that are intended to relieve pain and other symptoms of disease but not to cure.

Vertigo—The sensation of moving around in space, or objects moving around a person. It is a disturbance of equilibrium.

Precautions

Meclizine may cause drowsiness and fatigue. Drowsiness is the most common adverse reaction. Alcohol and other central nervous system depressants, such as pain medication and tranquilizers, may increase this effect. Patients should refrain from drinking alcoholic beverages and avoid driving or operating machinery or appliances when taking this drug.

Pediatric

The FDA recommends that children under age 12 do not take this drug, except under the direction of a physician.

Pregnant or breastfeeding

Pregnant women and those trying to become pregnant should not take this medication. Animal reproductive studies have shown some deformities at elevated doses. Women who are breastfeeding should discuss this medication with their doctors prior to taking it.

Other conditions and allergies

Patients with glaucoma, an enlarged prostate, bladder or bowel obstructions, or asthma or other breathing difficulties should discuss with the doctor the risks and benefits associated with this drug before taking it. Those who have experienced an allergic reaction to meclizine should not take it.

Side effects

Meclizine sometimes produces excitability, nervousness, restlessness, mood enhancement, or difficulty

sleeping. Rarely, it may cause a patient to see or hear things that are not present (hallucinations). Despite being used to treat nausea and vomiting, it may produce these effects. It may also cause constipation, diarrhea, an upset stomach, or a loss of appetite. Other side effects include frequent or difficult urination, incomplete emptying of the bladder, low blood pressure, and a rapid heart rate or palpitations. It may cause vision changes, a dry nose and throat, ringing in the ears, and a rash or hives.

Side effects may decrease as the body adjusts to the medication. Ice chips or sugarless hard candy or gum may help relieve dry mouth. If the feeling of a dry mouth persists for more than two weeks, the doctor should be notified.

Geriatric

Some of the side effects may be more pronounced in older adults.

Interactions

Patients should inform their doctor of all medications they are currently taking and should not start or stop any drugs without physician approval.

Drugs

Central nervous system depressants may increase drowsiness associated with meclizine. Pain medications, other antihistamines, seizure medications, sleeping pills, and muscle relaxants can depress the central nervous system. Taking this drug with some medications used to treat depression may increase the risk of side effects.

Herbs and supplements

The herbal supplement henbane may increase some of meclizine's side effects, including dry mouth and difficulty urinating.

Food and other substances

Alcohol can increase the sedative effect of meclizine and should be avoided.

Resources

PERIODICALS

Wang, Z., et al. "Meclizine Metabolism and Pharmacokinetics: Formulation on Its Absorption." *Journal of Clinical Pharmacology* 52, no. 9 (2012): 1343–49.

WEBSITES

A.D.A.M. Medical Encyclopedia. "Meclizine." University of Maryland, Baltimore Washington Medical Center. <http://www.mybwmc.org/library/41/080100> (accessed February 25, 2015).

Desmond, Alan L., and R. Brian Collie. "Meclizine—Does It Help?" Vestibular Disorders Association. <https://vestibular.org/news/10-07-2013/meclizine-%E2%80%93-does-it-help> (accessed February 25, 2015).

Lexi-Comp. "Meclizine." Merck Manual Professional Edition. <http://www.merckmanuals.com/professional/lexicomp/meclizine.html> (accessed February 25, 2015).

Physicians' Desk Reference. "Antivert." PDR Health. <http://www.pdrhealth.com/drugs/antivert> (accessed February 25, 2015).

ORGANIZATIONS

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Vestibular Disorders Association, 5018 NE 15th Avenue, Portland, OR 97211, (800) 837-8428 (VESTIBU), Fax: (503) 229-8064, info@vestibular.org, <https://vestibular.org/>.

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Medrol see **Methylprednisolone**

Medroxyprogesterone

Definition

Medroxyprogesterone acetate (MPA) is a synthetic derivative of the hormone progesterone. In healthy women, progesterone plays a major role in preparing the uterus for pregnancy. MPA is in a class of medications called progestins.

Purpose

Medroxyprogesterone acetate (MPA) is used as a contraceptive. MPA is also prescribed to women to restore normal menstrual cycles and to treat abnormal menstruation. It is sometimes used during cancer therapy to stop new cell growth in certain cancers.

Off-label uses

In males, MPA has been prescribed to control inappropriate sexual behavior by chemically castrating convicted sexual offenders.

Description

MPA works by changing the consistency of cervical mucus to make it more difficult for sperm to reach the egg, changing the uterine lining to prevent a fertilized egg from implanting in the uterus, and inhibiting ovulation. When used as prescribed, the medication is



Medroxyprogesterone, 150 mg/mL. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

effective as a form of birth control, though no method is considered 100% effective.

Additionally, MPA is used in conjunction with other medications to treat cancers in the endometrium, the lining of the uterus. Many cancerous tumors are sensitive to hormones. It appears that MPA in some way changes the hormonal climate of the tumor so that cells stop responding to other hormones and proteins that would normally stimulate their growth. This drug cannot specifically target cancer cells, so some normal cells are also killed during treatment. However, since cancer cells generally grow more rapidly than normal cells, more cancer cells are killed. MPA is considered very effective and relatively nontoxic.

MPA is available in tablet form and injection form. The tablet form is available in strengths of 2.5, 5, and 10 milligrams (mg). The injectable form is available in strengths of 150 mg per milliliter (mL) and 400 mg/mL. The injectable form must be injected by a healthcare provider in a medical setting; it is not prescribed for home use.

U.S. brand names

In the United States, MPA is sold under the brand names Depo-Provera and Provera.

Canadian brand names

In Canada, MPA is sold under the brand names Apo-Medroxy, Depo-Provera, Gen-Medroxy,

KEY TERMS

Chemical castration—Administration of pharmaceutical agents to decrease testosterone levels to prepubescent levels and suppress deviant sexual thinking and behavior.

Contraception—Prevention of becoming pregnant.

Endometrial cancer—Cancer of the uterus.

Medroxyprogesterone Acetate Sandoz, and Provera. A combination formulation is available under the brand name Premplus.

International brand names

MPA is most commonly sold internationally under the brand names Depo-Provera and Provera, but it is available under a wide variety of other brand names. In some countries, MPA is only one component of the medication, and there are other medications included in the formulation.

Origins

MPA was initially approved by the U.S. Food and Drug Administration (FDA) in 1959.

Recommended dosage

MPA comes as tablets or as a liquid that is given as an intramuscular injection. When prescribed in tablet form, the medication must be taken orally every day; if prescribed as an injectable, the medication must be given as an intramuscular shot every 12 to 14 weeks. If taken soon after giving birth, the injections should begin at 6 weeks post-delivery, or sooner if sexual activity is to be resumed prior to the 6-week guideline.

If an injection is not received at the 12- to 14-week mark, an alternate form of birth control should be used until the patient can discuss the plan with a healthcare provider. Occasionally, MPA is given in divided doses that are spaced evenly throughout the day.

For uterine (endometrial) cancer, MPA is usually given as a shot once a week at first, then once a month.

Pediatric

This medication may be used for birth control in teenage women but should not be used before the start of menstruation.

Geriatric

This medication should not be used in elderly women. Adequate studies have not been conducted on effects in the geriatric population.

Pregnant or breastfeeding

MPA carries the FDA pregnancy category X, meaning that it should not be used during pregnancy. Studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. This medication should not be used by anyone who is planning to become pregnant. Women who have become pregnant while taking MPA should stop taking the medication immediately and contact their physician.

MPA is excreted in breast milk but is considered to be compatible with breastfeeding.

Precautions

Individuals taking MPA daily should take it at the same time each day. The patient should be certain to space the medication at regular intervals, though it does not matter whether this medication is taken during the day or night.

MPA may cause the bones to lose calcium, which can lead to thin or weak bones. Calcium loss may continue for the entire duration of the prescription, but bones should start rebuilding calcium after MPA is stopped. This is a more serious problem in teenagers and women who smoke or drink alcohol regularly, have an eating disorder, or have any other disorders or take other medications that affect the bones (e.g., steroids).

There is a very slight chance that using MPA may cause an increased risk of breast cancer. Patients should discuss this risk with their doctor.

Side effects

The number and severity of side effects vary widely among people. Not only are they dependent on each person's unique body chemistry, but side effects also vary with the health of the patient and the other drugs being given. There is no way to predict who will experience side effects of MPA.

Among the more common side effects of MPA are:

- increased appetite and weight gain
- nausea
- swelling and fluid retention in the hands, legs, and breasts
- breakthrough vaginal bleeding
- muscle cramps
- fatigue
- emotional or mood changes
- headaches

- dizziness or faintness
- weakness or numbness in an arm or leg
- sleep disturbances
- hair growth on face
- acne

A less common but more serious side effect is the development of blood clots that can lead to heart attack or stroke. Individuals who have a history of clotting problems are not good candidates for using MPA.

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

MPA should not be taken when the patient is taking **tranexamic acid** unless approved by the doctor.

There are several medications that should not be taken with MPA. If the doctor feels that MPA is necessary and the benefits outweigh the risks, these medication combinations should be monitored closely by the doctor. These medications include:

- **carbamazepine**
- ceritinib
- dabrafenib
- eslicarbazepine acetate
- idelalisib
- insulin degludec
- **isotretinoin**
- mitotane
- nilotinib
- piperazine
- siltuximab
- theophylline

Using MPA with a number of commonly prescribed medications may contribute to certain side effects. The doctor and pharmacist should cross-check the patient's current medications with MPA due to several medications causing changes in side effects. These include but are in no way limited to:

- **alprazolam**
- isotretinoin

- mitotane
- nilotinib
- phenobarbital
- **phenytoin**
- piperazine
- **prednisone**
- **rifampin**
- siltuximab
- theophylline
- **warfarin**

Aminoglutethimide (Cytadren; an inhibitor of steroid biosynthesis), when given with MPA, decreases the effectiveness of MPA.

Resources

BOOKS

Chu, Edward, and Vincent T. DeVita Jr. *Physicians' Cancer Chemotherapy Drug Manual 2014*. Burlington, MA: Jones & Bartlett Learning, 2014.

PERIODICALS

Douglas, Thomas, et al. "Coercion, Incarceration and Chemical Castration: An Argument From Autonomy." *Journal of Bioethical Inquiry* 10, no. 3 (2013): 393–405.

Li, C. I., et al. "Effect of Depo-Medroxyprogesterone Acetate on Breast Cancer Risk among Women 20 to 44 Years of Age." *Cancer Research* 72, no. 8 (2012): 2028–35.

WEBSITES

American Cancer Society. "Hormone Therapy For Endometrial Cancer." <http://www.cancer.org/cancer/endometrialcancer/detailedguide/endometrial-uterine-cancer-treating-hormone-therapy> (accessed March 6, 2015).

MedlinePlus. "Medroxyprogesterone." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682470.html#other-name> (accessed March 6, 2015).

Micromedex. "Medroxyprogesterone (Intramuscular Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/medroxyprogesterone-intramuscular-route/side-effects/drg-20074661> (accessed March 6, 2015).

ORGANIZATIONS

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Tish Davidson, AM

Revised by Tracy Gardner Beno, RN

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Megace see **Megestrol**

Megestrol

Definition

Megestrol acetate is a synthetic derivative of the hormone progesterone. Megestrol acetate is in a class of medications called progestins.

Purpose

In tablet form, megestrol acetate is used to ease the suffering of patients with some advanced hormone-responsive cancers of the breast, kidney, and uterus.

In suspension form, megestrol acetate is used to treat anorexia, cachexia, or unexplained weight loss in patients with AIDS.

Off-label uses

Megestrol acetate has been used off label to treat cancer-related cachexia, prostatic hypertrophy (enlargement of the prostate gland in men), endometriosis, and endometrial hyperplasia.

Megestrol acetate has also been used to treat some types of cancer, including advanced breast and endometrial cancer.

Description

Megestrol acetate is used in larger doses to counteract weight loss. It is effective in reversing weight

loss and contributing to weight gain/increased fat storage in conditions such as cancer, anorexia-cachexia syndrome, AIDS, and other unexplained anorexia and cachexia. It is also used to treat some types of cancer.

The exact mechanism by which megestrol acetate stops tumor growth is unknown. Many tumors are sensitive to hormones. It appears that megestrol acetate in some way changes the hormonal climate of the tumor so that cells stop responding to other hormones and proteins that would normally stimulate their growth. This drug cannot specifically target cancer cells, so some normal cells are also killed during treatment. However, since cancer cells grow more rapidly than normal cells, more cancer cells are killed.

Megestrol acetate is available in tablet form in strengths of 20 and 40 milligrams (mg) and in suspension form in strengths of 40 mg per milliliter (mL) and 125 mg/mL (concentrated suspension).

U.S. brand names

In the United States, megestrol acetate is sold under the brand names Megace and Megace ES.

Canadian brand names

In Canada, megestrol acetate is sold under the brand names Apo-Megestrol and Megace OS.

International brand names

Internationally, megestrol acetate is most commonly sold under the brand name Megace, but it is available under a wide variety of other brand names. In some countries, megestrol acetate is only one component of the medication, and there are other medications included in the formulation; it may also be available for veterinary use.

Recommended dosage

For the palliative (pain-relieving) treatment of breast cancer, the recommended dose is 160 mg/day (40 mg oral tablets, taken four times a day).

For the palliative treatment of endometrial cancer, the recommended dose is 40–320 mg/day (oral tablets, taken in divided doses).

For the treatment of anorexia or cachexia, the recommended dose is 800 mg per day (liquid suspension) or 625 mg/5 mL per day (concentrated suspension).

For the treatment of unexplained weight loss in patients with AIDS, the recommended dose is 800 mg per day (liquid suspension) or 625 mg/5 mL per day (concentrated suspension).

To reduce tumor growth, the dose of megestrol acetate is individualized and depends on the type of



Megestrol, 20 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

AIDS—Acquired immune deficiency syndrome; a serious disease that affects the immune system and is caused by human immunodeficiency virus (HIV).

Anorexia—A serious physical and emotional illness in which an abnormal fear of being overweight leads to severe calorie restriction and dangerous weight loss.

Cachexia—General wasting and malnutrition usually associated with chronic disease.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, reproduction, metabolism, and mood.

Progesterone—A female hormone that prepares the uterus for pregnancy.

cancer, the patient's body weight and general health, which other drugs are being given, and how the tumor responds to hormones.

Precautions

Megestrol acetate may increase blood sugar levels. The doctor should monitor diabetic patients who are taking megestrol acetate closely.

Megestrol acetate may cause fluid retention, which can aggravate certain conditions, including migraine headaches and vision changes. The medication can also lead to worsening of breast conditions such as breast lumps or cysts.

Patients should inform the doctor, dentist, or surgeon that they are taking megestrol acetate any time they are scheduled to undergo surgery, including dental surgery.

Geriatric

While some studies have shown that this medication does not cause different effects on the elderly than on younger adults, there is concern that memory loss may be worsened when megestrol acetate is taken in patients suffering from dementia.

Pregnant or breastfeeding

In tablet form, megestrol acetate carries the FDA pregnancy category D, meaning that there is positive evidence of risk to the fetus. Women should consult with their physician about whether benefits outweigh possible risks to the fetus.

In suspension form, megestrol acetate carries the FDA pregnancy category X, meaning that human or animal studies have clearly demonstrated fetal abnormalities and/or there is positive evidence of risk to the fetus. Women who are pregnant or planning to become pregnant should not use megestrol acetate in suspension form.

There have been some reports that high doses of megestrol acetate may cause birth defects in the genitals of a male fetus and may also cause changes in a female fetus and female-like changes in a male fetus. Usually, these problems can be reversed when detected in utero. Low doses have not been shown to cause major problems when used accidentally during pregnancy. However, it is advisable to use some kind of birth control method while receiving high doses of megestrol acetate. If it is believed that megestrol acetate has caused birth defects in a child born to a mother taking the drug, the patient should call the Bristol Meyer Squibb patient assistance program at (800) 332-2056.

Megestrol acetate may change the quality or amount of the mother's breast milk if used during breastfeeding. Women should discuss the risks and benefits of using this medication with their doctor.

Other conditions and allergies

Patients who have a history of blood clots or bleeding disorders should not take megestrol acetate.

Side effects

Megestrol acetate has several rare but serious side effects. These include the development of sarcoma (tumors of the skin or connective tissue), Cushing syndrome (a hormonal imbalance in which people develop fatty deposits in the face and neck), diabetes, and osteoporosis. Rarely, megestrol acetate may also cause high blood pressure and other signs of fluid and salt (electrolyte) imbalances.

Common side effects of megestrol acetate include:

- worsening of diabetic symptoms
- pain in the chest or abdomen
- infection
- cessation of menstruation
- irregular heartbeat
- fluid retention
- breakthrough vaginal bleeding
- blood clots in the legs or lungs
- nausea or constipation
- dry mouth or increased salivation
- abnormal white blood cell count

- confusion or abnormal thinking
- emotional and psychological changes
- rash, itching, abnormal sweating, or skin disorders
- cough, sore throat, or lung disorders
- hair loss (alopecia)
- uncontrolled urination or urinary tract infection
- male impotence

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Certain medications are known to interact with megestrol acetate. The doctor should be notified if the patient is taking boceprevir, dofetilide, **tranexamic acid**, indinavir, and most antibiotics. Other medications that may require modified dosing and close monitoring during therapy include but are not limited to:

- carbamazepine
- fentanyl
- tizanidine
- theophylline

Food and other substances

Patients should tell their doctor if they are on a special diet, such as a low-salt or high-protein diet.

Resources

PERIODICALS

Ruiz, Garcia V., et al. "Megestrol Acetate for Treatment of Anorexia-Cachexia Syndrome." *Cochrane Database of Systematic Reviews* 3, art no. CD004310 (2013). <http://dx.doi.org/10.1002/14651858.CD004310.pub3> (accessed March 12, 2015).

Yaxley, A., et al. "Pharmacological Interventions For Geriatric Cachexia: A Narrative Review of the Literature." *Journal of Nutrition Health and Aging* 16, no. 2 (2012): 148–54.

WEBSITES

MedlinePlus. "Megestrol." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682003.html> (accessed March 7, 2015).

"Megestrol." Drugs.com. <http://www.drugs.com/mtm/megestrol.html> (accessed March 7, 2015).

Micromedex. "Progestin (Oral Route, Parenteral Route, Vaginal Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/progestin-oral-route-parenteral-route-vaginal-route/description/drg-20069443> (accessed March 7, 2015).

ORGANIZATIONS

American Cancer Society, 250 Williams Street NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Meloxicam

Definition

Meloxicam is part of a class of medications called nonsteroidal anti-inflammatory drugs (NSAIDs). It helps relieve swelling in joints by reducing certain hormones in the body.

Purpose

The anti-inflammatory properties of meloxicam can help relieve swelling and the associated symptoms of arthritis by blocking certain enzymes that help make



Meloxicam, 7.5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Osteoarthritis—The most common type of arthritis, this chronic condition affects the cartilage that cushions the joints and causes bones to rub against each other.

Rheumatoid arthritis—A chronic disease of the immune system that causes the body to attack the joints by mistake. The joints swell or become inflamed, and joints and organs become damaged.

Ulcer—A small sore or hole in the lining of the stomach or small intestine that can become painful and bleed.

chemicals that lead to inflammation. Patients who have osteoarthritis and rheumatoid arthritis can benefit from taking the medication. This includes some children who have certain types of juvenile rheumatoid arthritis.

Description

NSAIDs are prescribed more often than any other medications by doctors who treat arthritis. Arthritis can cause pain, stiffness, and limited mobility because of the swelling that occurs in the joints of people who have the disease. Although some NSAIDs such as **aspirin** and **ibuprofen** are available without a prescription, meloxicam requires a doctor's prescription. The medication comes in tablet or liquid form and is taken by mouth.

U.S. brand names

Meloxicam is sold in the United States in its generic form or under the brand name Mobic.

Recommended dosage

Meloxicam comes in 7.5- and 15-milligram (mg) tablets. The starting dose for adults with osteoarthritis or rheumatoid arthritis is 7.5 mg once a day. Patients should take the lowest dose that relieves symptoms, but adults can take up to 15 mg once a day.

Pediatric

Dosage of meloxicam for children with juvenile rheumatoid arthritis is based on the child's weight. The dose is 0.125 mg per kilogram (kg, or 2.2 lb.) of weight, once per day. This is equivalent to about 1 mL of the liquid meloxicam for a child who weighs 26 lb. (12 kg). The liquid is taken by mouth once a day for children age two years and older, up to 7.5 mg (liquid or tablet) once a day. Once a child reaches more than 132 lb. (60 kg), the child's dose levels at no more than 7.5 mg a day.

Precautions

Meloxicam carries a significant health warning about the increased risk of heart attack or stroke. The risk is higher for people who use meloxicam and similar NSAIDs for a long period of time, such as for chronic conditions or diseases. Anyone who has other diseases or participates in lifestyle behaviors that also increase the risk of heart attack or stroke should inform their doctor of these facts before taking meloxicam. Examples include smoking, high cholesterol, high blood pressure, and diabetes.

Meloxicam can also cause ulcers in the stomach or intestines of people who use the medication, and the ulcers can develop after short-term or long-term use with little or no warning. Ulcers can cause serious consequences, leading to internal bleeding and even death. It is important for people who take the drug to keep their doctor informed of how it is affecting their arthritis so that the doctor can prescribe the lowest dose possible to relieve symptoms effectively or stop the patient's use of the drug after symptoms are under control.

Pediatric

Studies have not shown more serious effects in children than in adults, but the dosage in children should be based on weight. Meloxicam has not been tested in children younger than two years old.

Geriatric

Older patients should be careful about the use of NSAIDs and may be more sensitive to their effects. Studies have not shown that meloxicam is any less effective or safe in geriatric patients than in other adults.

Pregnant or breastfeeding

Meloxicam is classified as pregnancy category C for women up to 30 weeks gestation. Women who have just become pregnant should only use meloxicam if the potential benefits of the medication outweigh the risks. Once the pregnancy reaches approximately 30 weeks, meloxicam should not be taken because of the effects the drug may have on the formation of a blood vessel between the heart and lungs of the fetus. The drug could cause a birth defect in the infant. It is possible that meloxicam is passed through breast milk, so a mother who is breastfeeding must work with her doctor to decide whether it is more important to continue the use of meloxicam and not breastfeed or to stop taking meloxicam while breastfeeding.

Other conditions and allergies

People who have severe kidney damage or disease should not take meloxicam. Anyone with ulcers and upper GI disease or high risk of stroke or heart attack

should discuss these conditions with their doctor before taking the medication. People who have anemia, asthma, or fluid retention (shown by swelling in the lower legs and feet) should also discuss these conditions with their doctors before taking meloxicam. It is recommended that patients inform their doctor or dentist about meloxicam use before having surgery, including dental surgery.

Side effects

Meloxicam can cause side effects in the GI tract, such as ulcers. Less serious side effects include:

- constipation
- diarrhea
- gas
- cough and runny nose
- sore throat

More serious side effects of meloxicam might indicate an allergic reaction. It is recommended to contact a doctor immediately. Some of the serious symptoms include:

- rash or hives
- itching
- fever
- blisters
- swelling of the eyes, mouth, hands, or lower limbs
- difficulty swallowing or breathing
- rapid heartbeat
- extreme fatigue or flu-like symptoms
- pain in the upper right area of the stomach

Interactions

Meloxicam may interact with other drugs, affecting how well one of the drugs works.

Drugs

Meloxicam interacts with several drugs:

- Aspirin heightens the concentration of meloxicam and can increase meloxicam's side effects.
- ACE inhibitors, which are drugs taken to manage high blood pressure, may become less effective if taken with meloxicam.
- **Warfarin** (Coumadin), a blood thinner, also increases the risk of GI bleeding, so patients who use both warfarin and meloxicam should be watched closely.

Food and other substances

Drinking alcohol while taking meloxicam could increase risk of bleeding in the stomach or intestines.

Resources

PERIODICALS

Marra, Carlo A., et al. "Risk of Gastrointestinal Events in Patients with Rheumatoid Arthritis after Withdrawal of Rofecoxib." *The Journal of Rheumatology* 39, no. 5 (2012): 910–15.

WEBSITES

American Academy of Orthopaedic Surgeons. "What Are NSAIDs?" OrthoInfo. <http://orthoinfo.aaos.org/topic.cfm?topic=a00284> (accessed December 18, 2014).

American Society of Health-System Pharmacists. "Meloxicam." MedlinePlus. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601242.html> (accessed December 18, 2014).

Boehringer Ingelheim. "Mobic (Meloxicam)." Mobic Tablet. <https://www.mobictablet.com/home> (accessed December 18, 2014).

Drugs.com. "Meloxicam." Drugs.com. <http://www.drugs.com/meloxicam.html> (accessed December 18, 2014).

RXList. "Mobic." RXList. <http://www.rxlist.com/mobic-drug.htm> (accessed December 18, 2014).

ORGANIZATIONS

American College of Rheumatology, 2200 Lake Boulevard NE, Atlanta, GA 30319, (404) 633-3777, Fax: (404) 633-1870, acr@rheumatology.org, <https://www.rheumatology.org/>.

Arthritis Foundation, 1330 W. Peachtree Street, Suite 100, Atlanta, GA 30309, (404) 872-7100, <http://www.arthritis.org/>.

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Memantine

Definition

Memantine is a type of drug known as an N-methyl-D-aspartate (NMDA) receptor antagonist.

Purpose

Memantine is used to treat moderate to severe Alzheimer's disease (AD). Randomized, double-blind, placebo-controlled clinical trials of memantine have demonstrated significant improvement of day-to-day functioning in moderate to severe AD.

Description

A recent theory concerning the mechanism underlying AD is that abnormal glutamate activity in the brain causes overexcitation of NMDA receptors, which may play a role in the development and progression of AD.



Namenda (memantine), 5 mg. (© Cengage Learning®.)

Memantine is an NMDA-receptor antagonist, which hypothetically allows the continued physiological activation of NMDA receptors for continued learning and memory. However, memantine does not appear to prevent or slow the degeneration of brain cells in patients with AD.

Studies have revealed that the use of memantine in combination therapy with **donepezil**, a cholinesterase inhibitor, is frequently more effective than the use of donepezil alone in the treatment of moderate to severe AD. Using memantine and donepezil in combination therapy does not affect the actions of either drug. Memantine has been shown to be both safe and effective in such combination therapy.

U.S. brand names

Memantine is sold under the brand name Namenda.

Recommended dosage

Memantine is available in tablet form or as an oral solution for patients who have difficulty swallowing tablets. Typically, patients are gradually put on memantine by taking 5 milligrams (mg) once a day for the first week, 5 mg twice a day for the second week (10 mg total per day), and 10 mg in the morning and 5 mg in the evening for the third week (15 mg total per day). After

KEY TERMS

Alzheimer's disease—Alzheimer's disease (AD) is a progressive neurologic disease in which dementia results from the degeneration of brain cells through the formation of senile plaques and neurofibrillary tangles. AD is the most common cause of dementia.

Clinical trial—A controlled scientific experiment designed to investigate the effectiveness of a drug or treatment in curing or lessening the symptoms of a disease or disorder.

Placebo—A preparation without pharmacological effect that is given in place of a drug in clinical trials to determine the effectiveness of the drug under study; a "sugar pill."

that, the maintenance dosage of memantine is 10 mg twice a day (20 mg total per day). Memantine is also available in an extended-release formation. It is dosed starting at 7 mg each day, increasing by 7 mg every week until the target dose of 28 mg daily is reached. Memantine can be taken with or without food.

Precautions

Clinical trials of memantine found it to be generally safe and well tolerated.

Other conditions and allergies

Anyone with a known hypersensitivity to memantine or any of the inert substances used as a vehicle for the drug should not take memantine. The dosage of memantine should be reduced for patients with severe kidney impairment.

Side effects

The most common adverse reactions to memantine are:

- dizziness
- confusion
- headache
- constipation
- agitation
- falling
- accidental injury

No significant difference has been found between patients taking memantine and patients taking a placebo

in vital signs, electrocardiogram values, or laboratory values (serum chemistry, hematology, and urinalysis). Compared with a placebo, memantine showed a lower level of gastrointestinal side effects (such as constipation, diarrhea, vomiting, or nausea).

Interactions

Studies on memantine have shown low potential for negative interaction with other drugs.

Resources

BOOKS

Burns, Alistair, and Bengt Winblad, eds. *Severe Dementia*. New York: John Wiley & Sons, 2006.

PERIODICALS

Lam, S., C. Smith, and I. H. Gomolin. "Memantine Standard Tablet and Extended-Release Dosing Considerations: A Pharmacokinetic Analysis." *Journal of the American Geriatrics Society* 63, no. 2 (2015): 383–84.

Schneider, Lon S., et al. "Lack of Evidence for the Efficacy of Memantine in Mild Alzheimer Disease." *Archives of Neurology* 68, no. 8 (2011): 991–98.

Serra, G., et al. "Memantine: New Prospective in Bipolar Disorder Treatment." *World Journal of Psychiatry* 4, no. 4 (2014): 80–90.

Xiong, G., and P. M. Doraiswamy. "Combination Drug Therapy for Alzheimer's Disease: What Is Evidence-Based, and What Is Not?" *Geriatrics* 60, no. 6 (2005): 22–26.

WEBSITES

AHFS Consumer Medication Information. "Memantine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a604006.html> (accessed February 25, 2015).

Alzheimer's Association. "Medications for Memory Loss." http://www.alz.org/alzheimers_disease_standard_prescriptions.asp (accessed February 25, 2015).

Alzheimer's Society. "Drug Treatments for Alzheimer's Disease." http://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=147 (accessed February 25, 2015).

Fisher Center for Alzheimer's Research Foundation. "Drug Facts: Namenda (Memantine)." <http://www.alzinfo.org/articles/drug-facts-namenda-memantine/> (accessed February 25, 2015).

UK National Health Service (NHS). "Memantine Hydrochloride (Memantine 10mg Tablets)." <http://www.nhs.uk/conditions/alzheimers-disease/pages/MedicineOverview.aspx?condition=Alzheimer%60s%20disease&medicine=Memantine%20hydrochloride> (accessed February 25, 2015).

ORGANIZATIONS

Alzheimer's Association, 225 N. Michigan Avenue, Floor 17, Chicago, IL 60601-7633, (312) 335-8700, (800) 272-3900, Fax: (866) 699-1246, TTY: (866) 403-3073, info@alz.org, <http://www.alz.org/>.

Alzheimer's Society, Devon House, 58 St Katharine's Way, London E1W 1LB, England, +44 0300 222 11 22,

Enquiries@alzheimers.org.uk, <http://www.alzheimers.org.uk/>.

Fisher Center for Alzheimer's Research Foundation, 110 East 42nd Street, 16th Floor, New York, NY 10017, (800) ALZ-INFO (259-4636), Fax: (212) 915-1319, info@alzinfo.org, <http://www.alzinfo.org/>.

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Mesalamine

Definition

Mesalamine is a drug that reduces inflammation. It is given to help treat ulcerative colitis and Crohn's disease and can be given orally or rectally.

Purpose

Mesalamine belongs to a class of drugs called anti-inflammatories. It has been approved by the U.S. Food and Drug Administration (FDA) to help treat ulcerative colitis. Mesalamine has been shown to help reduce the inflammation and negative effects associated with inflammatory bowel diseases.



Apriso (mesalamine), 0.375 g. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Off-label uses

Mesalamine is often used off label (meaning that it has not been approved by the FDA specifically for this use) to help treat Crohn's disease.

Description

Mesalamine reduces inflammation of the lining of the intestine. This inflammation is characteristic of ulcerative colitis and Crohn's disease. Reduction of the inflammation is associated with an improvement in symptoms, including diarrhea, and a reduction in or improvement of tissue damage. Mesalamine is used both to treat symptoms in patients with mild to moderate symptoms of ulcerative colitis or Crohn's disease and as a tool to help reduce the chance of recurrence of symptoms (flare-ups) in patients without current symptoms.

Mesalamine is available as immediate- or extended-release tablets taken orally, or as a rectal suppository. The strength in which the medication is available and recommended dosages vary by brand name. The appearance of the pills depends on the brand and strength of the pill.

U.S. brand names

Oral mesalamine is sold under the brand names Aspiro, Asacol HD, Delzicol, Lialda, and Pentasa in the United States. Mesalamine as a rectal suppository is sold as Rowasa and Casa.

Canadian brand names

Oral mesalamine is sold under the brand name Asacol 800 in Canada.

Recommended dosage

The recommended dosage depends on the type of treatment and the brand name of the drug being administered. For example, to treat mild to moderate ulcerative colitis using Asacol, the recommended dosage is 1,600 mg three times per day; to treat remission using the same brand, the recommended dosage is 1,600 mg daily divided into doses taken two hours before meals or one hour after meals. The recommended dosage for Crohn's disease using Asacol is 1,600 mg three times per day.

For treating mild to moderate ulcerative colitis, the recommended dosage of Delzicol is 800 mg three times each day, taken before or after meals. The recommended dosage of Lialda is 2,400 mg to 4,800 mg taken once daily with a meal, and the recommended dosage of Pentasa is 1,000 mg taken four times a day. Lialda and Pentasa are taken for up to eight weeks at a time. The recommended dosages for treatment of Crohn's disease with Lialda and Pentasa are the same as those for treating ulcerative colitis.

KEY TERMS

Anti-inflammatory drug—A drug that lowers inflammation; includes NSAIDs and corticosteroids.

Chronic renal failure—Progressive loss of kidney function over several years, which can result in permanent kidney failure requiring dialysis.

Crohn's disease—An inflammatory bowel disease that can cause damage to deep-tissue layers of the intestines, causing pain, severe diarrhea, weight loss, and malnutrition.

Inflammatory bowel disease (IBD)—A disease that causes inflammation of the colon and rectum.

Salicylates—A group of drugs that includes aspirin and related compounds. Salicylates are used to relieve pain, reduce inflammation, and lower fever.

Ulcerative colitis—A type of inflammatory bowel disease in which ulceration or erosion of the lining of the colon occur.

Treatment of ulcerative colitis using Rowasa is a single 60 mL capsule inserted rectally at bedtime each night for three to six weeks. The capsule should remain inserted for eight hours. Treatment using Casa is a single 1 g suppository inserted each night at bedtime for three weeks. The capsule should remain in place for at least one to three hours.

Dosing may differ depending on the severity of the symptoms, on previous responses to the same or similar drugs, or if an extended-release formulation is used. Individuals should follow their physician's directions and be aware if changing brands of mesalamine that different brands are formulated in different strengths.

Pediatric

The safety of mesalamine has not been established for use in children under age five. For children over age five, dosage depends on the child's weight and is split into doses given twice daily. Oral dosage should not exceed 1,200 mg per day in children up to 72 lb. (33 kg), 2,000 mg per day in children up to 119 lb. (54 kg), and 2,400 mg per day in children up to 198 lb. (90 kg). The safety of rectally administered mesalamine has not been established for use in children.

Geriatric

There are no specific recommendations for dosages for seniors. However, as the body ages, it is often not as

efficient at breaking down and clearing medications from the blood. Therefore, geriatric dosing should generally be done as conservatively as possible, and seniors should be monitored closely for side effects.

Precautions

Mesalamine should be used very cautiously in patients with chronic renal failure. Anyone who has previously been shown to be sensitive to salicylates (such as **aspirin**) or aminosaliclates should not take mesalamine.

Pediatric

Children with chickenpox or who have symptoms of influenza should not be given mesalamine.

Mesalamine should not be used in children under the age of 5. Studies of the use of mesalamine in children ages 5–12 years have not uncovered any safety risks in this age group. Dosing should be done taking the child's weight into account to ensure appropriate administration.

Geriatric

While no studies have shown specific risks for seniors taking mesalamine, seniors may benefit from lower dosages as aging can often lead to decreased kidney function, which can affect the rate at which drugs are broken down in the body.

Pregnant or breastfeeding

Mesalamine carries the FDA pregnancy category B or C depending on the form. Category B drugs are drugs believed to pose little or no threat to a developing fetus and may be acceptable for use with caution during pregnancy. Category C drugs are drugs that should only be used with caution if the benefits of using the drug outweigh the risks associated with it. Either studies have shown risk in animals but no human studies have been done, or no studies have been done on humans or animals, so the risk is not well understood.

There have been no studies done on the effects of taking mesalamine while breastfeeding, although the drug has been shown to pass to the infant through breast milk. Therefore, mesalamine should only be used with caution while breastfeeding.

Side effects

Serious allergic reactions to mesalamine are rare but can occur. Any patient experiencing a rash; swelling or itching of the tongue, throat, or face; difficulty breathing; or dizziness should seek emergency medical help right away, as these may be symptoms of a life-threatening allergic reaction.

Individuals who experience any of the following side effects should stop taking mesalamine and call their doctor promptly:

- severe abdominal or stomach pain
- chest pain
- shortness of breath
- dark urine or very little urine
- bloody diarrhea
- fever
- yellowing of the eyes or skin

Common but less serious side effects include:

- dry mouth
- decreased appetite
- nausea
- vomiting
- gas
- back pain
- muscle pain or joint stiffness
- itching
- sweating
- indigestion or heartburn

Interactions

It is important for patients to tell their doctor and pharmacist about all medications they are taking, both over-the-counter and prescription, and all vitamins and supplements, including herbal supplements. The doctor or pharmacist can check a complete list of the most accurate and up-to-date information about possible interactions.

Drugs

Mesalamine should not be taken with antacids, even over-the-counter antacids, as these drugs may affect the way the pills break down and the medicine is released into the body.

Mesalamine should not be taken with balsalazide, olsalazine, or **sulfasalazine**. It may cause false positives for some urine tests, including tests for normetanephrine levels.

Mesalamine should also not be taken by individuals who have had a recent measles, mumps, and rubella (MMR) vaccine, or who are taking certain other drugs, including **lansoprazole**, **nizatidine**, and **pantoprazole**.

Resources

BOOKS

Lichtenstein, Gary R. *Medical Therapy of Ulcerative Colitis*. New York: Springer, 2014.

PERIODICALS

Devlen, Jennifer, et al. "Barriers to Mesalamine Adherence in Patients with Inflammatory Bowel Disease: A Qualitative Analysis." *Journal of Managed Care & Specialty Pharmacy* 20, no. 3 (2014): 309–14.

Winter, Harland S., et al. "High- and Low-Dose Oral Delayed-Release Mesalamine in Children with Mild-to-Moderately Active Ulcerative Colitis." *Journal of Pediatric Gastroenterology and Nutrition* 59, no. 6 (2014): 767–72.

WEBSITES

MedlinePlus. "Mesalamine." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a688021.html> (accessed February 19, 2015).

Micromedex. "Mesalamine (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/mesalamine-oral-route/description/drg-20064708> (accessed February 19, 2015).

Micromedex. "Mesalamine (Rectal Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/mesalamine-rectal-route/description/drg-20068210> (accessed February 19, 2015).

"Treating Children and Adolescents." Crohn's & Colitis Foundation of America. <http://www.ccfa.org/resources/treating-children.html> (accessed February 19, 2015).

ORGANIZATIONS

American Gastroenterological Association (AGA), 4930 Del Ray Avenue, Bethesda, MD 20814, (301) 654-2055, (301) 654-5920, member@gastro.org, <http://www.gastro.org/>.

Crohn's & Colitis Foundation of America, 733 Third Avenue, Suite 510, New York, NY 10017, (800) 932-2423, info@ccfa.org, <http://www.ccfa.org/>.

International Foundation for Functional Gastrointestinal Disorders, 700 W. Virginia Street #201, Milwaukee, WI 53204, (414) 964-1799, (888) 964-2001
Fax: (414) 964-7176, iffgd@iffgd.org, <http://www.iffgd.org/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Tish Davidson, AM

REVIEWED BY KEVIN GLAZA, RPh



Metaxalone, 800 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Doctors prescribe metaxalone to treat the pain and discomfort that arises from muscle spasms and acute muscle injuries, including strains and sprains. In addition to prescribing this medication, doctors will often recommend additional measures, such as rest and physical therapy, to assist in patient recovery.

Description

Scientists do not know the details of how this muscle relaxant works, but metaxalone may have an overall depressive effect on the central nervous system (CNS). It does not appear to have a direct effect on the muscle itself. By depressing the CNS (producing sedative effects), it interferes with the brain's reception of nerve impulses that carry pain sensations from the affected muscle. This not only relieves pain but also helps to relax muscles that are in spasm.

Metaxalone is sold as 800 milligram (mg) tablets to be taken by mouth.

U.S. brand names

Metaxalone is available in the United States under the brand name of Skelaxin, produced by Pfizer. In 2010, the pharmaceutical company Sandoz launched the first generic version of metaxalone.

Metaxalone

Definition

Metaxalone is a muscle-relaxing drug that is used to relieve pain associated with muscle spasms and other muscle injuries.

KEY TERMS

Benedict's test—A diagnostic test typically used for diabetes.

Central nervous system—The brain and spinal cord.

Hepatic—Related to the liver.

Renal—Related to the kidney.

International brand names

Metaxalone is available as a combination drug in India. It is sold in combination with the nonsteroidal anti-inflammatory drug (NSAID) **diclofenac** under the brand names Fenaplus-RX and Metadol.

Origins

Metaxalone received U.S. Food and Drug Administration (FDA) approval in 1962 for the relief of pain and discomfort associated with acute musculoskeletal conditions. It continues to be a widely used muscle relaxant for musculoskeletal injuries and conditions, as well as muscle spasms.

Recommended dosage

Patients are directed to take metaxalone with food. The typical adult dosage is a single 800 mg tablet to be taken every 6 to 8 hours.

Pediatric

Children up to 12 years old should not take metaxalone. The dosage for children ages 13 and older is the same as the adult dosage: a single 800 mg tablet taken three to four times a day.

Geriatric

The dosage is the same as it is for younger adults.

Precautions

Deaths due to accidental or deliberate overdose have been associated with the use of metaxalone. These typically occur in conjunction with the use of other CNS depressants, such as narcotic drugs or alcohol.

Metaxalone use can cause drowsiness, which may affect the patient's ability to drive a vehicle or operate machinery safely. For this reason, patients should not undertake these activities until they understand how the drug affects them.

False-positive Benedict's tests (used to identify certain sugars in urine, typically as diagnostic measures for diabetes) have been reported when a patient is using metaxalone, so doctors may order separate glucose-specific tests for patients who have this procedure done.

Pediatric

The safety and efficacy of metaxalone have not been established for children aged 12 years old and younger.

Geriatric

Kidney or liver issues are more common in this population, and if these health conditions are present in a patient, they may impact a doctor's decision to prescribe metaxalone. A 2014 study evaluated the potential relationship between the use of muscle relaxants, including metaxalone, and increased falls and fractures, emergency-department (ED) visits, and hospitalizations among elderly patients. The study, published in *BMC Geriatrics*, noted that "exposure to either skeletal muscle relaxants or antihistamines in the elderly were associated with a greater than two-fold increase in ED visits and/or hospitalizations." Elderly patients (and their caregivers) should take this into account when using metaxalone.

Pregnant or breastfeeding

Metaxalone has not been assigned an FDA pregnancy category. However, as soon as a woman learns she is pregnant or when she begins trying to conceive, it is recommended that she stop taking metaxalone and consult with her doctor to determine whether the benefits of metaxalone outweigh any potential risks. It is not known if metaxalone is excreted into breast milk, so it is recommended that mothers stop using this drug while they are nursing.

Other conditions and allergies

Patients who are hypersensitive to metaxalone or any of the components of its formulations should not take this drug.

Doctors should use caution in prescribing this medication to patients who currently have or who have ever had seizures, a blood disorder, or kidney (renal) or liver (hepatic) disease. For patients who have preexisting liver damage, doctors will order liver-function studies to help ensure patient safety. Individuals who have severe kidney (renal) or liver (hepatic) disease or who have anemia (an insufficient supply of healthy red blood cells) should not take this medication.

Side effects

Most patients tolerate this medication well, but some side effects have been reported. Patients who use metaxalone should take the time to learn which side effects may be cause for concern, and report any concerning issues to the doctor.

Side effects associated with metaxalone include:

- drowsiness
- irritability
- upset stomach
- headache
- dizziness
- nervousness
- seizures
- weakness
- unusual bruising or bleeding, and/or dark, tarry stools (a sign of bleeding)
- skin rash, which can be severe
- difficulty breathing, including shortness of breath
- yellowing of the skin or eyes (jaundice)
- discolored urine

Interactions

Patients should tell the doctor about all other medications they are taking, especially any sedatives or tranquilizers. The use of any herbs and supplements should also be reported, as well as any known allergies.

Drugs

A variety of prescription and over-the-counter drugs may exacerbate the side effects of metaxalone. These include medicines for colds, allergies, seizures, depression, and anxiety, as well as sleeping pills, narcotic pain medications, and other muscle relaxers. Patients should consult the package insert for details, and when in doubt, should contact the doctor's office before taking drugs with metaxalone.

Herbs and supplements

No specific interactions are noted, but patients should still inform their doctors about any herbs or supplements they are taking.

Foods and other substances

Alcohol can cause drowsiness in addition to the drowsiness caused by metaxalone use, so patients should not consume alcohol when taking metaxalone.

Resources

BOOKS

- Kapoor, A. K., and S. M. Raju. "Skeletal Muscle Relaxants." In *Illustrated Medical Pharmacology*. New Delhi, India: Jaypee Brothers Medical Publishers, Ltd., 2013.
- Kaye, Alan David, Adam M. Kaye, and Richard D. Urman, eds. *Essentials of Pharmacology for Anesthesia, Pain Medicine, and Critical Care*. New York: Springer, 2014.

PERIODICALS

- Alvarez, Carlos A., et al. "Association of Skeletal Muscle Relaxers and Antihistamines on Mortality, Hospitalizations, and Emergency Department Visits in Elderly Patients: A Nationwide Retrospective Cohort Study." *BMC Geriatrics* 15, no. 2 (2015): e-pub ahead of print. <http://www.biomedcentral.com/1471-2318/15/2> (accessed March 7, 2015).
- Hetland, Amanda, and David B. Carr. "Medications and Impaired Driving: A Review of the Literature." *Annals of Pharmacotherapy* 48, no. 4 (2014): 494–506.

WEBSITES

- Center for Drug Evaluation and Research. "Application Number: 13-217/S-044, Clinical Pharmacology/Biopharmaceutic Review(s)." FDA.gov. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/013217_S044_SKELTIN_BIOPHARM.pdf (accessed March 7, 2015).
- MedlinePlus. "Metaxalone." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682010.html> (accessed March 7, 2015).
- "Metaxalone." Drugs.com. <http://www.drugs.com/cdi/metaxalone.html> (accessed March 7, 2015).
- "Metaxalone." DrugBank. <http://www.drugbank.ca/drugs/DB00660> (accessed March 7, 2015).
- Micromedex. "Metaxalone (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/metaxalone-oral-route/description/drg-20071948> (accessed March 7, 2015).
- Physicians' Desk Reference. "Skelaxin." PDR Health. <http://www.pdrhealth.com/drugs/skelaxin> (accessed March 7, 2015).
- "Skelaxin." RxList.com. <http://www.rxlist.com/skelaxin-drug.htm> (accessed March 7, 2015).
- U.S. Food and Drug Administration. "Skelaxin (Metaxalone) Tablets." FDA.gov. http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/013217s0461bl.pdf (accessed March 7, 2015).
- U.S. National Library of Medicine. "Metaxalone." LiverTox. <http://livertox.nih.gov/Metaxalone.htm> (accessed March 7, 2015).
- U.S. National Library of Medicine. "Robaxin—Skelaxin—Metaxalone Tablet." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cb47d76e-a7e3-4bac-8074-8d7e95c6a6eb> (accessed March 7, 2015).

ORGANIZATIONS

National Institute of Arthritis and Musculoskeletal and Skin Diseases, 1 AMS Circle, Bethesda, MD 20892-3675, (301) 495-4484, (877) 22-NIAMS (226-4267), Fax: (301) 718-6366, niamsinfo@mail.nih.gov, <http://www.niams.nih.gov/>.

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Metformin

Definition

Metformin is an oral antihyperglycemic medication in the biguanide class. It lowers blood glucose levels by suppressing glucose production in the liver, decreasing the amount of sugar absorbed by the body from food and increasing the body's sensitivity to insulin. It does not affect the body's production of insulin.

Purpose

Metformin is used most commonly in the treatment of type 2 diabetes in overweight or obese patients with normal kidney function, either by itself or together with

insulin or a sulfonylurea oral diabetes medication. It is considered a first-line drug of choice for these individuals. It is also used alongside insulin in the treatment of gestational diabetes. In addition, metformin is used in the treatment of polycystic ovary syndrome (PCOS); it is considered an orphan drug for this condition.

Metformin cannot be used to treat patients with type 1 diabetes.

Off-label uses

Metformin has three major off-label uses:

1. weight control in patients who have gained weight while taking such antipsychotic medications as **olanzapine**
2. as an addition to insulin therapy in patients with type 1 diabetes who are severely overweight, require large daily doses of insulin, or have poorly controlled diabetes
3. as a preventive measure against the development of type 2 diabetes in at-risk patients

A fourth off-label use of metformin is to treat HIV-associated lipodystrophy, a condition in which body fat is redistributed from the patient's face, buttocks, arms, and legs to the abdomen and upper back as a side effect of antiretroviral drugs.

As of 2015, metformin was being studied as a treatment for atherosclerosis and for other disorders associated with insulin resistance. It was also being investigated for its anticancer properties in diabetic patients—it has been found to extend survival time in diabetic patients diagnosed with breast, colorectal, or late-stage lung cancer.

Description

Metformin hydrochloride itself is a white powder easily soluble in water. It is dispensed as white, film-coated tablets in both a standard and an extended-release form. The standard tablets are available in three strengths: 500, 850, or 1,000 milligrams (mg). The extended-release form is available as 500 mg or 750 mg tablets.

Metformin is also available as an oral solution under the trade name Riomet, formulated to contain 500 mg per 5 milliliters (mL).

Metformin is sometimes prescribed in fixed-dose combinations with other antihyperglycemic drugs such as **pioglitazone**, **saxagliptin**, and **rosiglitazone**.

U.S. brand names

Metformin is sold in the United States under the brand names Fortamet, Glucophage, Glucophage XR,



Metformin, 500 mg. (© Cengage Learning®.)

KEY TERMS

Antihyperglycemic—Any medication given to lower blood glucose levels. Metformin is an antihyperglycemic.

Atherosclerosis—Stiffening of large- and medium-sized arteries as a result of the formation of fatty plaques along the vessel walls. The process of plaque formation may eventually interfere with blood flow to vital organs.

Biguanides—A class of medications used primarily in the treatment of type 2 diabetes; some drugs in this class are used in the prophylactic treatment of malaria.

Diabetic ketoacidosis (DKA)—A potentially life-threatening complication of diabetes in which a shortage of insulin causes the body to burn fatty acids and produce acidic ketone bodies, resulting in such symptoms as nausea, vomiting, and intense thirst.

Gestational diabetes—A condition in which women without previously diagnosed diabetes develop high blood sugar levels during pregnancy.

Insulin resistance—A condition in which the cells of the body fail to respond normally to insulin and are unable to use it effectively.

Lactic acidosis—A condition characterized by a buildup of lactate in the blood. It may result from an overdose of metformin.

Lipodystrophy—Abnormal distribution or degeneration of the body's adipose (fatty) tissue. It may be congenital or acquired as a side effect of antiretroviral drugs given to treat HIV infection.

Orphan drug—A medication that has been developed to treat a rare disease, defined in the United States as a disease or disorder affecting fewer than 200,000 people.

Polycystic ovary syndrome (PCOS)—An endocrine disorder in women characterized by ovarian cysts, infertility, amenorrhea (absence of menstrual periods), acne, and a male pattern of body hair. It is also known as Stein-Leventhal syndrome.

Glumetza, and Riomet. The tablets are also available in generic formulations.

Canadian brand names

Metformin is sold in Canada under the brand names Glucophage, Glumetza, Apo-Metformin, Avandamet,

Gen-Metformin, Janumet, Novo-Metformin, and Nu-Metformin.

International brand names

Metformin is sold by a number of pharmaceutical companies worldwide under a number of brand names, including Glucophage, Glumetza, Atformin, Clormin, Diaformin, Formin, Glucomet, Glyformin, Metformin Teva, Metsulina, Reformin, and Zoform.

Origins

Metformin was originally synthesized in the 1920s and found to reduce blood sugar levels, but it was largely forgotten after the discovery of insulin in 1922. It was not until 1957 that a French physician named Jean Sterne published the results of a clinical trial of metformin as a treatment for diabetes. Metformin was approved in the United Kingdom in 1958, Canada in 1972, and by the U.S. Food and Drug Administration (FDA) in March 1995, when the drug was introduced by Bristol-Myers Squibb. The FDA approved the extended-release formulation of metformin in October 2000. The drug went off patent in the United States in 2002. Riomet, the liquid formulation, was developed by Ranbaxy and approved by the FDA in September 2003.

Recommended dosage

Patients prescribed either form of metformin tablet should always take the tablets with meals, as this precaution lowers the risk of digestive side effects with the drug. Patients taking the extended-release tablets should swallow them whole with a glass of water; they should not crush, chew, or break the tablets. They should not be concerned if a part of the tablet passes into the stool, as the body will have absorbed all of the active ingredient.

Patients who are prescribed the liquid formulation of metformin should use a marked measuring spoon, an oral syringe, or a medicine cup to measure the dose, as ordinary household teaspoons or tablespoons vary in the amount of liquid they hold and may not provide an accurate dose. The pharmacist can also supply the patient with a measuring device.

Adults

TYPE 2 DIABETES. For treatment with an immediate-release tablet or Riomet solution, the initial dosage is 500 mg by mouth every 12 hours or 850 mg by mouth every day with meals. The dosage is increased every two weeks. The maintenance dosage is 1,500–2,550 mg per day by mouth, divided into doses given every 8–12 hours

with meals. The total dose should not exceed 2,550 mg per day.

For treatment with extended-release tablets, the dosage varies depending on the brand used.

- Glucophage XR: Initial dosage should be 500 mg by mouth each day with dinner; may be adjusted by 500 mg per day each week. Total dose should not exceed 2,000 mg per day.
- Fortamet: Initial dosage should be 500–1,000 mg by mouth each day; may be adjusted by 500 mg per day each week. Total dose should not exceed 2,500 mg per day.
- Glumetza: Initial dosage should be 1,000 mg by mouth each day; may be adjusted by 500 mg per day each week. Total dose should not exceed 2,000 mg per day.

For the prevention of type 2 diabetes (off label use), the initial dosage should be 850 mg of metformin by mouth each day, with a target dose of 850 mg every 12 hours.

POLYCYSTIC OVARY SYNDROME. For the treatment of PCOS, the initial dosage should be 500 mg by mouth once daily. This is increased to 500 mg twice a day after one week, then to 500 mg three times daily after another week. The most effective dose of metformin for PCOS is 500 mg taken three times a day.

Pediatric

For the treatment of type 2 diabetes with immediate-release tablets:

- Youths between 10 and 16 years of age are started with an initial dose of 500 mg by mouth every 12 hours, followed by a maintenance dose adjusted upward by 500 mg each week. The total dose should not exceed 2,000 mg per day.
- Adolescents 17 and older may take an initial dose of 500 mg by mouth every 12 hours or 850 mg by mouth each day with meals. This dose may be adjusted upward every two weeks.
- The maintenance dose is 1,500–2,550 mg per day, divided into doses taken every 8 to 12 hours with meals. The total dose should not exceed 2,550 mg per day.

For the treatment of type 2 diabetes in adolescents 17 and older with extended-release tablets, the dosage depends on the specific brand that is used:

- Glucophage XR: Initial dose is 500 mg by mouth each day with dinner, adjusted upward by 500 mg per day each week. Total daily dose should not exceed 2,000 mg.
- Fortamet: 500–1,000 mg is taken by mouth each day, adjusted upward by 500 mg per day each week. Total dose should not exceed 2,500 mg per day.

Extended-release tablets should not be used in children younger than 17 years of age.

Precautions

Patients scheduled for any diagnostic imaging test that requires injection of a contrast dye will be asked to discontinue metformin temporarily before the test. The reason for this precaution is that contrast dyes may cause a short-term reduction in kidney function, thus leading to the retention of metformin in the body and an increased risk of lactic acidosis. Patients should not resume taking metformin until 48 hours after the test.

Patients who take an overdose of metformin may develop the symptoms of lactic acidosis (weakness, increasing sleepiness, slow heart rate, cold feeling, muscle pain, shortness of breath, stomach pain, feeling lightheaded, and fainting). They should call for emergency help or call the Poison Control hotline at 1 (800) 222-1222.

Pediatric

Children younger than 10 should not use metformin.

Geriatric

Metformin should be used with caution in older adults, as they often have impaired kidney function. The drug should not be given to patients over 80 years unless normal kidney function can be established.

Pregnant or breastfeeding

Metformin carries the FDA pregnancy category B, which means that studies of animal reproduction do not indicate potential harm to a human fetus. Metformin is considered safe for use by breastfeeding women.

Other conditions and allergies

Metformin should not be used in the following groups of patients:

- patients with impaired liver function
- patients with impaired kidney function
- patients known to be allergic to metformin
- patients in a state of diabetic ketoacidosis (DKA), a medical emergency that requires immediate treatment with a short-acting insulin, among other measures
- patients with acute congestive heart failure; increased risk of lactic acidosis
- patients with sepsis (blood poisoning)
- patients with type 1 diabetes

Patients with any of the following conditions should tell their doctor before they take metformin:

- history of kidney, heart, or liver disease
- history of heavy drinking
- hypoglycemia
- anemia
- malnutrition
- dehydration
- underactive thyroid or pituitary gland
- recent fever, infection, surgery, or trauma
- vitamin B₁₂ deficiency

Side effects

Side effects are more common in the immediate-acting form of metformin than in the extended-release form of the drug. The most common side effects include:

- diarrhea
- nausea or vomiting
- flatulence (intestinal gas)
- weakness
- indigestion
- abdominal cramping
- headache

Patients who have any of the following side effects should contact their doctor at once:

- symptoms of the allergic reaction angioedema, which include sudden swelling of the face, arms, legs, eyes, lips, or tongue; hives; wheezing; or problems with swallowing or breathing
- chest pain
- signs of lactic acidosis, which include feeling tired or weak; having muscle pain, trouble breathing, or severe stomach pain; feeling cold, dizzy, or light-headed; having a slow or irregular heartbeat
- symptoms of hypoglycemia (low blood sugar), which may include anxiety; behavioral changes that resemble those of alcohol intoxication; difficulty in thinking clearly; cold sweats; nervousness; difficulty sleeping; tremor; slurred speech; tingling sensations in the hands, feet, or tongue; excessive hunger; drowsiness; and light-headedness or dizziness
- symptoms of high blood sugar, which may include increased hunger, thirst, or volume of urination; blurred vision; fatigue; fruity breath odor; dry mouth; shortness of breath; and nausea or vomiting

Interactions

Individuals should tell both their doctor and pharmacist about any medications (over-the-counter and

prescription), vitamins, herbs, or supplements that they are taking, because there are many substances and medications that can interact with metformin.

Drugs

Metformin interacts with a wide variety of other drugs. Drugs that increase the risk of high blood sugar when taken with metformin include:

- decongestants (pseudoephedrine and phenylephrine)
- diuretics (e.g., **hydrochlorothiazide**, **furosemide**, ethacrynic acid, **torsemide**, metolazone)
- estrogens (hormone replacement therapy, birth control pills)
- phenothiazines (e.g., chlorpromazine, fluphenazine, thioridazine, perphenazine)
- corticosteroids (e.g., **prednisone**, cortisone, hydrocortisone, **triamcinolone**, prednisolone, fludrocortisone)
- **phenytoin**
- thyroid medications
- antiseizure medications

Other interactions include:

- Calcium channel blockers (e.g., verapamil, **diltiazem**, amlodipine, nicardipine, felodipine) reduce the effectiveness of metformin.
- Fluoroquinolone antibiotics (e.g., **ciprofloxacin**, ofloxacin, norfloxacin, **levofloxacin**) make it difficult to adequately control blood glucose levels.
- Cimetidine increases levels of metformin in the blood.

The patient's dosage of metformin should be monitored carefully if the drug is being used together with any insulin or another oral antidiabetic medication, as there is an increased risk of low blood sugar.

Herbs and supplements

Patients taking metformin should avoid cinnamon, bitter melon, American ginseng, and horse chestnut because they increase the effects of metformin.

Food and other substances

Patients taking metformin should not drink alcohol. It lowers blood sugar and increases the patient's risk of lactic acidosis. Patients taking metformin should also avoid using marijuana because it lowers the effectiveness of metformin.

Resources

BOOKS

- Bagchi, Debasis, and Nair Sreejayan, eds. *Nutritional and Therapeutic Interventions for Diabetes and Metabolic Syndrome*. Waltham, MA: Elsevier Academic Press, 2012.
- Bailey, Clifford J., et al, eds. *Metformin: The Gold Standard*. Hoboken, NJ: John Wiley and Sons, 2007.
- Unger, Jeff. *Diabetes Management in Primary Care*. 2nd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2013.

PERIODICALS

- Forouzandeh, F., et al. "Metformin beyond Diabetes: Pleiotropic Benefits of Metformin in Attenuation of Atherosclerosis." *Journal of the American Heart Association* 3, no. 6 (2014): e001202. <http://dx.doi.org/10.1161/JAHA.114.001202> (accessed March 6, 2015).
- Jain, S. S., et al. "Pathogenesis and Treatment of Human Immunodeficiency Virus Lipodystrophy." *Indian Journal of Endocrinology and Metabolism* 16, suppl. 1 (2012): S20–S26.
- Klein, J., R. Charach, and E. Sheiner. "Treating Diabetes during Pregnancy." *Expert Opinion on Pharmacotherapy* 16, no. 3 (2015): 357–68.
- Lin, J. J., et al. "Survival of Patients with Stage IV Lung Cancer with Diabetes Treated with Metformin." *American Journal of Respiratory and Critical Care Medicine* 191, no. 4 (2015): 448–54.

WEBSITES

- AHFS Consumer Medication Information. "Metformin." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a696005.html> (accessed March 6, 2015).
- "Metformin Hydrochloride." Drugs.com. <http://www.drugs.com/monograph/metformin-hydrochloride.html> (accessed February 19, 2015).
- Micromedex. "Metformin (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/metformin-oral-route/description/drg-20067074> (accessed February 19, 2015).
- National Cancer Institute. "Metformin: Can a Diabetes Drug Help Prevent Cancer?" <http://www.cancer.gov/cancertopics/research-updates/2013/metformin> (accessed March 6, 2015).
- Sease, Julie M. "Is Metformin Effective for Type 1 Diabetes?" Medscape Reference. <http://www.medscape.com/viewarticle/756139> (accessed February 19, 2015).

ORGANIZATIONS

- American Diabetes Association, 1701 North Beauregard Street, Alexandria, VA 22311, (800) DIABETES (342-2383), <http://www.diabetes.org/>.
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 9000 Rockville Pike, Bethesda, MD 20892-2560, (301) 496-3583, <http://www.niddk.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Rebecca J. Frey, PhD
REVIEWED BY KEVIN GLAZA, RPH

Metformin/sitagliptin see **Sitagliptin/metformin**

Methadone

Definition

Methadone is a powerful narcotic drug that is classified as an opioid (an analgesic that is used for severe pain).

Purpose

Methadone is used in the long-term maintenance treatment of narcotic addiction. It has been used successfully to treat narcotic addiction for over twenty years in the United States, and it is the only agent in its class that is approved by the U.S. Food and Drug Administration (FDA) for the maintenance treatment of narcotic addiction.



Methadone, 10 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Methadone may also be prescribed for pain relief, but in these cases, the physician should note this use on the prescription. Methadone for pain relief is primarily used for moderate to severe pain that has not responded to therapy with other opiate pain relievers, or pain that requires continuous analgesia (relief).

Description

Both heroin and methadone are opioids; as such, methadone and heroin bind to the same places in the brain. Methadone, however, is the opioid of choice for the treatment of narcotic addiction, since it is longer lasting and patients do not experience the “high” associated with heroin. In opioid maintenance therapy, a person addicted to heroin receives methadone instead of heroin. The dose of methadone may then be decreased over time so that the person can overcome his or her opioid addiction without experiencing withdrawal symptoms, or, after a person has received methadone for a period of time, he or she may choose to go through detoxification with the drug **clonidine**.

Methadone for maintenance treatment is dispensed in methadone clinics. The program needs to be registered with the Drug Enforcement Administration (DEA). For admission to methadone treatment in clinical programs, federal standards mandate a minimum of one year of opiate addiction as well as current evidence of addiction.

Methadone is available in 5 and 10 milligram (mg) tablets and as well as solutions in formulations of 10 mg per milliliter (mL), 5 mg/5 mL, and 10 mg/5 mL.

U.S. brand names

In the United States, methadone is also known as Dolophine and Methadose.

Recommended dosage

The initial dose of methadone for narcotic addiction is 20 mg daily with an additional 10 mg given four to eight hours later. After achieving initial dosing of about 40 mg daily, the dose should be increased since there is evidence that the relapse rate is significantly lower in patients on 80–100 mg daily rather than 40–50 mg daily. The stabilization to maintenance dosing requires one to three months.

The minimum effective dose is 60 mg daily. Patients on lower maintenance doses have recently been studied and have shown shorter treatment retention and continued heroin use. If patients are stable on methadone for six months or longer, their methadone dose should not be increased by 33% or more, as this sudden increase in dose is associated with an increase in craving for the

KEY TERMS

Analgesic—Any agent that relieves pain.

Central nervous system (CNS) depressant—Any drug that tends to reduce the activity of the central nervous system. The major drug categories included in this classification are: alcohol, anesthetics, anti-anxiety medications, antihistamines, antipsychotics, hypnotics, narcotics, sedatives, and tranquilizers.

Narcotic—Any drug that produces insensibility or stupor and/or generally causes effects similar to those caused by morphine.

Opiate—Any narcotic analgesic derived from a natural source, such as morphine from the opium poppy.

Opioids—One of the major classes of semi- or fully synthetic psychoactive drugs that includes methadone.

Tolerance—A progressive decrease in the effectiveness of a drug with long-term use, requiring higher doses to achieve the desired effect.

drugs that were previously abused. Some heroin patients need to be on doses up to 180 mg daily to provide adequate maintenance and to prevent relapse.

Pain therapy is very individualized. A clinician must complete a comprehensive review of the patient and all factors that would contribute to successful pain therapy. The lowest effective dosage should be initiated, then monitored over time to ensure that an effective pain relieving dose is achieved while avoiding drug tolerance and side effects.

Precautions

Methadone is a powerful narcotic. It can cause some people to feel drowsy, dizzy, or light-headed. People taking methadone should not drive a car or operate machinery.

Methadone magnifies the effects of alcohol and other central nervous system depressants, such as antihistamines, cold medicines, sedatives, tranquilizers, other prescription and over-the-counter (OTC) pain medications, barbiturates, seizure medications, muscle relaxants, and certain anesthetics including some dental anesthetics. Alcohol and other central nervous system depressants should not be used while methadone is being taken.

Intentional or accidental overdose of methadone can lead to unconsciousness, coma, or death. The signs of methadone overdose include confusion, difficulty speaking, seizures, severe nervousness or restlessness, severe dizziness, severe drowsiness, and/or slow or troubled breathing. These symptoms are increased by alcohol or other central nervous system (CNS) depressants. Anyone who feels that he or she, or someone else, may have overdosed on methadone or a combination of methadone and other central nervous system depressants should seek emergency medical attention at once.

Pregnant or breastfeeding

Pregnant women can be in methadone maintenance programs if they are at risk of returning to drug dependence. Methadone is associated with smaller birth weights and smaller head circumference.

Other conditions and allergies

Methadone should not be used in patients with a hypersensitivity to methadone. Patients who experience an allergic reaction to other opioids, such as **morphine**, **hydromorphone**, oxymorphone, or codeine, may still try methadone. They are less likely to develop the same reaction, because methadone has a different chemical structure. Methadone should be administered carefully in patients with pre-existing respiratory problems, a history of bowel obstruction, glaucoma, kidney problems, or hyperthyroidism, and in patients who are currently taking antidepressants. The prescribing physician should also be informed of any current case or history of:

- alcohol abuse
- brain disease or head injury
- colitis
- drug dependency, particularly of narcotics
- emotional problems
- emphysema, asthma, or other chronic lung disease
- enlarged prostate
- gallstones or gallbladder disease
- heart disease
- liver disease
- problems with urination
- seizures

Side effects

Most adverse effects of methadone are mild and seen only in the beginning of therapy. Some of the more common adverse effects of methadone include:

- constipation
- dizziness

- drowsiness
- itching
- nausea
- urine retention
- vomiting

Initially, patients may develop sedation and analgesia. It takes about four to six weeks for tolerance to these effects to develop. Tolerance to constipation and sweating may take longer to develop.

A few patients who are on larger doses of methadone may experience respiratory problems. Patients should be monitored for this at initiation of therapy and after dosage increases. These patients also may experience unwanted cardiac effects.

A small number of patients report a decrease in libido; impotence; and premature, delayed, or failed ejaculation. There are a few reports of occasional menstrual irregularities in female patients on methadone.

Other less common side effects include:

- abnormally fast or slow heartbeat
- blurred or double vision
- cold, clammy skin
- depression or other mood changes
- dry mouth
- fainting
- hallucinations
- hives
- loss of appetite
- nightmares or unusual dreams
- pinpoint pupils of the eyes
- redness or flushing of the face
- restlessness
- rigid muscles
- ringing or buzzing in the ears
- seizure
- severe drowsiness
- skin reaction at the site of injection
- stomach cramps or pain
- sweating
- trouble sleeping (insomnia)
- yellowing of the skin or whites of the eyes

Interactions

Patients should inform the treating physician of all drugs they currently taking to avoid the risk of interactions.

Drugs

Life-threatening interactions with other drugs have not been identified. One of the initial side effects of methadone could include dizziness and sedation, and these effects are worsened if the patient is also taking other narcotics or benzodiazepines.

Methadone magnifies the effects of other central nervous system depressants, such as antihistamines, cold medicines, sedatives and related drugs, tranquilizers, other prescription and over-the-counter (OTC) pain medications, barbiturates, seizure medications, muscle relaxants, and certain anesthetics including some dental anesthetics.

Monoamine oxidase inhibitors (MAOIs), such as Parnate (tranylcypromine) and Nardil (phenelzine), should be avoided by people taking methadone. Medications like naltrexone and naloxone should never be used concurrently with methadone. People must stop taking methadone for 7 to 10 days before starting naltrexone or naloxone.

Food and other substances

Alcohol should be avoided while methadone is being taken.

Resources

BOOKS

Albers, Lawrence J., Rhoda K. Hahn, and Christopher Reist. *Handbook of Psychiatric Drugs*. Laguna Hills, CA: Current Clinical Strategies Publishing, 2010.

PERIODICALS

Aziz, Z., and N. J. Chong. "A Satisfaction Survey of Opioid-Dependent Patients with Methadone Maintenance Treatment." *Journal of Substance Abuse Treatment* (December 30, 2014): e-pub ahead of print. <http://dx.doi.org/10.1016/j.jsat.2014.12.008> (accessed February 26, 2015).

Chan, Y. Y., et al. "Inflammatory Response in Heroin Addicts Undergoing Methadone Maintenance Treatment." *Psychiatry Research* (January 13, 2015): e-pub ahead of print. <http://dx.doi.org/10.1016/j.psychres.2014.12.053> (accessed February 26, 2015).

Lee, C. H., et al. "Familial Expressed Emotion among Heroin Addicts in Methadone Maintenance Treatment: Does It Matter?" *Addictive Behaviors* 45 (June 2015): 39–44. <http://dx.doi.org/10.1016/j.addbeh.2015.01.014> (accessed February 26, 2015).

OTHER

Drug Policy Alliance. *About Methadone and Buprenorphine*. 2nd ed. New York: Drug Policy Alliance, 2006. <http://www.drugpolicy.org/docUploads/aboutmethadone.pdf> (accessed February 26, 2015).

Substance Abuse and Mental Health Services Administration. *How to Use Methadone Safely*. U.S. Department of Health

and Human Services. http://dpt.samhsa.gov/methadone-safety/downloads/follow_directions_methadone_brochure.pdf (accessed February 26, 2015).

WEBSITES

AHFS Consumer Medication Information. "Methadone." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682134.html> (accessed February 26, 2015).

Center for Substance Abuse Research. "Methadone." University of Maryland. <http://www.cesar.umd.edu/cesar/drugs/methadone.asp> (accessed February 26, 2015).

Substance Abuse and Mental Health Services Administration. "Opioid Treatment Program Directory." <http://dpt2.samhsa.gov/treatment/directory.aspx> (accessed February 26, 2015).

ORGANIZATIONS

Substance Abuse and Mental Health Services Administration, 1 Choke Cherry Road, Rockville, MD 20857, (877) SAMHSA-7 (726-4727), TTY: (800) 487-4889, <http://www.samhsa.gov/>.

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REVIEWED BY GREGORY A. PRATT, RPh

Methocarbamol

Definition

Methocarbamol is a muscle-relaxing drug that is used to relieve pain associated with muscle strains, sprains, and other injuries.

Purpose

Doctors prescribe methocarbamol to treat the pain and discomfort that arises from various muscle injuries and muscle spasms. It is frequently prescribed with other measures, such as rest and physical therapy. Methocarbamol is also used to treat tetanus, which is a sometimes fatal bacterial infection (with the bacterium *Clostridium tetani*) that can cause severe muscle spasms. In addition, doctors sometimes prescribe methocarbamol for patients who are going through opiate withdrawal and experiencing muscle spasms and/or pain.

Description

Scientists do not know the details of how this muscle relaxant works, but in general, methocarbamol slows activity in the central nervous system (CNS), produces sedative effects, and allows the muscles to relax. Due to



Methocarbamol, 500 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

its action on the CNS, methocarbamol is considered a CNS depressant. Chemically, methocarbamol is known as (RS)-2-hydroxy-3-(2-methoxyphenoxy)propyl carbamate, and it is synthesized from a cold medication called guaifenesin. Guaifenesin is an over-the-counter expectorant medication that is used to help patients cough up phlegm from the airways.

Combination medications that pair methocarbamol with other drugs, such as **aspirin** (acetylsalicylic acid), acetaminophen (paracetamol), or ibuprofen, are available. These combination drugs are designed to enhance pain-relieving effects.

Some muscle relaxants carry a fairly high potential for abuse. Although substance abuse is not a major issue with methocarbamol compared to other muscle relaxants, abuse does sometimes occur.

Methocarbamol is sold as 500 and 750 milligram (mg) tablets to be taken by mouth. It is also available as a liquid formulation that is administered intramuscularly (via injection) or intravenously. The liquid formulations provide quick delivery of the medication into the bloodstream.

Methocarbamol is sold for veterinary use as well as human use.

U.S. brand names

Methocarbamol is available in the United States under the brand name Robaxin.

Canadian brand names

Methocarbamol is sold in Canada under the brand name Robaxin.

International brand names

Methocarbamol is available internationally as Robaxin, and under a variety of other brand names, including:

- Bolaxin
- Carbaflex
- ColoVisan
- Fubaxin
- Lumirelax
- Manobaxine
- Mioflex
- Miorel
- Musxan
- Myomethol
- Ortoton
- Rebamol
- Robinax
- Sinaxar
- Taspan

Origins

In the 1940s, scientists began studying drugs known as propanediol derivatives, which have short-lived muscle-relaxant properties. One of those drugs was guaifenesin, now typically sold as a cold medication. Scientists sought a longer-lasting version of the drug, and that work gave rise to guaifenesin carbamate, which was renamed methocarbamol. The U.S. Food and Drug Administration (FDA) granted its initial approval for methocarbamol (as Robaxin) in 500 mg and 750 mg tablets in July 1957. In June 1959, the FDA approved methocarbamol liquid solution (100 mg/mL).

Recommended dosage

Typical adult dosages vary by use:

- For muscle spasms using the tablet form, the typical dosage is a single 500 mg tablet four times a day for the first two to three days, followed by a maintenance dosage of 4,000 to 4,500 mg/day in divided doses as prescribed.
- For muscle spasms using intravenous or intramuscular administration, the typical dosage is 1,000 mg every eight hours as necessary, for no more than the first three days. After waiting two days, this regimen may be repeated if needed. As soon as the patient finds it

tolerable, he or she should be switched from intramuscular/intravenous administration to tablets taken orally.

- For tetanus using intravenous administration, the typical dosage is 1–2 grams (g) up to twice a day (maximum daily dose of 3 g). As soon as possible, the patient should be administered crushed tablets in water and saline solution, which is delivered via nasogastric tube (passes from the nose through the throat and into the stomach). The maximum daily dosage of tablets is 24 g.

Pediatric

For children with tetanus, the typical dosage is intravenous administration of 15 mg per kilogram (kg, or 2.2 lb.) of body weight or 500 mg per square meter (m²) of the patient's body surface area. This may be repeated every six hours as needed. The maximum daily dose is 1.8 g/m²/day for three days.

The safety and efficacy of methocarbamol for muscle spasms have not been established for children younger than 16 years old. Children older than 16 may follow the adult dose for this application.

Geriatric

For muscle spasms, dosage typically starts at about one-third of the normal adult dose and is increased as necessary over time. Typically, however, doctors will prescribe an alternate muscle relaxant in this age group.

Precautions

Methocarbamol use can cause drowsiness, which may affect the patient's ability to drive a vehicle or operate machinery safely. For this reason, patients should not undertake these activities until they understand how the drug affects them.

Pediatric

The safety and efficacy of methocarbamol use for muscle spasms have not been established for this age group.

Geriatric

Doctors will often prescribe a muscle relaxant other than methocarbamol for older adults because other options are typically deemed to be safer and more effective alternatives in this age group. As is the case with many medications, the risk of side effects associated with methocarbamol use may be heightened in older patients.

KEY TERMS

Central nervous system (CNS)—The brain and spinal cord.

Hypotension—Abnormally low blood pressure.

Tetanus—Also known as lockjaw, tetanus is a sometimes fatal infection with the bacterium *Clostridium tetani*. Primary symptoms are muscle spasms, which can be severe.

Pregnant or breastfeeding

Methocarbamol carries the FDA pregnancy category C, which indicates a potential risk to the fetus. As soon as a woman learns that she is pregnant or begins trying to conceive, she should consult with a doctor to determine whether the benefits of methocarbamol outweigh the risks to the fetus. Women should also ask the doctor about the risks of using this drug while they are nursing, because animal studies indicate that it is excreted into milk.

Other conditions and allergies

Patients who are hypersensitive to methocarbamol or any of the components of its formulations should not take this drug.

Individuals who have kidney (renal) or liver (hepatic) disease may experience worsened side effects with the use of this medication and should discuss this possibility with the doctor.

Side effects

Patients who use methocarbamol may experience certain side effects. These include:

- drowsiness
- upset stomach, nausea, and/or vomiting
- blurred or double vision
- discoloration of the urine
- headache
- fever
- hypotension (abnormally low blood pressure), which may be accompanied by dizziness
- confusion and/or forgetfulness
- seizures
- chest pain and/or abnormal heartbeat
- swelling, particularly of the face or tongue, which can be serious
- skin rash, which can be severe

Interactions

Interactions between methocarbamol and other drugs have been noted. Patients should tell their doctor about all other medications they are taking, especially any sedatives or tranquilizers, as well as prescription and over-the-counter drugs used to treat seizures, depression, colds, or coughs.

Drugs

Overdose of methocarbamol does occur. This is often associated with the use of psychotropic drugs or other CNS depressants (sedatives and tranquilizers that slow brain activity). Overdose may result in symptoms such as blurred vision, hypotension, seizures, and coma, or in death.

Herbs and supplements

No specific interactions are noted, but patients should still inform their doctor about any herbs or supplements they are taking.

Foods and other substances

Alcohol is a CNS depressant, as is methocarbamol. When overdose with methocarbamol occurs, it is often associated with the use of alcohol.

Resources

BOOKS

- Kapoor, A. K., and S. M. Raju. "Skeletal Muscle Relaxants." In *Illustrated Medical Pharmacology*. New Delhi, India: Jaypee Brothers Medical Publishers, Ltd., 2013.
- Lo, Joyce C., and Alan David Kaye. "Benzodiazepines and Muscle Relaxants." In *Essentials of Pharmacology for Anesthesia, Pain Medicine, and Critical Care*, edited by Alan David Kaye, Adam M. Kaye, and Richard D. Urman. New York: Springer, 2014.
- Nita, Dragos A., and Teesta B. Soman. "Movement Disorders in the ICU." In *Pediatric Critical Care Medicine, Volume 2: Respiratory, Cardiovascular, and Central Nervous Systems*, edited by Derek S. Wheeler, Hector R. Wong, and Thomas P. Shanley. 2nd ed. New York: Springer, 2014.

PERIODICALS

- Marulappa, Vamadeva Giriyaipura, et al. "A Ten Year Retrospective Study on Adult Tetanus at the Epidemic Disease (ED) Hospital, Mysore in Southern India: A Review of 512 Cases." *Journal of Clinical & Diagnostic Research* 6, no. 8 (2012): 1377–80.

WEBSITES

- EMC Medicine Guides. "Methocarbamol 750mg Tablets." NHS. <http://www.medicines.org.uk/guides/methocarbamol/Muscle%20spasm> (accessed March 6, 2015).
- Lau, Elaine. "Methocarbamol." The Hospital for Sick Children. <http://www.aboutkidshealth.ca/En/HealthAZ/Drugs/Pages/Methocarbamol.aspx> (accessed March 6, 2015).

MedlinePlus. "Methocarbamol." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682579.html> (accessed March 6, 2015).

"Methocarbamol." Drugs.com. <http://www.drugs.com/methocarbamol.html> (accessed March 6, 2015).

Micromedex. "Methocarbamol (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/methocarbamol-oral-route/description/drg-20071962> (accessed March 6, 2015).

U.S. National Library of Medicine. "Robaxin — Methocarbamol Injection, Solution." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=1254> (accessed March 6, 2015).

U.S. National Library of Medicine. "Robaxin — Methocarbamol Tablet, Film Coated." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0db1e8dd-b4fa-491b-a529-0fb939710759> (accessed March 6, 2015).

ORGANIZATIONS

National Institute of Arthritis and Musculoskeletal and Skin Diseases, 1 AMS Circle, Bethesda, MD 20892-3675, (301) 495-4484(877) 22-NIAMS (226-4267), Fax: (301) 718-6366, niamsinfo@mail.nih.gov, <http://www.niams.nih.gov/>.

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Methotrexate

Definition

Methotrexate is in a class of medications called antimetabolites. It works by blocking an enzyme that is needed by cells to live. This interferes with abnormal cell growth (e.g., the cell growth that occurs with cancers). The cells that are blocked are eventually destroyed by the body.

Purpose

Methotrexate is administered to cancer patients diagnosed with various malignancies. These conditions may include breast cancer, lung cancer, non-metastatic bone cancer, cancers associated with the head and neck, acute lymphocytic leukemia, meningeal leukemia, advanced non-Hodgkin lymphoma, and uterine tumors. Certain other cancers may be treated with methotrexate as prescribed by the oncologist.

Methotrexate is also used to treat rheumatoid arthritis (RA) as well as severe psoriasis; it may work



Methotrexate, 2.5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

for these conditions by improving the immune system. This medication is often prescribed for noncancer diagnoses when other medications have failed at effectively treating the conditions.

Off-label uses

Methotrexate is sometimes used to treat Crohn's disease, a condition in which the immune system attacks the lining of the digestive tract, causing diarrhea, weight loss, and fever. Doctors may also prescribe methotrexate for the treatment of multiple sclerosis (MS), a condition in which the immune system attacks the nerves, causing weakness; numbness; loss of muscle coordination; and problems with speech, vision, and bladder control. The medication may work by the same mechanism of action that allows it to work for other autoimmune disorders, such as RA.

Description

Methotrexate is a highly effective chemical compound that targets a specific enzyme required by cells for normal function. When this enzyme activity is blocked by methotrexate, certain processes within the cell are shut down, and cell death results. The growth of some normal cells may be affected by methotrexate. However, because this is a process associated with actively dividing cells, the accelerated rate at which cancer cells grow and divide makes them more susceptible to the effects of methotrexate.

Methotrexate may be given as a single agent, often followed by leucovorin rescue. Methotrexate may also be administered in a combination regimen with steroids to produce and maintain the rapid remission of certain cancers or as part of an adjuvant therapy regimen with doxorubicin, cisplatin, or the BCD combination of bleomycin, cyclophosphamide, and dactinomycin.

Methotrexate is a folic acid derivative that interferes with folic acid metabolism (folate antagonist). It is a cytotoxic agent (a chemical that is directly toxic to cells) with multiple characteristics and may be described as an antimetabolite, antineoplastic, and immunosuppressant, which is why it is effective in the treatment of autoimmune disorders, rheumatoid arthritis, and psoriasis. In psoriasis, methotrexate slows the growth of skin cells to stop scales from forming. In RA, methotrexate decreases the overactivity of the immune system.

Methotrexate is available in injectable and tablet forms.

U.S. brand names

In the United States, methotrexate is sold under the brand names Rheumatrex and Trexall. It is available as a generic under the names amphotericin and MTX.

Canadian brand names

In Canada, methotrexate is sold under the brand names Apo-Methotrexate, Methotrexate Hospira, Methotrexate Pfizer, Methotrexate, Metoject, and ratio-Methotrexate Sodium.

International brand names

Methotrexate is sold under a variety of brand names internationally.

Origins

Methotrexate was granted FDA approval in 1986.

Recommended dosage

Methotrexate is available in two forms: injectable and tablet. The injectable form may be given intravenously (IV), intramuscularly (IM), or intrathecally (directly into the spinal fluid).

The dosage amount for methotrexate varies widely for patients receiving methotrexate. When used cyclically rather than continually, the final dose and treatment cycle will be determined by the physician based on what the medication is being used for, whether methotrexate is being used as a single agent or in concert with other drugs, and the method by which the medication is being administered.

KEY TERMS

Antimetabolite—Anticancer drugs that prevent cells from growing and dividing by blocking the chemical reactions required in the cells to produce DNA.

Antineoplastic—Agents that inhibit or prevent the development of cancers by stopping the maturation and proliferation of malignant cells.

BCD—The combined chemotherapy treatment of bleomycin, cyclophosphamide, and dactinomycin.

Cytotoxic—Chemicals that are toxic to cells and prevent their reproduction or growth.

Hodgkin lymphoma—A human malignant disorder of the lymph tissue that appears to originate in a particular lymph node and later spreads to the spleen, liver, and bone marrow.

Immunosuppressant—A drug that suppresses the activity of the immune system.

Leucovorin—The antidote for high-dose treatments of methotrexate.

Lymphocytic leukemia—An acute form of childhood leukemia characterized by the development of abnormal cells in the bone marrow and lymph cells found in blood-forming tissues.

Metastatic—Refers to the spread of a cancer from its place of origin to another site in the body.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Oncologist—A physician who specializes in the diagnosis and treatment of patients with cancer.

Psoriasis—A skin disease that causes reddened and rough patches with occasional white scales.

Rheumatoid arthritis (RA)—A usually chronic disease that is frequently considered an autoimmune disorder. RA is characterized by pain, stiffness, inflammation, swelling, and sometimes the destruction of joints.

It is extremely important to take methotrexate in the correct timetable as prescribed by the physician. If a dose is missed, the patient should not take the missed dose at a later time or double the next prescribed dose. Rather, the

patient should maintain the schedule prescribed and notify the doctor about the missed dose.

Pediatric

Studies performed to date have not demonstrated pediatric-specific problems that would limit methotrexate use for the treatment of cancer and juvenile idiopathic arthritis in children. Safety and efficacy have not been established in children with psoriasis.

Geriatric

Studies have not demonstrated geriatric-specific problems that would limit the use of methotrexate. However, elderly patients are more likely to have age-related kidney problems. Special consideration and caution in adjusting dose should be used.

Precautions

Methotrexate carries important warnings about its use. Because the medication affects a person's immune system, methotrexate can be potentially damaging to several organ systems in certain situations. The patient should always advise the doctor of all medications being taken and all existing medical conditions prior to beginning treatment with methotrexate.

To maximize treatment effects, patients receiving methotrexate should observe certain guidelines. These guidelines should include regular visits with the doctor who prescribed the medication, as well as regular laboratory testing for white blood cell count and kidney, liver, and bone marrow function.

Patients taking methotrexate should avoid any immunizations not approved or prescribed by the doctor; they should also avoid contact with individuals taking or who have recently taken the oral polio vaccine or who have an active infection. When necessary, patients should wear a protective face mask.

Patients taking methotrexate should avoid prolonged or direct exposure to sunlight, as some patients experience an increased sensitivity.

Patients taking methotrexate should ask for specific instructions on oral hygiene procedures to reduce the risk of gum abrasion.

Patients taking methotrexate should avoid touching the eye and nasal areas unless hands have been properly washed immediately prior to contact.

To reduce bleeding and bruising complications, patients taking methotrexate should exercise extreme caution when handling sharp instruments and decline participation in contact sports.

PATIENT PROFILE

Methotrexate (Trexall) was prescribed as a first-line treatment for a 45-year-old woman who had been diagnosed with severe rheumatoid arthritis (RA), which had manifested as painful, swollen joints and a low-grade fever for three months prior to seeking treatment. RA is a chronic autoimmune disorder characterized by inflammation of joint tissue. It can affect the toes, ankles, knees, hips, fingers, wrists, and shoulders on both sides of the body, resulting in joint destruction. It is caused by the overactivity of specialized white blood cells of the immune system called T cells that begin attacking the body's own cells as though they were foreign. Methotrexate is a cytotoxic drug that kills cells or interferes with cell growth. It is used at high doses to treat cancers such as leukemias and lymphomas and at lower doses to treat autoimmune diseases such as RA. Methotrexate is a disease-modifying anti-rheumatic drug (DMARD) that works for RA by inhibiting the activity of certain enzymes involved in metabolism, which suppresses activation of certain immune system cells. This mechanism weakens the immune system, which may make reduce a patient's ability to fight infection.

The initial methotrexate regimen was 15 mg taken orally as three 5.0 mg doses 12 hours apart once a week, always on the same day, for 12 weeks. The patient was also advised to take a nonsteroidal anti-inflammatory drug (NSAID) as needed to relieve pain. Although the usual initial dose is 7.5 mg once weekly, this patient's disease was diagnosed late, and her doctor felt that a higher starting dose was necessary to stop joint destruction. Her doctor's plan was to reduce the initial dosage and extend treatment to 52 weeks on a maintenance dose

if the initial treatment slowed disease activity in the joints. After three weeks of treatment, the patient reported having less pain and swelling and more mobility but also indicated that she was feeling nauseous, with abdominal pain and fatigue. However, since laboratory tests done at her doctor's office indicated reduced disease activity, her doctor believed it was important to continue the current regimen for the full 12-week period, with the thought that symptoms might diminish with continued treatment.

At her 6-week follow-up visit, while still taking 15 mg of methotrexate per week, the patient reported that persistent nausea, abdominal discomfort, and a general feeling of malaise were keeping her from her work and normal lifestyle. Although she had less pain and stiffness in the affected joints, she said she could not continue with the drug if it meant feeling sick all the time. Her doctor advised that, rather than stop treatment when her RA was responding well to methotrexate, he would reduce the dose by half (a single dose of 7.5 mg once a week) to reduce symptoms and add another medication, adalimumab (Humira), to be given as a 40 mg injection every other week. Adalimumab is a human monoclonal antibody that works differently from methotrexate and might help to further reduce the inflammatory response of RA. Studies have shown that the adalimumab/methotrexate combination almost doubles the response rate of methotrexate alone. Over the next two weeks, the patient reported feeling better, with less nausea and abdominal pain and almost no joint pain. She and her doctor were both encouraged by the reduction of symptoms and effectiveness of the combination therapy on reducing disease progression and joint destruction.

Only prescribed medications or over-the-counter drugs approved by the physician should be taken by a patient receiving methotrexate.

Pregnant or breastfeeding

Methotrexate carries the FDA pregnancy category X, meaning that studies in animals and in pregnant women have demonstrated positive evidence of fetal abnormalities. This medication should not be used in women who are or may become pregnant. Women of childbearing age taking methotrexate should use a reliable birth control method.

Methotrexate use in breastfeeding women has been demonstrated to have harmful effects on infants. An alternative should be prescribed or the patient should stop breastfeeding while using this medication.

Other conditions and allergies

The presence of comorbidities or other medical problems should always be discussed with the doctor before using methotrexate, as they may affect its use and outcome. Some conditions that should be monitored very closely during therapy for a potential interaction include but are not limited to:

- ascites (extra fluid in the abdomen)
- kidney disease
- thrombocytopenia (low platelet level)
- weakened immune system
- liver disease
- anemia
- diabetes

Other conditions that may cause complications include past or present cases of gout, kidney stones, chickenpox, shingles, intestinal blockage, colitis, immunosuppression, stomach ulcers, mouth sores, or a history of allergic reactions to various drugs.

Side effects

The beneficial effects of methotrexate are usually accompanied by less desirable side effects. Side effects correlate in severity with dose amount and length of treatment. It is important for patients to discuss any side effects that may occur with their doctor. Some side effects do not require medical attention but may still cause the patient concern. Side effects that fall into this category may include loss of hair (alopecia) and appetite (anorexia), nausea or vomiting, skin rash with itching, pale skin tone, and the appearance of boils or acne. These side effects tend to diminish as the body adjusts to the therapy; if they become bothersome, the physician may prescribe interventions.

Side effects that should be reported immediately to the prescribing physician include:

- mouth sores
- back, lower side, joint, or stomach pain
- fever or chills
- headaches
- bloody or dark urine
- blurred vision
- sudden loss of vision
- confusion
- sudden weakness or difficulty moving one or both sides of the body
- black, tarry stools
- bloody stools or vomit
- redness or pinpoint red spots on the skin
- swelling of the feet or lower legs
- development of a cough or hoarseness
- shortness of breath

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Anti-inflammatory medications should be avoided while the patient is receiving methotrexate. These drugs elevate the effects of methotrexate to potentially harmful levels. Vaccines should be avoided due to the immunosuppressive action of methotrexate.

Food and other substances

Alcohol should be avoided to reduce the risk of liver complications. Additionally, patients using methotrexate are advised not to drink cola during treatment.

Resources

PERIODICALS

Westlake, S. L., et al. "The Effect of Methotrexate on Cardiovascular Disease in Patients with Rheumatoid Arthritis." *Rheumatology* 49, no. 2 (2010): 295–307.

WEBSITES

MedlinePlus. "Methotrexate." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682019.html> (accessed March 7, 2015).

Micromedex. "Methotrexate." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/methotrexate/description/drg-20072776> (accessed March 7, 2015).

ORGANIZATIONS

American Cancer Society, 250 Williams Street NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org/>.
U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Methylphenidate

Definition

Methylphenidate is a mild, central nervous system stimulant.

Purpose

Methylphenidate is used primarily in the treatment of attention deficit hyperactivity disorder (ADHD) in children and adults. It also may be used to treat narcolepsy, a sleep disorder. In rare cases, it is used to decrease sedation and lethargy from opioid pain medications and to help improve the mood of a terminally ill person suffering from depression.



Methylphenidate, 20 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

The mode of action for methylphenidate is not fully understood. It is thought to activate the brain stem arousal system and cortex to produce a stimulant effect. The brain stem arousal system increases levels of electrical activity in the brain. The effect of methylphenidate is to produce increased alertness. Although symptoms of ADHD include overactivity and decreased attention spans, methylphenidate actually decreases motor restlessness and increases attention span.

Methylphenidate is offered in various forms of administration:

- oral, available in 5, 10, and 20 milligram (mg) tablets
- chewable, available in 2.5, 5, and 10 mg tablets
- extended release, available in 18, 36, and 54 mg tablets
- long acting, available in 10, 20, 40, 50, and 60 mg capsules
- liquid solution, available as either 5 mg per 5 milliliters (mL) or 10 mg/5 mL
- topical patch, available in 10, 15, 20, and 30 mg strengths

U.S. brand names

Brand names for methylphenidate include:

- oral: Methylin, Ritalin
- extended release: Metadate ER, Metadate CD, Ritalin SR
- long acting: Concerta, Ritalin LA
- topical patch: Daytrana

Recommended dosage

The recommended dosage of methylphenidate is determined by trial and error based on individual responses. Methylphenidate is usually administered in two or three separate doses each day, preferably 45 minutes before a meal. For children with ADHD, the initial recommended dosage is 5 mg twice daily before breakfast and lunch, increased by 5–10 mg per week to a maximum of 60 mg per day. The average total dosage is 20–30 mg per day, although doses anywhere from 10 to 60 mg are not uncommon.

For narcolepsy in adults, the recommended dose is 5–20 mg two to three times a day, taken 30–45 minutes before meals.

Individuals taking methylphenidate should take their last dose of the day before 6 P.M. to decrease sleep difficulties. The tablet should not be broken or crushed, especially the extended-release (long-acting) formula. If the normal time of administration is missed, persons should take the drug as soon as possible. However, two tablets should not be taken at the same time.

Precautions

The drug should be taken exactly as directed. Methylphenidate can become habit forming if taken in greater amounts or for longer periods than necessary, as the drug has a great potential to produce physical and mental dependence. Administration should not be stopped abruptly. Such action can cause withdrawal symptoms, including depression, paranoid feelings, thoughts of suicide, anxiety, agitation, and sleep disturbances. Methylphenidate should not be given to persons with extreme anxiety, tension, agitation, severe depression, mental or emotional instability, or a history of alcohol or drug abuse.

Individuals taking methylphenidate should not drive or operate machinery until they understand how this drug affects them. They should not drive if they become light-headed or dizzy. Methylphenidate may cause irregularities in the composition of the blood and produce changes in liver function. People taking methylphenidate should receive regular blood tests.

Pediatric

Methylphenidate should not be prescribed to children younger than six years of age, as its safety has not been determined in this age group.

KEY TERMS

Attention deficit hyperactivity disorder (ADHD)—A developmental disorder characterized by distractibility, hyperactivity, impulsive behaviors, and the inability to remain focused on tasks or activities.

Depression—A mental state characterized by feelings of sadness, despair, discouragement, and low energy, often with oversleeping and/or overeating.

Narcolepsy—A disorder characterized by frequent and uncontrollable attacks of deep sleep.

Stimulant—A type of psychoactive substance that increases alertness or wakefulness. Stimulants may be prescribed to treat disorders such as autism or attention deficit hyperactivity disorder but are also illegally abused.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

Pregnant or breastfeeding

Methylphenidate is not typically given to women during their childbearing years unless the physician determines that the benefits outweigh the risks. It should be used with caution in women who are breastfeeding.

Other conditions and allergies

Methylphenidate is not indicated for use by individuals with Tourette syndrome, tic disorders, glaucoma, or certain mental health conditions. The drug should be used cautiously in persons with high blood pressure or a history of seizures.

Side effects

The most common side effects are nervousness, difficulties with sleep, tachycardia (fast heart rate), and increased blood pressure. Reducing the dose or changing the time the drug is taken may reduce some side effects. Affected persons should discuss any adverse reactions with their healthcare professional. Individuals taking methylphenidate should receive regular blood pressure and pulse checks. Methylphenidate may also cause dizziness, irritability, vision changes, drowsiness, and poor appetite. Less common side effects include chest pain, palpitations, joint pain, skin rash, and uncontrolled movements or speech. Side effects may also include a rapid or irregular heartbeat, stomach upset, nausea, headache, blood in the

urine or stool, muscle cramps, red dots on the skin, or bruises. At higher dosages or with long-term use, people may experience weight loss or mental changes such as confusion, false beliefs, mood changes, hallucinations, or feelings that they or their environment are not real.

Interactions

Individuals should discuss all potential drug interactions with their healthcare provider, including interactions between methylphenidate and over-the-counter drugs or supplements.

Drugs

Several drugs may interact adversely with methylphenidate, including anticoagulants and drugs to prevent seizures, combat depression, and treat high blood pressure. The dosages of these drugs may be reduced when taken simultaneously with methylphenidate.

Resources

BOOKS

- Albers, Lawrence J., Rhoda K. Hahn, and Christopher Reist. *Handbook of Psychiatric Drugs*. Laguna Hills, CA: Current Clinical Strategies, 2010.
- American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda, MD: ASHP, 2015.
- Barkley, Russell A. *Taking Charge of ADHD: The Complete, Authoritative Guide for Parents*. 3rd. ed. New York: Guilford Press, 2013.
- Chandler, Chris. *The Science of ADHD: A Guide for Parents and Professionals*. New York: Wiley-Blackwell, 2011.
- North, Carol, and Sean Yutzy. *Goodwin and Guze's Psychiatric Diagnosis*. 6th ed. New York: Oxford University Press, 2010.
- Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger, 2013.

PERIODICALS

- Maia, C. R., et al. "Long-Term Efficacy of Methylphenidate Immediate-Release for the Treatment of Childhood ADHD: A Systematic Review and Meta-Analysis." *Journal of Attention Disorders* (December 10, 2014): e-pub ahead of print. <http://dx.doi.org/10.1177/1087054714559643> (accessed February 26, 2015).
- Mohammadi, M. R., et al. "A Comparison of Effectiveness of Regulation of Working Memory Function and Methylphenidate on Remediation of Attention Deficit Hyperactivity Disorder (ADHD)." *Iranian Journal of Psychiatry* 9, no. 1 (2014): 25–30.
- Wang, Liang-Jen, Chih-Ken Chen, and Yu-Shu Huang. "Neurocognitive Performance and Behavioral Symptoms in Patients with Attention-Deficit/Hyperactivity Disorder

during Twenty-Four Months of Treatment with Methylphenidate.” *Journal of Child and Adolescent Psychopharmacology* (January 9, 2015): e-pub ahead of print. <http://dx.doi.org/10.1089/cap.2014.0015> (accessed February 26, 2015).

WEBSITES

AHFS Consumer Medication Information. “Methylphenidate.” American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682188.html> (accessed February 26, 2015).

Children and Adults with Attention-Deficit/Hyperactivity Disorder. “Evaluation and Treatment.” <http://www.chadd.org/Understanding-ADHD/Parents-Caregivers-of-Children-with-ADHD/Evaluation-and-Treatment/ADHDMedicationsAnOverview.aspx> (accessed February 26, 2015).

National Institute on Drug Abuse. “DrugFacts: Stimulant ADHD Medications: Methylphenidate and Amphetamines.” National Institutes of Health. <http://www.drugabuse.gov/publications/drugfacts/stimulant-adhd-medications-methylphenidate-amphetamines> (accessed February 26, 2015).

UK National Health Service (NHS). “Methylphenidate Hydrochloride (Methylphenidate 5mg Tablets).” <http://www.nhs.uk/Medicine-Guides/Pages/MedicineOverview.aspx?condition=Attention-deficit%20hyperactivity%20disorder&medicine=Methylphenidate%20hydrochloride> (accessed February 26, 2015).

U.S. Drug Enforcement Administration. “Methylphenidate (Ritalin).” http://www.dea.gov/druginfo/concern_meth.shtml#methylphenidate (accessed February 26, 2015).

ORGANIZATIONS

American Academy of Child and Adolescent Psychiatry, 3615 Wisconsin Avenue NW, Washington, DC 20016-3007, (202) 966-7300, Fax: (202) 966-2891, <http://aacap.org/>.

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.

Children and Adults with Attention-Deficit/Hyperactivity Disorder, 4601 Presidents Drive, Suite 300, Lanham, MD 20706, (301) 306-7070, (800) 233-4050, Fax: (301) 306-7090, <http://www.chadd.org/>.

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Methylprednisolone

Definition

Methylprednisolone is a synthetic corticosteroid medication used as an anti-inflammatory agent and immunomodulator. It is a variant of prednisolone, the active metabolite of **prednisone** that is also manufactured



Methylprednisolone, 4 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

as a synthetic corticosteroid. The major difference between methylprednisolone and prednisolone is the addition of a methyl group to the prednisolone molecule.

Purpose

Methylprednisolone is approved by the U.S. Food and Drug Administration (FDA) to treat several conditions, including:

- acute childhood leukemia
- acute flare-ups of multiple sclerosis
- allergic conditions (asthma, seasonal allergies, contact dermatitis)
- endocrine disorders (adrenocortical insufficiency, congenital adrenal hyperplasia [CAH])
- eye disorders (herpes zoster infection of the eye, keratitis, iritis, allergic conjunctivitis)
- flare-ups of ulcerative colitis
- idiopathic thrombocytopenic purpura (ITP)
- osteoarthritis
- the parasitic infection trichinosis
- respiratory disorders (sarcoidosis, aspiration pneumonia, tuberculosis)
- rheumatic disorders (rheumatoid arthritis, ankylosing spondylitis, gouty arthritis)
- skin disorders (psoriasis, pemphigus, mycosis fungoides)

- systemic lupus erythematosus
- tennis elbow (epicondylitis)

Off-label uses

Methylprednisolone is used off label in humans to treat such conditions as *Pneumocystis jirovecii* pneumonia in patients with AIDS, acute spinal cord injury, and severe lupus nephritis.

Description

Methylprednisolone is available as 2, 4, 8, 16, 24, and 32 milligram (mg) tablets to be taken by mouth. The tablets are usually white and either round or oval in shape. It is also prescribed in an injectable solution as methylprednisolone acetate. This is available in three strengths: 20 mg per milliliter (mL), 40 mg/mL, and 80 mg/mL. Methylprednisolone acetate is intended for injection into joints, soft tissue, muscle, or skin lesions; it is not used intravenously (into a vein).

Methylprednisolone sodium succinate is a powder meant to be mixed with a diluent. It is available in varying amounts, but all formulations of methylprednisolone sodium succinate powder must be used within 48 hours after mixing with the diluent.

The injectable forms of methylprednisolone are administered only by a physician or nurse in a hospital; patients are prescribed the oral form of methylprednisolone for use at home.

U.S. brand names

Methylprednisolone tablets are sold in the United States by Pfizer under the brand names Medrol and Medrol Dosepak (prepackaged sets of 4 mg tablets intended to be taken over six days in decreasing numbers) and MethylPREDNISolone Dose Pack.

Methylprednisolone sodium succinate powder and single-use vials of its solution are sold by Pfizer under the brand name Solu-Medrol in the United States. Methylprednisolone acetate is sold as an injectable solution under the brand names A-Methapred and Depo-Medrol.

Canadian brand names

Canadian brand names for methylprednisolone include Medrol, Depo-Medrol, Solu-Medrol, and Methylprednisolone Acetate Sandoz.

International brand names

Methylprednisolone is sold under a variety of other brand names in other countries or as part of combination products with other drugs.

Origins

Methylprednisolone was developed in the mid-1950s by Pharmacia & Upjohn and was approved in the form of oral tablets by the FDA in October 1957. On May 18, 1959, the FDA approved the injectable form of methylprednisolone sodium succinate, also introduced by Pharmacia & Upjohn. This was followed nine days later by the FDA's approval of the same company's injectable form of methylprednisolone acetate. In December 1977, the FDA approved a rectal enema formulation of methylprednisolone, also made by Pharmacia & Upjohn, but this formulation of the drug was eventually discontinued.

Methylprednisolone went off patent in 1978 and is manufactured in generic formulations by a number of pharmaceutical companies worldwide.

Recommended dosage

Because methylprednisolone is prescribed for such a wide range of conditions, there are few universal guidelines for recommended dosages. The prescribing physician will take into account not only the specific condition being treated but also its severity; the patient's age, sex, and general health; other medications the patient is taking; and any concurrent medical or psychiatric disorders that the patient may have. The patient's dosage needs may change in the event of severe emotional stress, serious illness or infection, fever, scheduled surgery, or a medical emergency. General dosage ranges for adults for the three formulations of methylprednisolone are as follows:

- oral tablets: 2–60 mg per day in divided doses every 6–24 hours
- methylprednisolone acetate injection: 10–80 mg intramuscularly every one or two weeks
- methylprednisolone sodium succinate injection: 10–250 mg intramuscularly or intravenously up to every 4 hours as needed

If methylprednisolone acetate is used as a temporary substitute for oral methylprednisolone, methylprednisolone acetate is given as a daily intramuscular dose equal to the daily oral dose. For a prolonged effect, it may be given as a weekly intramuscular dose equal to seven times the daily oral dose.

Recommended dosages for some specific indicated conditions in adults are as follows:

- Allergic conditions are usually treated with a 21-tablet dosepak of oral prednisolone. Six tablets are taken on the first day: at breakfast (two tablets), after lunch, after dinner, and at bedtime (two tablets). Five tablets are

KEY TERMS

Ankylosing spondylitis—An inflammatory disease of the joints that primarily affects the spine and the sacroiliac joint in the pelvis. It is most common among younger men in their 20s and 30s.

Congenital adrenal hyperplasia (CAH)—A term used to describe a group of autosomal recessive genetic disorders characterized by a deficiency of cortisol, a steroid hormone produced in the cortex of the adrenal glands.

Contact dermatitis—A localized rash or patch of inflamed skin caused by contact with an irritant or allergen, often nickel or chromium, or the oily toxins produced by poison oak, poison ivy, and poison sumac.

Corticosteroids—A class of drugs based on hormones formed in the adrenal gland, used to reduce inflammation.

Cushing syndrome—A disorder caused by prolonged exposure to high levels of the hormone cortisol. Symptoms include upper body obesity, rounded “moon” face, increased fat around the neck, thin arms and legs, fatigue, weakness, high blood pressure, and mood disorders. It is named for Harvey Cushing (1869–1939), the American physician who first described the syndrome in 1932.

Epicondylitis—Inflammation of either of the two epicondyles, the rounded ends of the humerus bone. Lateral epicondylitis is commonly known as tennis elbow, and medial epicondylitis as golfer’s elbow or pitcher’s elbow.

Epidural—Referring to the space that is the outermost portion of the spinal canal. An epidural injection is one that is administered into this space, which lies between the vertebrae of the spine and the meninges covering the spinal cord.

Idiopathic thrombocytopenic purpura (ITP)—A bleeding disorder in which the patient has a low platelet count in the absence of other causes of this condition. ITP is characterized by a purple skin rash and an increased tendency to bleed.

Iritis—Inflammation of the iris of the eye.

Keratitis—Inflammation of the cornea, the clear front portion of the eye.

Multiple sclerosis—A degenerative nervous system disorder in which the protective covering of the nerves in the brain are damaged, leading to tremor and paralysis.

Mycosis fungoides—The most common form of T-cell lymphoma of the skin; symptoms include rash, tumors, skin lesions, and itchy skin.

Pemphigus—A blistering autoimmune disease that affects the skin and mucous membranes.

Pseudotumor cerebri—A condition characterized by increased pressure around the brain in the absence of a tumor or other identifiable disorder. It is also called idiopathic intracranial hypertension.

Sarcoidosis—A disorder characterized by small groups of inflammatory cells (granulomas) that form as nodules in the lungs or other organs.

Trichinosis—A parasitic disease caused by eating raw or undercooked pork infested with a roundworm called *Trichinella spiralis*.

taken on the second day at the same times but with only one at breakfast; four tablets are taken on the third day but with only one tablet taken at each interval. On the fourth day, three tablets are taken—one at breakfast, one after lunch, and one at bedtime. Two tablets are taken on the fifth day, one before breakfast and one at bedtime, and on the sixth day, the last tablet is taken before breakfast.

- For acute flare-ups of multiple sclerosis, 160 mg of Solu-Medrol is given intravenously once daily for one week, then 64 mg is given intravenously every other day for one month.

Methylprednisolone oral tablets should be stored at room temperature away from heat, moisture, and direct

light; kept from freezing; and kept out of the reach of children and pets.

Pediatric

Recommended dosages for children and adolescents are as follows:

- usual dosage range for oral methylprednisolone in children and adolescents: 0.117–1.66 mg per kilogram (kg) of body weight per day, given in divided doses every 6 to 8 hours
- usual dosage range for methylprednisolone sodium succinate in children and adolescents: 0.03–0.2 mg/kg given intramuscularly every 12 to 24 hours

- severe asthma in children and adolescents: 2 mg/kg either intravenously or intramuscularly once, then 2 mg/kg per day in divided doses every 6 hours
- inflammatory conditions in children and adolescents: 0.5–1.7 mg/kg per day, by mouth or by intravenous or intramuscular injection, in divided doses every 12 hours

Precautions

In March 2014, the FDA issued a warning against the epidural injection of methylprednisolone sodium succinate or methylprednisolone acetate, as injecting corticosteroids into this area of the spinal column may result in stroke, blindness, paralysis, or death. The FDA has not approved the administration of injectable corticosteroids in this region of the body.

Other precautions include the following:

- Avoid close contact with others who have active infections while taking methylprednisolone.
- Take the medication exactly as directed by the healthcare provider.
- Do not discontinue the drug suddenly without consulting the doctor; patients who miss a dose of methylprednisolone should call their doctor and ask for instructions.
- Inform other doctors and dentists when taking methylprednisolone.
- Wear a medical alert tag or carry a card indicating current treatment with methylprednisolone, as this is important information for emergency medical personnel.
- Avoid receiving **vaccinations** with any vaccine made from a live virus, and avoid close contact with others who have recently received such vaccines.

Methylprednisolone may affect the results of certain skin tests.

Pediatric

Children taking methylprednisolone should be monitored for normal growth, as the drug can slow the growth of the long bones and cause other bone problems in children who receive high doses of the drug over long periods of time.

Solu-Medrol and Depo-Medrol should not be used in newborn or premature infants.

Pregnant or breastfeeding

Methylprednisolone in all its formulations carries the FDA pregnancy category C, which means that the drug has been shown to harm the fetus in animal reproduction studies, but no data from human studies are available. Therefore, risk to the fetus cannot be ruled out. It is recommended that women taking methylprednisolone

avoid becoming pregnant while taking the medication; if a woman does become pregnant while taking methylprednisolone, she should tell her physician at once. The drug should not be used by breastfeeding women unless the benefits to the mother outweigh the possible side effects (most commonly underfunctioning of the adrenal glands) in the infant.

Other conditions and allergies

People with a known allergy to methylprednisolone or who have fungal infections anywhere in the body should not use methylprednisolone.

People with any of the following conditions should inform their doctor before taking methylprednisolone:

- a recent history of any kind of infection (bacterial, viral, fungal, protozoal, helminthic)
- stomach ulcers, ulcerative colitis, a history of stomach bleeding, or any illness that causes diarrhea
- history of seizures or epilepsy
- a recent head injury
- cerebral malaria
- high levels of calcium in the blood related to cancer
- myasthenia gravis or other muscle disorder
- osteoporosis
- pinworm or other parasitic roundworm infestation
- heart disease or high blood pressure
- liver disease, including cirrhosis
- kidney disease
- thyroid disorders
- history of mental illness or depression
- low blood levels of calcium or potassium
- glaucoma, cataracts, or a herpes infection of the eye
- tuberculosis

Side effects

Common side effects of methylprednisolone include:

- stomach irritation
- mood changes, often irritability or aggression
- headaches
- insomnia
- agitation or anxiety
- decrease in urine output
- fast, slow, pounding, or irregular heartbeat
- increased appetite and weight gain
- thinning or easily bruised skin
- swelling of the hands, feet, or lower legs

- numbness or tingling sensations in the arms or legs
- acne

Long-term side effects of methylprednisolone, particularly at higher dosages, may include:

- osteoporosis
- Cushing syndrome
- increased intracranial pressure (pseudotumor cerebri)
- muscle weakness and loss of muscle mass
- peptic ulcer
- tendon rupture, particularly of the Achilles tendon
- hypertension (high blood pressure)
- congestive heart failure in at-risk patients
- type 2 diabetes
- increased intraocular pressure, glaucoma, and cataracts
- weight gain

Patients taking methylprednisolone who notice any of the following side effects should contact their doctor at once:

- signs of a severe allergic reaction, including hives, difficulty breathing, or swelling of the face, lips, tongue, or throat
- symptoms of glaucoma, which include blurred vision, eye pain, and seeing halos around lights
- symptoms of pancreatitis, which include severe pain in the upper stomach spreading to the back, nausea and vomiting, and abnormally fast heart rate
- symptoms of severe edema (fluid retention), which include rapid weight gain, feeling short of breath, and swelling
- symptoms of hypokalemia (low blood potassium level), which include mental confusion, uneven heart rate, extreme thirst, increased urination, leg discomfort, and muscle weakness
- symptoms of dangerously high blood pressure, which include severe headache, blurred vision, buzzing or ringing in the ears, anxiety, confusion, chest pain, shortness of breath, uneven heartbeat, and seizures
- symptoms of depression or another mood disorder, which include feelings of extreme happiness or sadness, severe depression, rapid mood changes, and other changes in personality or behavior
- blood in the stools, tarry-looking stools, or coughing up blood (hemoptysis)
- seizures or convulsions

Interactions

Individuals should tell both their doctor and pharmacist about any medications (over-the-counter and

prescription), vitamins, herbs, or supplements that they are taking, because there are many substances and medications that can interact with methylprednisolone.

Drugs

Methylprednisolone interacts with a large number of other medications.

Drugs that reduce the effectiveness of methylprednisolone include:

- barbiturates (e.g., phenobarbital, secobarbital, butalbital, amobarbital)
- **phenytoin**
- rifamycin antibiotics (**rifampin**, rifabutin, rifapentine); may cause life-threatening interactions

Methylprednisolone decreases the effectiveness of the following drugs:

- benzodiazepine tranquilizers (e.g., **alprazolam**, **diazepam**, midazolam)
- diabetes medications (both insulins and oral diabetes medications)
- ergot medications (e.g., ergotamine tartrate, dihydroergotamine); may cause life-threatening interactions
- **methadone**
- **oral contraceptives** and hormone replacement therapy
- statins (e.g., **lovastatin**, **atorvastatin**, **simvastatin**); may also increase toxicity of methylprednisolone
- triptans (drugs used to treat migraine headaches); methylprednisolone reduces the effectiveness of these drugs
- **warfarin**

The following drugs increase the toxicity of methylprednisolone:

- antifungal medications (e.g., posaconazole, itraconazole, voriconazole)
- nonsteroidal anti-inflammatory drugs (e.g., **ibuprofen**, naproxen, **ketorolac**, **ketoprofen**, **celecoxib**)
- salicylates (**aspirin**, diflunisal, salsalate); combination also increases risk of ulcers

Other interactions include:

- Diuretics (e.g., **hydrochlorothiazide**, **furosemide**, ethacrynic acid, **torsemide**, metolazone) increase risk of hypokalemia.
- Fluoroquinolone antibiotics (e.g., **ciprofloxacin**, ofloxacin, norfloxacin, **levofloxacin**) increase the patient's risk of tendon rupture.
- Methylprednisolone interacts with other medications containing cortisone (e.g., cortisone, hydrocortisone, fludrocortisone).

- Monoclonal antibodies (e.g., golimumab, denosumab, infliximab, **adalimumab**) increase the patient's risk of infection.
- Patients taking methylprednisolone should not take mifepristone (abortifacient).

Patients taking methylprednisolone should not receive vaccines made from live viruses, including measles, mumps, influenza (nasal flu vaccine), poliovirus (oral form), rotavirus, Japanese encephalitis, rabies, anthrax, yellow fever, zoster, chickenpox, smallpox, bacillus Calmette-Guérin, and rubella. Patients should also not receive diphtheria-tetanus toxoids, hepatitis B vaccine, human papillomavirus (HPV) vaccine, or acellular pertussis vaccine. Patients taking methylprednisolone should avoid close contact with anyone who has recently received any of these vaccines.

Herbs and supplements

Patients taking methylprednisolone should avoid the use of herbal preparations containing squill or St. John's wort, as these herbs decrease the effectiveness of methylprednisolone and may produce life-threatening interactions.

Food and other substances

Patients taking methylprednisolone should avoid smoking marijuana or ingesting food products made with it, as it increases the effects of the medication. They should also avoid grapefruit and grapefruit juice for the same reason.

Resources

BOOKS

- Colburn, Nona. *Review of Rheumatology*. New York: Springer, 2012.
- Rice, Peter J. *Understanding Drug Action: An Introduction to Pharmacology*. Washington, DC: American Pharmacists Association, 2014.
- Turley, Susan M. *Understanding Pharmacology for Health Professionals*. 5th ed. Upper Saddle River, NJ: Pearson Education, 2014.

PERIODICALS

- Giuliano, J. S., Jr., et al. "Corticosteroid Therapy in Critically Ill Pediatric Asthmatic Patients." *Pediatric Critical Care Medicine* 14, no. 5 (2013): 467–70.
- Grau-López, L., et al. "Similar Biological Effect of High-Dose Oral versus Intravenous Methylprednisolone in Multiple Sclerosis Relapses." *Multiple Sclerosis* (August 21, 2014): e-pub ahead of print. <http://dx.doi.org/10.1177/1352458514546786> (accessed February 19, 2015).
- Harrop, S. J. "Spinal Cord Injury: Debating the Efficacy of Methylprednisolone." *Neurosurgery* 61, suppl. 1 (2014): 30–31.

Self, T. H., et al. "Action Plans to Reduce Hospitalizations for Chronic Obstructive Pulmonary Disease Exacerbations: Focus on Oral Corticosteroids." *Current Medical Research and Opinion* 30, no. 12 (2014): 2607–15.

WEBSITES

- AHFS Consumer Medication Information. "Methylprednisolone Oral." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682795.html> (accessed March 4, 2015).
- Healthwise. "Methylprednisolone Oral." Mercy Hospital. <http://www.mercy.net/healthinfo/d00293a1> (accessed March 4, 2015).
- Micromedex. "Methylprednisolone (Injection Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/methylprednisolone-injection-route/description/drg-20075216> (accessed February 19, 2015).
- Micromedex. "Methylprednisolone (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/methylprednisolone-oral-route/description/drg-20075237> (accessed February 19, 2015).
- PubMed Health. "Methylprednisolone Oral." U.S. National Library of Medicine. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0001175/> (accessed March 4, 2015).

ORGANIZATIONS

- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rebecca J. Frey

REVIEWED BY KEVIN GLAZA, RPh

Metoclopramide

Definition

Metoclopramide is a drug in a class of medications called prokinetic agents.

Purpose

Metoclopramide is used to prevent the nausea, vomiting, and heartburn caused by a variety of health conditions, including chemotherapy, diabetic neuropathy, gastroparesis, and gastroesophageal reflux disease (GERD). Metoclopramide speeds the healing of ulcers and sores that occur in the esophagus as a result of GERD. Metoclopramide is also used to help prevent aspiration of fluid into the lungs during surgical



Metoclopramide, 5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

procedures and to treat persistent hiccups and vascular headaches.

Off-label uses

Metoclopramide is used off label to ease postoperative nausea and vomiting.

Description

Metoclopramide is widely used in patients who have heartburn and GERD. If left untreated, GERD can cause erosion of the esophagus, leading to sores in the lining of the esophagus. This occurs as a result of highly acidic stomach contents back-flowing into the esophagus.

Metoclopramide works by increasing the movements or contractions of the stomach and intestines, which helps improve emptying of the stomach in people with gastroparesis. This condition may be caused by diabetes or surgery. In treating the symptoms of slow stomach emptying, the symptoms will not improve immediately. Metoclopramide affects the symptoms of nausea and loss of appetite early in treatment, which continue to improve over the course of about three weeks. The feeling of fullness associated with this condition also takes time to resolve.

When used as an antiemetic, metoclopramide helps decrease the persistent nausea and vomiting that may occur in cancer treatment with chemotherapy. Nausea and vomiting are among the most common side effects of

chemotherapy; they are also among the most unpleasant and upsetting side effects for patients. If left untreated, persistent nausea and vomiting can lead to dehydration, dental decay, digestive abnormalities, and nutritional deficiencies. In addition, persistent vomiting may force some patients to stop receiving chemotherapy treatment and risk a recurrence of cancer. It is therefore very important that these symptoms be adequately treated.

For the majority of cancer patients, nausea and vomiting can be successfully treated with antiemetic medication, and metoclopramide is one of the most widely used and effective antiemetics for treating delayed nausea and vomiting caused by chemotherapy. Metoclopramide works in two ways: it affects a part of the brain known to trigger vomiting and also affects the speed of intestinal motion. As a result, the stomach empties into the intestines more quickly, and the contents of the intestines move more quickly in the correct direction.

Metoclopramide is most often used as an antiemetic in patients receiving cisplatin (Platinol) chemotherapy. Cisplatin is used to treat a wide range of cancers, including bladder cancer, ovarian cancer, and non-small cell lung cancer. Compared with other cancer chemotherapy, cisplatin is often considered to cause the most severe nausea and vomiting. For 60%–70% of patients taking cisplatin, however, metoclopramide provides adequate control of nausea and vomiting.

Metoclopramide is available in tablet form in 5 and 10 milligram (mg) strengths, as a syrup in 5 mg per 5 milliliter (mL) strength, as an orally disintegrating tablet in strengths of 5 mg and 10 mg, and as a solution for intravenous use in 5 mg/mL strength.

U.S. brand names

In the United States, metoclopramide is sold under the brand names Reglan and Metozolv ODT.

Canadian brand names

In Canada, metoclopramide is sold under the brand names Apo-Metoclop and Nu-Metoclop.

International brand names

Metoclopramide is sold under a variety of brand names internationally. In some countries, metoclopramide is only one component of the medication, and there are other medications included in the formulation; it may also be available for veterinary use.

Recommended dosage

Metoclopramide is available in tablet form, as a syrup, as an orally disintegrating tablet, and as a solution

KEY TERMS

Antiemetic—A drug that prevents nausea and vomiting.

Cancer—A disease caused by uncontrolled growth of the body's cells.

Gastroparesis—Partial paralysis of the stomach, characterized by nausea, vomiting, and abdominal distension.

GERD—Gastroesophageal reflux disease; esophageal irritation from the backward flow of gastric acid into the esophagus.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Palliative care—Care given to relieve pain and other symptoms of a disease, but not to cure the disease.

Tardive dyskinesia—A neurological condition characterized by involuntary, uncontrollable movements, especially of the mouth, tongue, trunk, and limbs; occurs especially as a side effect of prolonged use of certain medications.

for intravenous use. If taking the disintegrating tablet, the patient should use dry hands to remove the tablet from the package just before taking the dose. The tablet should be placed on the tip of the tongue and will usually dissolve in about one minute, or it may be swallowed with saliva. Metozolv ODT is a rapidly dissolving tablet that gets into the bloodstream quickly for faster relief.

When used for the treatment of GERD, metoclopramide should be taken at intervals—30 minutes prior to meals and again at bedtime—for best effectiveness. A dose of 10 to 15 mg up to four times per day is prescribed for GERD.

Although metoclopramide can be taken either orally or intravenously, cancer patients receiving chemotherapy treatment are usually given the drug intravenously. Metoclopramide is typically given 30 minutes before chemotherapy, and then two more times after chemotherapy at two-hour intervals.

The recommended dose of metoclopramide varies from patient to patient and depends on the severity of the symptoms it is being prescribed for. A dose of 10 mg is standard when the medication is prescribed for nausea. A higher dose will be given to patients with severe symptoms. Higher doses will also be given to patients

receiving drugs, such as cisplatin, that are known to cause severe nausea and vomiting.

Some patients receiving cisplatin may be given a combination of three different drugs to help combat their nausea: metoclopramide, dexamethasone (Dexone), and **lorazepam** (Ativan). The three drugs work on different areas of the body and produce a greater effect together than they do when given separately. This trio is a commonly used combination of drug therapies to counteract symptoms caused by cancer treatment.

Pediatric

Teenagers may take the standard adult dose as prescribed by their doctor. In children, the doctor should determine a safe and effective dose.

Geriatric

The doctor should decide whether the metoclopramide dose needs to be adjusted for elderly patients.

Precautions

Taking metoclopramide for longer than 12 weeks may cause patients to develop a muscle problem called tardive dyskinesia. Tardive dyskinesia may not go away even after the patient stops taking the medication. The longer a person takes metoclopramide, the greater the risk of developing tardive dyskinesia. The risk also increases if the patient is already taking medications for mental disorders or has diabetes. Women and the elderly are also at increased risk for tardive dyskinesia. The doctor should be notified immediately if any of the following uncontrollable body movements are noticed while taking metoclopramide:

- lip smacking
- mouth puckering
- chewing
- frowning
- scowling
- sticking out the tongue
- eye movements
- blinking
- shaking of the arms or legs

Metoclopramide can cause sleepiness and lack of concentration. Patients should avoid tasks that require mental alertness, such as driving or operating machinery. Patients should also be aware that metoclopramide may enhance their response to alcohol and drugs that depress the central nervous system. Because metoclopramide can cause depression, patients with a history of serious clinical depression should take this drug only if absolutely necessary.

Geriatric

Studies have not demonstrated geriatric-specific problems that would limit the use of metoclopramide in the elderly. However, elderly patients are more likely to experience side effects such as tardive dyskinesia, confusion, drowsiness, and age-related kidney problems.

Pregnant or breastfeeding

Metoclopramide carries the FDA pregnancy category B, meaning that animal studies have not revealed any evidence of harm to the fetus. However, there have been no adequate studies in pregnant women. Metoclopramide is excreted in breast milk, which means the medication is passed on to the infant in some concentration. Women who are pregnant or breastfeeding should discuss the use of metoclopramide with their doctor.

Other conditions and allergies

Metoclopramide can worsen the symptoms of Parkinson's disease, and patients with a history of seizures should not take metoclopramide because the frequency and severity of the seizures may increase. Additionally, the drug should not be used in patients with intestinal problems such as bleeding, tears, or blockages.

The patient should inform the doctor of any and all medical conditions prior to beginning metoclopramide therapy. Some conditions need to be closely monitored and evaluated for stability during therapy. These include but are not limited to:

- cirrhosis of the liver
- high blood pressure
- asthma
- kidney disease

Side effects

The most frequent side effects of metoclopramide, occurring in about 10% of patients, are restlessness, drowsiness, and fatigue. Less common side effects, occurring in 5% of patients, include insomnia, headache, and dizziness. Feelings of anxiety or agitation may also occur, especially after a rapid intravenous injection of the drug. Some women may experience menstrual irregularities.

Metoclopramide may cause serious side effects, and the doctor should be notified immediately if any of the following occur:

- speech problems
- depression
- fever
- confusion

- difficulty falling or staying asleep
- agitation
- fast, slow, or irregular heartbeat
- any symptoms of tardive dyskinesia, including muscle stiffness, slow or stiff movements, uncontrollable shaking of a part of the body, and tongue rolling

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Patients who are also taking cabergoline (Dostinex), a drug used to treat hormonal problems and Parkinson's disease, should not take metoclopramide.

Because metoclopramide affects the functioning of the intestines, it can interfere with the absorption of certain drugs. The effect of digoxin (Lanoxin), for example, may be reduced, whereas the effects of other drugs like **aspirin**, **cyclosporine** (Neoral, Sandimmune, SangCya), and tetracycline (Minocin, Vibramycin) may be enhanced.

There are several medications that metoclopramide should not be taken with. These include but are not limited to:

- **amitriptyline**
- **citalopram**
- **clozapine**
- **doxepin**
- **escitalopram**
- **fluoxetine**
- **trazodone**
- **venlafaxine**

Other medications may be safe to take while using metoclopramide, but they should be closely monitored by the doctor in case dosage or scheduling adjustments are necessary to avoid potential interactions. These medications include but are not limited to:

- **cyclosporine**
- **digoxin**
- **levodopa**
- **linezolid**
- **sertraline**
- **tramadol**

Food and other substances

Metoclopramide can increase the effects of alcohol.

Resources

BOOKS

Karch, Amy M. *Lippincott's Nursing Drug Guide*. Springhouse, PA: Lippincott Williams & Wilkins, 2014.

Resources

PERIODICALS

Dahl, E., and A. L. Diskin. "Long-Lasting Adverse Effects after Short-Term Low-Dose Treatment with Metoclopramide for Vomiting." *International Maritime Health* 65, no. 1 (2014): 16–19.

Roila, F., et al. "Aprepitant versus Metoclopramide, Both Combined with Dexamethasone, for the Prevention of Cisplatin-Induced Delayed Emesis: A Randomized, Double-Blind Study." *Annals of Oncology* (March 5, 2015): e-pub ahead of print. <http://dx.doi.org/10.1093/annonc/mdv132> (accessed April 6, 2015).

Vrachnis, N., D. Zygouris, and Z. Iliodromiti. "Fetal Outcomes Associated with Metoclopramide Use in Pregnancy." *JAMA* 311, no. 6 (2014): 623–24.

Resources

WEBSITES

MedlinePlus. "Metoclopramide." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a684035.html> (accessed March 8, 2015).

Micromedex. "Metoclopramide (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/metoclopramide-oral-route/side-effects/drg-20064784> (accessed March 8, 2015).

ORGANIZATIONS

National Cancer Institute, 9609 Medical Center Drive, BG 9609 MSC 9760, Bethesda, MD 20892-9760, (800) 4-CANCER (422-6237), <http://www.cancer.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Tracy Gardner Beno, RN

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Metoprolol

Definition

Metoprolol (pronounced meh-TOH-pro-lol) is a heart medication classified as a beta blocker. This class of drugs works to manage cardiac arrhythmias (irregular



Toprol XL (metoprolol), 100 mg. (© Cengage Learning®.)

heartbeats) and hypertension by blocking the action of the stress hormones adrenaline and noradrenaline on beta adrenergic receptors in the sympathetic nervous system. The sympathetic nervous system is the subsystem of the nervous system that governs the body's fight-or-flight response. Metoprolol is a selective beta₁ receptor blocker, which means that it acts on beta receptors located in the heart and the kidneys.

Purpose

Metoprolol is approved by the U.S. Food and Drug Administration (FDA) for the following indications:

- treatment of acute heart attack
- prevention of a second heart attack
- angina
- congestive heart failure (CHF)
- high blood pressure (in children as well as in adults)

Off-label use

Because metoprolol is a selective beta₁ receptor blocker, it is often used off label to treat patients with performance anxiety, social anxiety disorder, and some other anxiety disorders. Other off-label uses include rapid heartbeat (tachycardia), migraine headaches, and hyperthyroidism.

KEY TERMS

Angina—A sensation of pain, squeezing, or pressure in the chest due to inadequate oxygen supply to the heart muscle.

Beta adrenergic receptors—A class of G protein-coupled receptors that are targeted by the stress hormones adrenaline and noradrenaline. They are also called beta adrenoceptors.

Heart block—A disorder of the electrical system of the heart, causing light-headedness, fainting, and palpitations.

Raynaud's phenomenon—A condition in which small blood vessels in the ears, nose, fingers, and toes go into vasospasm in response to cold or stress, resulting in markedly reduced blood flow in these areas. The condition is named for Maurice Raynaud (1834–1881), a French physician.

Sick sinus syndrome—A general term for a group of cardiac arrhythmias caused by a malfunction of the sinus node, which is the heart's pacemaker.

Sympathetic nervous system—The subsystem of the autonomic nervous system that regulates the body's fight-or-flight response.

Tachycardia—An abnormally rapid heart rate.

Description

Metoprolol is dispensed as 25, 50, or 100 milligram (mg) standard tablets to be taken by mouth. The injectable solution of metoprolol tartrate is dispensed as single-use 5 milliliter (mL) vials containing 5 mg of the drug in sterile water. The extended-release form is a slightly different formulation of the drug known as metoprolol succinate. Extended-release metoprolol tablets are available in 25 mg, 50 mg, 100 mg, and 200 mg dosages. They are usually white and either round or oval in shape.

The injectable form of metoprolol tartrate is administered intravenously by a physician or nurse in a hospital; patients are prescribed an oral form of metoprolol for use at home.

U.S. brand names

Metoprolol is sold in the United States under the brand name Lopressor for the standard oral tablets and the intravenous solution, and Toprol-XL for the extended-release tablets. The standard tablets are also available as generic metoprolol tartrate tablets, and the extended-release formulation as generic metoprolol succinate ER tablets.

Canadian brand names

Metoprolol is sold in Canada under the brand names Apo-Metoprolol, Betaloc, Gen-Metoprolol, Lopressor, Metoprolol Tartrate Sandoz, Nu-Metop, Teva-Metoprolol, and Toprol-XL.

International brand names

International brand names for metoprolol include Asoprol, Betaloc Zok, Betaprol, Egilok, Emzok, Grandil, Logimax, Lopresor, Metol, Metolar, Metoprolol EG, Metoprolol Stada, PMS-Metoprolol, Presolol, Saneloc, Topol-XL, Vasocard, Vasocardin, Vivalol, and Zoticus.

Origins

Metoprolol was developed in the late 1970s and approved in its oral tablet formulation by the FDA in August 1978. The injectable solution formulation of the drug was introduced by Novartis and approved by the FDA in March 1984. The first extended-release tablet, again introduced by Novartis, was approved by the FDA in December 1989. The drug went off patent in 1993 and is now produced by a number of pharmaceutical companies worldwide.

Recommended dosage

Indicated conditions in adults

ACUTE HEART ATTACK, EARLY THERAPY. A rapid intravenous infusion of 5 mg is given every 2 minutes, up to three doses. Fifteen minutes after the last IV dose, 50 mg is given by mouth every 6 hours for 48 hours, followed by 50–100 mg by mouth every 12 hours.

CONGESTIVE HEART FAILURE. Oral metoprolol succinate is given in a dose of 25 mg by mouth each day initially, then increased every two weeks as needed. The target dosage is 200 mg per day.

HYPERTENSION. If taking metoprolol tartrate, 100 mg is given per day by mouth initially as a single dose or in divided doses every 12 hours. The dose may be increased at intervals of one week or longer but is not to exceed 450 mg per day. If taking metoprolol succinate, 25–100 mg is given by mouth each day initially; the dose may be increased at intervals of one week or longer. The usual range is 50–100 mg per day, not to exceed 400 mg per day.

ANGINA. If taking metoprolol tartrate, 100 mg is given per day in divided doses every 12 hours. The dose may be increased at intervals of one week or longer but is not to exceed 400 mg per day. If taking metoprolol succinate, 100 mg is given by mouth each day initially; the dose may be increased at intervals of one week or longer but is not to exceed 400 mg per day.

Off-label conditions in adults

HYPERTHYROIDISM. A dose of 25–60 mg is taken by mouth every 6 hours.

ACUTE TACHYARRHYTHMIA. A dose of 5 mg of metoprolol tartrate is given intravenously over 1–2 minutes every 5 minutes; the total dose should not exceed 15 mg.

MIGRAINE. For the prevention (prophylaxis) of migraine headaches, 500–100 mg of metoprolol tartrate is given by mouth every 12 hours.

ATRIAL FIBRILLATION OR FLUTTER. Intravenous metoprolol tartrate is given at a dose of 2.5–5 mg every 2–5 minutes, not to exceed 15 mg over a period of 10–15 minutes. Intravenous metoprolol is followed by a maintenance dose of oral metoprolol, which is 25–100 mg by mouth every 12 hours.

Patients taking either form of oral metoprolol should take it with a meal or right after a meal. Metoprolol succinate extended-release tablets may be broken in half if the doctor orders, but the half tablet should be swallowed whole without chewing or crushing. Whole extended-release tablets should also be swallowed whole without chewing or crushing. All forms of metoprolol should be stored away from heat and light.

Pediatric

For treatment of hypertension in children and adolescents:

- Metoprolol tartrate: Children and adolescents from 1 to 17 years of age may take 1–2 mg per kilogram (kg, or 2.2 lb.) of body weight per day by mouth, divided into two doses. The total dose should not exceed 6 mg/kg per day or 200 mg per day.
- Metoprolol succinate: Children and adolescents over 6 years of age may take 1 mg/kg by mouth each day; the dose should not exceed 50 mg/day initially. The dose is adjusted on the basis of patient response but is not to exceed 2 mg/kg per day (or 200 mg per day).

Geriatric

The standard adult dosage for management of hypertension is lowered when treating older adults for this specific condition.

Other conditions and allergies

Patients with impaired liver function being given metoprolol succinate should be started on a lower initial dose than the basic adult recommendation and monitored closely as the dosage is increased.

Precautions

Metoprolol may cause drowsiness, confusion, or slow reaction time; patients taking metoprolol should avoid driving or operating dangerous machinery until they know how the drug affects them.

Patients taking metoprolol should not discontinue the drug abruptly, as angina and ischemic heart disease may become worse after abrupt discontinuation. In addition, patients are at increased risk of a heart attack. Patients on long-term metoprolol therapy should have their dosage tapered gradually by their doctor and monitored carefully as the dosage is reduced.

Patients scheduled for dental work or surgery should tell the dentist or surgeon that they are taking metoprolol.

Pregnant or breastfeeding

The FDA has classified metoprolol as a pregnancy Category C medication. This classification implies that a risk of harm to the fetus cannot be ruled out, although there are no controlled data for human pregnancies. Metoprolol is known to pass into human breast milk and may harm a nursing infant. Women should tell their doctor if they are pregnant or nursing or plan to become pregnant before taking metoprolol.

Other conditions and allergies

Patients with the following conditions or disorders should not take metoprolol:

- allergy to metoprolol itself, to other beta blockers (**atenolol**, **carvedilol**, **labetalol**, **nadolol**, **nebivolol**, **propranolol**, **sotalol**, etc.), or to the inert ingredients in the tablets
- heart block
- sick sinus syndrome
- history of slow heart rate
- CHF severe enough to require hospitalization
- severe circulatory problems

Patients with any of the following conditions should inform their doctor before being given metoprolol:

- angina
- low blood pressure
- bradycardia (abnormally slow heartbeat)
- history of heart failure or ischemic heart disease
- lung disease
- peripheral circulatory disorders, including Raynaud's phenomenon
- diabetes, hypoglycemia, or hyperthyroidism (metoprolol may mask some of the symptoms of these disorders)
- pheochromocytoma (tumor of the adrenal gland)
- liver disease

Side effects

The most common side effects of metoprolol are:

- sweating
- confusion or memory problems
- heartburn
- mild depression
- unusual tiredness or weakness
- postural hypotension (dizziness, faintness, or lightheadedness when getting up suddenly from a lying or sitting position)
- diarrhea
- nightmares or trouble sleeping
- mild skin rash or itching

Patients taking metoprolol should notify their doctor at once if they notice any of the following symptoms:

- signs of a severe allergic reaction, including hives; difficulty breathing; swelling of the face, lips, tongue, or throat
- symptoms of severe edema (fluid retention) or congestive heart failure: rapid weight gain, feeling short of breath even with mild exertion, and swelling
- very slow heart rate
- feeling about to pass out or lose consciousness; may indicate dangerously low blood pressure
- cold feeling in the hands and feet

Interactions

Drugs

Metoprolol interacts with a large number of other drugs, including:

- Alpha blockers (drugs that block alpha-adrenoceptors; they include carvedilol, doxazosin, **terazosin**, prazosin, alfuzosin, and labetalol) may cause abnormally low blood pressure.
- Calcium channel blockers (verapamil, **diltiazem**, **amlodipine**, nifedipine, felodipine, etc.) may cause abnormally low blood pressure or slow heart rate.
- SSRI antidepressants (**fluoxetine**, **paroxetine**, **duloxetine**, **citalopram**, **sertraline**, etc.) may increase the level of metoprolol in the body.
- Antipsychotics (**haloperidol**, thioridazine, and chlorpromazine) may increase the level of metoprolol in the body.
- Arrhythmia medications (sotalol, amiodarone, lidocaine, disopyramide, propafenone, quinidine) may cause a dangerously slow heart rate when combined with metoprolol.

- NSAIDs (**ibuprofen**, naproxen, **ketorolac**, **ketoprofen**, **celecoxib**, etc.) interfere with the ability of metoprolol to lower blood pressure.
- Other beta blockers (atenolol, propranolol, nebivolol, nadolol, **timolol**, etc.) increase the risk of serious side effects.
- Barbiturates (phenobarbital, secobarbital, butalbital, amobarbital, etc.) reduce the effectiveness of metoprolol.
- Ergot medications (dihydroergotamine, ergonovine, ergotamine, methylergonovine, etc.) interact with metoprolol.
- Salicylates (**aspirin**, diflunisal, salsalate) increase serum potassium levels when used together with metoprolol.
- Cimetidine, **diphenhydramine**, and **hydroxychloroquine** may cause an increased level of metoprolol in the body.
- **Terbinafine** increases the level of metoprolol in the body.
- **Digoxin** increases toxicity of metoprolol.
- **Bupropion** increases the level of metoprolol in the body.

Food and other substances

Patients taking metoprolol should avoid smoking marijuana or ingesting food products made with it, as it increases the effects of metoprolol.

Patients taking metoprolol should be cautious in drinking alcoholic beverages, as alcohol can interact with metoprolol to lower blood pressure and cause dizziness or light-headedness.

Resources

BOOKS

- Cruickshank, John Malcolm. *The Modern Role of [Beta]-Blockers (BBS) in Cardiovascular Medicine*. Shelton, CT: Peoples Medical Publishing House-USA, 2011.
- Guthrie, Robert M. *Hypertension and Dyslipidemia Management Essentials*. Sudbury, MA: Physicians Press/Jones and Bartlett Publishers, 2010.
- Opie, Lionel H., ed. *Drugs for the Heart*. 8th ed. Philadelphia: Elsevier/Saunders, 2013.
- Ramrakha, Punit, and Jonathan Hill. *Oxford Handbook of Cardiology*. 2nd ed. New York: Oxford University Press, 2012.

PERIODICALS

- Chatterjee, S., et al. "Benefits of Beta Blockers in Patients with Heart Failure and Reduced Ejection Fraction: Network Meta-Analysis." *BMJ* 346 (January 16, 2013): f155.
- Chaturvedi, S., et al. "Pharmacological Interventions for Hypertension in Children." *Evidence-Based Child Health* 9 (September 2014): 498–580.

Dees, B., R. Coleman-Jackson, and L. A. Hershey. "Managing Migraine and Other Headache Syndromes in Those over 50." *Maturitas* 76 (November 2013): 243–46.

Ripley, T. L., and J. J. Saseen. "Beta-Blockers: A Review of their Pharmacological and Physiological Diversity in Hypertension." *Annals of Pharmacotherapy* 48 (June 2014): 723–33.

WEBSITES

AHFS Consumer Medication Information. "Metoprolol." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682864.html> (accessed April 6, 2015).

"Metoprolol." <http://www.drugs.com/metoprolol.html> (accessed January 20, 2015).

"Metoprolol Succinate ER." <http://www.drugs.com/mtm/metoprolol-succinate-er.html> (accessed January 20, 2015).

Micromedex. "Metoprolol (Intravenous Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/metoprolol-intravenous-route/description/drg-20071194> (accessed January 20, 2014).

Micromedex. "Metoprolol (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/metoprolol-oral-route/description/drg-20071141> (accessed January 20, 2015).

ORGANIZATIONS

American College of Cardiology (ACC), Heart House, 2400 N Street NW, Washington, DC 20037, (202) 375-6000, ext. 5603, Fax: (202) 375-7000, (800) 253-4636, ext. 5603, resource@acc.org, <http://www.cardiosource.org/>.

American Heart Association (AHA), 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rebecca J. Frey, PhD
REVIEWED BY KEVIN GLAZA, RPh

Metronidazole

Definition

Metronidazole is an antibiotic in the class called nitroimidazoles. It is used to treat infections with bacteria, protozoans, and parasites. It is considered a broad-spectrum agent, meaning that it has activity against a wide variety of parasites.



Metronidazole, 250 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Metronidazole is frequently prescribed to treat vaginal infections, including trichomoniasis, gardnerella, bacterial vaginosis, and others. Metronidazole can also treat other types of gynecological infections, such as pelvic inflammatory disease, as well as meningitis; pneumonia; and infections of the stomach, skin, bones, joints, and heart. Metronidazole is used to treat peritonitis, amoebic dysentery, tetanus, clostridial diarrhea, liver abscesses, periodontal disease, and the bacteria that causes stomach ulcers.

Description

Metronidazole can be taken by mouth, administered into a vein (intravenously), or applied topically or intravaginally. Oral metronidazole is available in round or oval tablets and in capsules. These come in white and in blue. Dosage strengths include 375 milligram (mg) capsules and 250 or 500 mg round or oval tablets. Colors and imprints on the tablets depend on the specific manufacturer.

Metronidazole is on the World Health Organization's list of essential medicines.

U.S. brand names

Metronidazole is sold under the brand name Flagyl in the United States. It is also manufactured as a generic by many different companies.

KEY TERMS

Bacteria—A type of single-celled organism. Some bacteria can cause disease. Bacteria are members of the larger group called eukaryotes.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Parasite—An organism that survives within another living host and nourishes itself by using that host's energy stores without providing the host with any benefit.

Protozoa—A type of single-celled organism. Some protozoa can cause disease. Protozoa are members of the larger group called prokaryotes.

Canadian brand names

Metronidazole is sold under the brand names Flagyl and Novo-Nidazol in Canada.

International brand names

Metronidazole is sold in many countries worldwide under a variety of names, including Acuzole (South Africa), Amebidal (Mexico), Anabact (United Kingdom), Biogyl (Thailand), Clont (Germany), and Rosazol (Netherlands). In some countries, metronidazole is only one component of the medication, and there are other medications included in the formulation. In some locations, it is only available for veterinary, not human, use.

Recommended dosage

Doses for metronidazole drug therapy vary depending on the specific condition being treated and the frequency and length of dosing. In general, doses for adults may range from 250 to 2,000 mg and may be dosed between one and three times per day. Additionally, length of treatment can vary from a single dose to 14 days depending on the specific infection, infection location, and other patient characteristics.

Pediatric

Children are dosed by weight, generally between 30 and 50 mg per kilogram (kg, or 2.2 lb.) of body weight per day, divided into three equal doses administered every eight hours. Adolescent patients (ages 12–17) are usually dosed as adults.

Geriatric

Metronidazole should be prescribed cautiously to the elderly, as this age group is generally more sensitive to the drug's adverse effects.

Other conditions and allergies

If an individual has known kidney or liver impairment, a lower dose may be necessary.

Precautions

The following precautions apply to all individuals:

- This drug's labeling contains a special boxed warning stating that metronidazole has been associated with cancer in lab animals. Therefore, it is important to use metronidazole only when truly necessary.
- Metronidazole should be taken for the entire length of the prescription, even if symptoms subside. Failure to take a complete course of the medication can result in a return of the infection.
- Oral tablets and capsules can be taken with food to avoid stomach upset.
- Extended-release tablets should never be split, crushed, or chewed, and they should be taken on an empty stomach (at least an hour before or at least two hours after a meal).
- Patients should use an effective form of birth control while on this medication to avoid pregnancy.
- Metronidazole may make the skin more sensitive to sun exposure and tanning lights, resulting in more easily (and potentially severely) burned skin.

Metronidazole use increases the risk of:

- diarrhea due to infection with the bacteria *C. difficile*
- colon inflammation (pseudomembranous colitis)
- yeast infection (candidiasis)

Metronidazole use also increases the risk of central nervous system conditions. Metronidazole can cause meningitis (inflammation of the covering of the brain and spinal cord) within hours of taking the drug. Other CNS effects include seizures; numbness and tingling in arms, legs, hands, or feet; dizziness; balance problems; vision changes; and difficulty speaking. People who take high doses or use metronidazole over a prolonged period of time have a higher risk of these effects.

Pregnant or breastfeeding

Metronidazole carries the FDA pregnancy category B, meaning that research in animals has revealed evidence of risk to a developing fetus, but not in human

studies. If possible, use of this drug should be avoided or delayed until the second or (preferably) third trimester.

Metronidazole passes into breast milk. Breastfeeding mothers should be treated with another agent whenever possible or should be advised to feed their baby a formula alternative and to pump and dispose of breast milk for 12–24 hours after taking the final dose of metronidazole.

Other conditions and allergies

Metronidazole should not be taken by individuals who are hypersensitive to metronidazole, nitroimidazole drugs, or any other ingredient of the preparation.

Metronidazole should be used with particular caution in individuals with:

- seizure disorders
- blood disorders
- decreased liver function
- decreased kidney function
- stomach ulcers caused by infection with the bacteria *H. pylori*

Side effects

Side effects of metronidazole treatment can influence many body systems and organs, including:

- heart: EKG changes, flushing, swelling and pain in a vein when given an IV, fainting
- nervous system: headache, metallic taste in the mouth, dizziness, sensation of the room spinning, inflammation and irritation of the lining of the brain and spinal cord (aseptic meningitis), balance problems, problems with coordination, confusion, depressed mood, nausea/vomiting/flushing/abdominal cramps when alcohol is used during treatment, pain with intercourse, trouble sleeping, irritability, numbness and tingling, seizures, weakness
- skin: red rash, itching, hives, severe skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) involving a severe rash with blisters and detachment of the skin
- gastrointestinal: nausea/vomiting, abdominal pain or cramping, diarrhea, dry mouth, sore and swollen tongue, severely decreased appetite, constipation
- genitourinary: vaginal inflammation, itchiness in the genitalia, painful menstrual periods, burning/frequency/urgency with urination, urinary tract infections, loss of interest in sex, vaginal dryness, vaginal yeast infection.
- blood: decreased white count, decrease platelet count
- immunologic: joint pain

- infection: bacterial and/or yeast infections
- eyes: vision changes, problems with eye movements
- kidneys: passing large amounts of very dilute urine
- respiratory: cold and flu symptoms, sore throat, stuffed nose, runny nose, sinus problems

Rare but serious signs of a significant allergic reaction to metronidazole should prompt the individual to seek immediate medical care. These include:

- difficulty breathing
- wheezing
- fever
- cough
- blue skin or lips
- seizures
- swollen face, lips, tongue, or throat

Interactions

It is important for patients to tell their doctor and pharmacist about all medications they are taking, both over-the-counter and prescription, including all vitamins and supplements, including herbal supplements. The doctor or pharmacist can check a complete list of the most accurate and up-to-date information about possible interactions.

Drugs

Metronidazole increases the blood levels of **aripiprazole**, busulfan, carbocisteine, disulfiram, **fluorouracil**, fosphenytoin, hydrocodone, lomitapide, lopinavir, pimozone, tegafur, tipranavir, and **warfarin**.

Metronidazole decreases the blood levels and/or therapeutic effects of the TB vaccine called BCG, mycophenolate, sodium picosulfate, and the typhoid vaccine.

Metronidazole levels and therapeutic effects may be decreased by fosphenytoin, phenobarbital, **phenytoin**, and primidone.

Metronidazole's toxic effects may be increased by disulfiram and **mebendazole**.

Food and other substances

Patients should not use alcohol while taking metronidazole and should avoid it for three days after finishing a course of treatment. The use of alcohol or products containing alcohol while taking metronidazole can lead to severe abdominal cramps, nausea and vomiting, facial flushing, and headache.

Resources

BOOKS

- Bennett, John E., Raphael Dolin, and Martin J. Blaser. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia: Saunders, 2014.
- Cherry, James, et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Saunders, 2014.
- Lexicomp. *Drug Information Handbook*. 23rd ed. Hudson, OH: Lexicomp Inc., 2014.
- Magill, Alan, et al. *Hunter's Tropical Medicine and Emerging Infectious Diseases*. Philadelphia: Saunders, 2013.
- Rang, Humphrey, et al. *Rang and Dale's Pharmacology*. 7th ed. London: Churchill Livingstone, 2012.

WEBSITES

- MedlinePlus. "Metronidazole Injection." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601159.html> (accessed February 20, 2015).
- MedlinePlus. "Metronidazole Oral." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a689011.html> (accessed February 20, 2015).
- MedlinePlus. "Metronidazole Topical." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682244.html> (accessed February 20, 2015).
- "Metronidazole." Drugs.com. <http://www.drugs.com/metronidazole.html> (accessed February 20, 2015).
- U.S. National Library of Medicine. "LactMed: Metronidazole." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+440> (accessed February 20, 2015).

ORGANIZATIONS

- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, Atlanta, GA 30329, (404) 639-3534, (800) CDC-INFO (800-232-4636), TTY: (888) 232-6348, inquiry@cdc.gov, <http://www.cdc.gov/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rosalyn Carson-DeWitt, MD

REVIEWED BY KEVIN GLAZA, RPh

Mevacor see **Lovastatin**

Micardis see **Telmisartan**

Micronase see **Glyburide**

Micronized estradiol see **Estradiol, micronized**

Microzide see **Hydrochlorothiazide**

Milnacipran

Definition

Milnacipran is an oral drug used for the management of fibromyalgia. It is in a class of medications called serotonin and norepinephrine reuptake inhibitors (SNRIs).

Purpose

Fibromyalgia is a poorly understood chronic condition that includes widespread pain, muscle stiffness and tenderness, fatigue, and sleep disturbances. It affects an estimated 6 to 12 million people in the United States. Milnacipran does not cure fibromyalgia, but it may help control symptoms in adults ages 18 and over. Clinical studies have found that it reduces pain and improves overall symptoms and physical functioning in many people with fibromyalgia. It does not provide significant pain relief in all patients. Milnacipran appears to help relieve fatigue as an effect distinct from its pain-relieving effects. Milnacipran may be prescribed for other purposes.

Description

Serotonin and norepinephrine are neurotransmitters that reduce the transmission of pain signals in the brain. SNRIs increase their levels in areas of the central nervous system (CNS) by preventing their reuptake by nerve



Milnacipran. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

endings. SNRIs are generally used to treat depression and other mental disorders. Although milnacipran is prescribed for major depressive disorder in many other countries around the world, in the United States it is approved by the U.S. Food and Drug Administration (FDA) only for the treatment of fibromyalgia.

Although the cause of fibromyalgia is unknown, many experts believe that it is associated with improper processing of pain signals in the brain and spinal cord, and milnacipran appears to inhibit this processing in the central nervous system. Although milnacipran is a potent inhibitor of norepinephrine and serotonin reuptake by neurons, the mechanism by which it relieves fibromyalgia is unknown. Milnacipran inhibits norepinephrine uptake more strongly than serotonin uptake.

Milnacipran is available as:

- 12.5 milligram (mg) round, blue tablets with “F” on one side and “L” on the other
- 25 mg round, white tablets with “FL” on one side and “25” on the other
- 50 mg oval, white tablets with “FL” on one side and “50” on the other
- 100 mg oval, pink tablets with “FL” on one side and “100” on the other side

U.S. brand names

Milnacipran is marketed as Savella in the United States.

Canadian brand names

Milnacipran is marketed as Savella in Canada.

International brand names

Milnacipran is marketed under the brand name Ixel in most other countries. It is also marketed as:

- Dalcipran in Argentina and Slovakia
- Milnace in India
- Milnacipran Arrow in France
- Milpran in Taiwan
- Misulvan in Chile
- Tivanyl in Mexico
- Toledomin and Milnacipran Hydrochloride followed by various supplier names in Japan

Origins

Milnacipran hydrochloride (HCL) was the first drug introduced for the primary purpose of treating fibromyalgia. It was approved by the FDA in 2009, and as of

KEY TERMS

Fibromyalgia—A chronic disorder characterized by widespread tenderness, pain, and stiffness of muscles and associated connective tissues, often accompanied by fatigue, headache, and sleep disturbances.

Hyponatremia—Blood sodium deficiency.

Monoamine oxidase inhibitors (MAOIs)—A class of antidepressants that may interact with milnacipran.

Neurotransmitter—A chemical, such as serotonin or norepinephrine, that carries nerve impulses from one nerve cell to another across a synapse.

Norepinephrine—Noradrenaline; a neurotransmitter in the sympathetic nervous system and a blood-pressure-raising (vasoconstricting) adrenal hormone.

Selective serotonin reuptake inhibitors (SSRIs)—A class of antidepressants that increase levels of serotonin in the brain by preventing its reuptake by nerve-cell endings.

Serotonin—5-Hydroxytryptamine; a neurotransmitter in the brain and blood.

Serotonin and norepinephrine reuptake inhibitors (SNRIs)—A class of antidepressants, including milnacipran, that increase levels of serotonin and norepinephrine by preventing their reuptake.

Serotonin syndrome—A potentially life-threatening reaction to excess serotonin that can result from drugs that increase serotonin or its effects.

Triptans—A class of drugs that bind to serotonin receptors and mimic the action of serotonin; used to treat migraine headaches.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

early 2015 it was one of only three FDA-approved medications for fibromyalgia.

Recommended dosage

The recommended milnacipran dosage is 50 mg twice daily, for a total of 100 mg per day. It is generally introduced as follows:

- day 1: 12.5 mg once
- days 2–3: 12.5 mg twice daily
- days 4–7: 25 mg twice daily

- after day 7: 50 mg twice daily
- depending on patient response, dosage may be increased to 100 mg twice daily

Although milnacipran may be taken with or without food, taking it with food decreases the risk of stomach upset. It should be taken at about the same times every day. A missed dose should be taken as soon as it is remembered, unless it is almost time for the next dose, in which case the dose should be skipped.

Other conditions and allergies

The dose should be adjusted (possibly decreased) for patients with severe kidney impairment.

Precautions

Although milnacipran is not prescribed as an antidepressant in the United States, it is in an antidepressant drug class and therefore carries the same boxed warning of potential risks as other antidepressants in its class. Milnacipran can affect the mental health of children, teenagers, and adults, causing them to become suicidal, especially at the start of treatment or whenever the dosage is increased or decreased. The potential risks and benefits of milnacipran should be discussed with the doctor before starting treatment, and the healthcare provider should be visited often while taking milnacipran, especially at the start of treatment. The risk of becoming suicidal is higher for people who have depression or another mental disorder. It is also higher if the patient or any family members has or has ever had bipolar disorder, mania, or suicidal thoughts or attempts. The doctor should be called immediately or emergency help summoned if any of the following symptoms occur:

- new or worsening depression
- thoughts of, planning for, or attempts at self-harm or suicide
- extreme worry
- anxiety
- agitation
- panic attacks
- difficulty falling asleep or staying asleep
- hostility
- aggressive behavior
- irritability
- impulsivity or acting without forethought
- severe restlessness
- extreme hyperactivity
- abnormal frenzied excitement

- unusual changes in behavior, mood, thoughts, or feelings
- other new or worsening symptoms

Other precautions include the following:

- Milnacipran can cause drowsiness. Patients should not drive or operate machinery until they know how the drug affects them.
- Serotonin syndrome, a serious and potentially fatal reaction to high serotonin levels, can occur when milnacipran is taken with other drugs that act on serotonin but has also been reported in patients taking milnacipran alone.
- Milnacipran may increase blood pressure and heart rate. Blood pressure and pulse should be checked before treatment and regularly during treatment.
- Doctors and dentists should be informed of milnacipran treatment before performing any type of surgery.

Symptoms of milnacipran overdose can include:

- extreme sleepiness
- confusion
- dizziness
- coma
- slowed or stopped heartbeat and breathing

Milnacipran cannot be stopped abruptly; the dose must be gradually decreased. Suddenly stopping milnacipran can cause withdrawal symptoms, including:

- mood changes
- irritability, anxiety, or confusion
- tiredness
- agitation
- abnormal excitement
- dizziness
- numbness or tingling in the hands or feet
- headache
- sleep problems
- ringing in the ears
- seizures

Pediatric

Milnacipran has not been approved for use in patients under age 18; however, in some cases, a doctor may decide that it is the best medication for a child. In clinical studies, a small number of children, teenagers, and young adults up to age 24 have become suicidal when taking an SNRI.

Geriatric

No overall differences in the safety and effectiveness of milnacipran have been observed between geriatric and

younger patients. However, kidney function should be considered when prescribing milnacipran for elderly patients, since milnacipran is excreted via the kidneys and kidney function generally decreases with age. Milnacipran, as well as other SNRIs and selective serotonin reuptake inhibitors (SSRIs), has also been associated with significantly low blood sodium (hyponatremia) in the elderly.

Pregnant or breastfeeding

Milnacipran carries the FDA pregnancy category C, which means that although there have been no definitive studies in pregnant women, based on animal studies, the drug may cause fetal harm. Babies exposed to SNRIs or SSRIs late in the third trimester of pregnancy have developed complications following birth. Milnacipran should be used during pregnancy only if potential benefits outweigh potential risks to the fetus. Milnacipran is excreted in breast milk and should be used with caution by breastfeeding women.

Other conditions and allergies

Patients should inform their doctor and pharmacist if they are allergic to milnacipran, any ingredients in milnacipran, or any other medications. Milnacipran cannot be used in patients with uncontrolled narrow-angle glaucoma. It should be used with caution in patients who drink alcohol, have ever consumed large amounts of alcohol, or have ever had:

- high blood pressure
- irregular heartbeat
- seizures
- enlarged or inflamed prostate
- difficulty urinating
- bleeding problems
- cardiovascular, kidney, or liver disease

Side effects

The most common side effects of milnacipran are:

- nausea
- vomiting
- constipation
- headache
- dizziness
- insomnia
- hot flush
- excessive sweating
- palpitations
- increased heart rate

- dry mouth
- increased blood pressure

The doctor should be contacted if any of the following symptoms are severe or persistent:

- nausea
- vomiting
- constipation
- stomach pain
- weight loss
- dry mouth
- extreme facial warmth and/or redness
- headache
- blurred vision
- decreased sexual desire or ability
- pain or swelling of the testicles
- difficulty urinating
- rash
- itching

Serious side effects that require immediately contacting the healthcare provider or seeking emergency medical assistance are:

- signs of serotonin syndrome, including agitation, hallucinations, muscle twitching, sweating or fever, severe muscle stiffness, dizziness, or diarrhea
- increased blood pressure or heart rate
- seizures or convulsions
- signs of life-threatening liver problems, such as itching, right upper-belly pain, dark urine, yellow skin or eyes, or unexplained flu-like symptoms
- abnormal bleeding or bruising, nosebleeds, or tiny red spots directly under the skin, especially if also using anticoagulant drugs such as **warfarin** or nonsteroidal anti-inflammatory drugs (NSAIDs) such as **ibuprofen**, naproxen, or **aspirin**
- manic episodes, including very high energy, severe trouble sleeping, racing thoughts, reckless behavior, grandiose ideas, excessive happiness or irritability, and excessive or faster talking
- urination problems, such as decreased urine flow or inability to pass urine
- confusion
- difficulty concentrating
- memory problems
- uncontrollable shaking of a part of the body
- weakness
- unsteadiness
- fainting

- difficult, slowed, or stopped breathing
- fast or pounding heartbeat
- extreme tiredness
- lack of energy
- loss of appetite
- black, tarry stools
- blood in stools
- bloody vomit
- vomit that looks like coffee grounds
- coma

Geriatric

Signs of hyponatremia include headache, weakness, confusion, difficulty concentrating, or memory problems.

Other conditions and allergies

Males with a history of obstructive urinary problems may be at increased risk for genitourinary side effects.

Interactions

It is very important that the doctor and pharmacist be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

Milnacipran increases the risk of serotonin syndrome if taken together with other drugs that increase serotonin levels for treating migraines or mood or psychotic disorders. Taking milnacipran within two weeks after taking a monoamine oxidase inhibitor (MAOI) or taking an MAOI within five days after stopping treatment with milnacipran can result in serotonin syndrome. MAOIs include isocarboxazid (Marplan), **linezolid** (Zyvox), methylene blue, phenelzine (Nardil), selegiline (Eldepryl, Emsam, Zelapar), and tranylcypromine (Parnate). Other drugs that increase the risk of developing serotonin syndrome include:

- SSRIs such as **citalopram** (Celexa), **escitalopram** (Lexapro), fluoxetine (Prozac, Sarafem), **fluvoxamine** (Luvox), **paroxetine** (Paxil), and **sertraline** (Zoloft)
- other SNRIs such as **duloxetine** (Cymbalta), desvenlafaxine (Pristiq), and **venlafaxine** (Effexor)
- triptans such as **almotriptan** (Axert), eletriptan (Relpax), frovatriptan (Frova), naratriptan (Amerge), **rizatriptan** (Maxalt), **sumatriptan** (Imitrex), and **zolmitriptan** (Zomig)

- tricyclic antidepressants such as **amitriptyline** (Elavil), amoxapine (Asendin), clomipramine (Anafranil), **desipramine** (Norpramin), doxepin (Adapin, Sinequan), **imipramine** (Tofranil), **nortriptyline** (Pamelor), protriptyline (Vivactil), and trimipramine (Surmontil)

• fentanyl

• lithium

• tramadol

• buspirone

Aspirin, NSAIDs such as ibuprofen (Advil, Motrin) or naproxen (Aleve, Naprosyn), and blood thinners such as warfarin (Coumadin) increase the risk of bleeding if taken with milnacipran. Other drugs that may interact with milnacipran include:

• clonidine (Catapres)

• digoxin (Lanoxicaps, Digitek, Lanoxin)

• diuretics (“water pills”)

• epinephrine (EpiPen, Primatene Mist)

• sedatives and tranquilizers

• sleeping pills

Herbs and supplements

Tryptophan and St. John’s wort may increase the risk of serotonin syndrome if taken with milnacipran.

Food and other substances

Patients should talk to their doctor about drinking alcohol while taking milnacipran.

Resources

BOOKS

Smith, Howard S., Marco Pappagallo, and Stephen M. Stahl. *Essential Pain Pharmacology: The Prescriber’s Guide*. New York: Cambridge University, 2012.

Stahl, Stephen M. *Stahl’s Essential Psychopharmacology: Prescriber’s Guide*. 5th ed. New York: Cambridge University, 2014.

WEBSITES

MedlinePlus. “Milnacipran.” U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a609016.html> (accessed February 20, 2015).

“Milnacipran.” Drugs.com. <http://www.drugs.com/cdi/milnacipran.html> (accessed February 20, 2015).

National Institute of Arthritis and Musculoskeletal and Skin Diseases. “Questions and Answers about Fibromyalgia.” http://www.niams.nih.gov/Health_Info/Fibromyalgia/default.asp (accessed February 20, 2015).

U.S. Food and Drug Administration. “Living with Fibromyalgia, Drugs Approved to Manage Pain.” <http://www.fda.gov/>

ForConsumers/ConsumerUpdates/ucm107802.htm
(accessed February 20, 2015).

ORGANIZATIONS

National Institute of Arthritis and Musculoskeletal and Skin Diseases, Information Clearinghouse, 1 AMS Circle, Bethesda, MD 20892-3675, (301) 495-4484, Fax: (301) 718-6366, (877) 22-NIAMS (226-4267), NIAMSinfo@mail.nih.gov, <http://www.niams.nih.gov>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY GREGORY A. PRATT, RPh

Minocin see **Minocycline**

Minocycline

Definition

Minocycline is an antibiotic medication in the **tetracycline** class of drugs.

Purpose

Minocycline treats a variety of infections, particularly of the respiratory tract, urinary tract, and skin. Some of the organisms it is effective against include the causes of anthrax, acne, Lyme disease, Rocky Mountain spotted fever and other tick-borne infections, syphilis, plague, cholera, gonorrhea, chlamydia, and stomach ulcers. Other organisms against which minocycline has activity include *E. coli*, *E. aerogenes*, *Shigella*, *H. influenzae*, *Klebsiella*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*.

Description

Minocycline is available as a capsule in 50, 75, and 100 milligram (mg) strengths. The capsules may be a solid pink, green, or yellow or two-toned, often grey and yellow, grey and white, or maroon and pink. The imprint on the capsules depends on the manufacturer.

Minocycline tablets are round or oblong and white, tan, pink, or yellow, imprinted with the manufacturer codes. They are available in 50 mg, 75 mg, and 100 mg strengths.

The medication is taken by mouth and must be prescribed by a physician. Minocycline is used internationally and is also frequently used in veterinary medicine.



Minocycline, 100 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Injectable forms of minocycline may be administered intravenously for more severe infections.

U.S. brand names

In the United States, minocycline is sold under the brand names Dynocin, Minocin, and Solodyn and is also manufactured as a generic by many different companies.

Canadian brand names

In Canada, minocycline is sold as Apo-Minocycline, Arestin Microspheres, Dom-Minocycline, Minocin, Mylan-Minocycline, Novo-Minocycline, PHL-Minocycline, PMS-Minocycline, ratio-Minocycline, Riva-Minocycline, and Sandoz-Minocycline.

International brand names

Minocycline is sold under a large variety of brand names internationally, including Arestin in Sweden, Borymycin in Taiwan, Drenix in Argentina, Seboclear in Peru, Klinotab in Belgium, Mynocine in France, and Cycline in Greece. In some countries, minocycline is only one component of the medication, and there are other medications included in the formulation. In some locations, it is only available for veterinary, not human, use.

Recommended dosage

IV and oral dosing for adults is 200 mg as an initial loading dose, followed by 100 mg every 12 hours. The

KEY TERMS

Anaphylaxis—A severe, systemic allergic reaction that can potentially be life-threatening.

Secondary infection—An infection by a microbe that occurs because the body is weakened by a primary infection caused by a different kind of microbe; also called an opportunistic infection.

duration of treatment depends on the specific infection being treated. Ranges include:

- gonorrhea: at least 4 days
- cellulitis: 5–10 days
- chlamydia: 7 days
- syphilis: 10–15 days

Acne treatment should not exceed 12 weeks and is usually dosed with 50–100 mg twice daily.

Pediatric

Minocycline should absolutely not be used in children under the age of eight due to the fact that minocycline causes permanent stains on developing teeth. In children older than eight years, minocycline is dosed by weight, with an initial loading dose of 4 mg per kilogram (kg, or 2.2 lb.) of body weight, followed by 2 mg/kg every 12 hours.

Other conditions and allergies

The dosage of minocycline may need to be decreased or the dosing interval increased in individuals with renal impairment or on dialysis. The total dose in individuals with renal impairment should not exceed 200 mg per day.

Precautions

The following precautions apply to all individuals:

- Minocycline should be taken for the entire length of the prescription. Failure to take a complete course of the medication can result in the return of symptoms.
- Minocycline should be taken on an empty stomach, one hour before or two hours after eating.
- Minocycline should be taken with a large (at least 16 oz.) glass of water to avoid irritation to the esophagus from the drug.
- Minocycline makes the skin more sensitive to sun exposure and tanning lights, resulting in more easily (and potentially severely) burned skin.

- Individuals with a history of kidney or liver problems or who are on dialysis should tell their doctor before taking this drug.
- The use of minocycline over a long period of time can increase the risk of developing another fungal or bacterial infection (secondary infection).
- *C. difficile*-associated diarrhea and pseudomembranous colitis have both been associated with the long-term use of minocycline, even months after the drug has been discontinued.
- Minocycline should be discarded on its expiration date, as expired medications can cause an anemia syndrome.
- Minocycline can cause an increase in pressure inside the skull. Women of childbearing age are at particular risk, as are individuals who have had this type of adverse effect from minocycline or other agents previously. Individuals who develop headaches or vision changes should consult their healthcare provider immediately.

Pregnant or breastfeeding

Minocycline carries the FDA pregnancy category D, meaning that it can cause harm to the developing fetus and is known to damage the development of teeth and bones. Minocycline passes into breast milk. Women who are pregnant or breastfeeding should not use minocycline.

Other conditions and allergies

Individuals should not take minocycline if they are allergic to minocycline or other drugs in its class (e.g., doxycycline, tetracycline, or demeclocycline) or have developed jaundice and liver problems when taking minocycline in the past.

Individuals with a history of severe allergies; asthma; or prior reactions involving anaphylaxis, hives, or the severe swelling called angioedema are at higher risk for serious reactions to minocycline.

Side effects

Serious and sometimes fatal reactions can occur in individuals who are allergic to minocycline. Anyone who has had a severe reaction to any drug should alert the physician before taking this drug.

The most common side effects of minocycline for all age groups tend to be mild. They include:

- upset stomach
- loose stools or diarrhea
- nausea and vomiting
- headache

These side effects should be brought to the doctor's attention if they do not go away within a few days.

Whitish vaginal discharge or white coating of the tongue and inside of the mouth should also be reported to the doctor.

A doctor should be notified immediately if any of these less common but more serious side effects occur:

- wheezing, difficulty breathing or swallowing (may indicate a severe allergic reaction and require immediate medical attention)
- hoarse voice
- severe skin rash, itching, or hives; blistering or separating skin
- swelling
- yellowing of the skin or the whites of the eyes
- nail discoloration
- vaginal itching or discharge
- sores or pain in the mouth or genital area
- joint pain or stiffness
- numbness, tingling, or pain in the extremities
- severe headache
- vision or hearing changes
- seizures
- abdominal pain with fever
- dizziness, fainting
- severe, watery, and/or bloody diarrhea, even if it occurs two months after ending minocycline treatment
- easy bruising or bleeding or purple pinpoint rash
- very dark urine
- severe muscle weakness or unusual loss of muscle control

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients should tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Minocycline is known to interact with the following pharmaceutical drugs. Other interactions are possible. An individual who develops any unusual or unexpected symptoms should contact a physician.

- Some agents may decrease the absorption of tetracycline derivatives, including antacids, bile acid sequestrants, bismuth, calcium salts, lanthanum, magnesium salts, strontium ranelate, sucralfate, sucroferriic oxyhydroxide, and zinc salts.
- Minocycline may decrease the serum concentration of atazanavir and iron salts.
- Minocycline may decrease the effects of the BCG vaccine, penicillins, sodium picosulfate, and the typhoid vaccine.
- Minocycline may increase the effects (and potential toxicity) of neuromuscular-blocking agents, retinoic acid derivatives, and vitamin K antagonists.

Women taking **oral contraceptives** should ask their healthcare provider if they should use a second form of contraception while using rifampin, as this drug can interfere with the effectiveness of the birth control pill.

Minocycline should be taken two hours before or after taking antacids or laxatives.

Food and other substances

Minocycline should be taken two hours before or after taking iron supplements, multivitamins, or calcium supplements.

Minocycline should not be taken with dairy products.

Resources

BOOKS

- Bennett, John E., Raphael Dolin, and Martin J. Blaser. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia: Saunders, 2014.
- Cherry, James, et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Saunders, 2014.
- Lexicomp. *Drug Information Handbook*. 23rd ed. Hudson, OH: Lexicomp Inc., 2014.
- Magill, Alan, et al. *Hunter's Tropical Medicine and Emerging Infectious Diseases*. Philadelphia: Saunders, 2013.
- Rang, Humphrey, et al. *Rang and Dale's Pharmacology*. 7th ed. London: Churchill Livingstone, 2012.

WEBSITES

- MedlinePlus. "Minocycline Oral." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682101.html> (accessed February 20, 2015).
- "Minocycline." Drugs.com. <http://www.drugs.com/minocycline.html> (accessed February 20, 2015).
- U.S. National Library of Medicine. "LactMed: Minocycline." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+183> (accessed February 20, 2015).

ORGANIZATIONS

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

Centers for Disease Control and Prevention (CDC) 1600 Clifton Road, Atlanta, GA 30329, (404) 639-3534, (800) CDC-INFO (800-232-4636), TTY: (888) 232-6348, inquiry@cdc.gov, <http://www.cdc.gov/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rosalyn Carson-DeWitt, MD

REVIEWED BY KEVIN GLAZA, RPh

Mirapex see **Pramipexole**

Mirtazapine

Definition

Mirtazapine is most commonly used to treat depression.

Purpose

Mirtazapine is best known for treating depression. However, it may also be used for treating anxiety or to make people drowsy just before surgery.



Mirtazapine, 15 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

Mirtazapine is usually thought of as an antidepressant, or a drug that alleviates symptoms of depression. It is believed to alter the activities of some chemicals in the brain and reduce chemical imbalances responsible for causing depression and anxiety. As with all antidepressants, it may take several weeks of treatment before full beneficial effects are seen. Mirtazapine is broken down by the liver and eliminated from the body mostly by the kidneys. It is supplied in 15, 30, and 45 milligram (mg) tablets.

U.S. brand names

Mirtazapine is available in the United States under the trade names of Remeron and Remeron SolTab. Remeron is swallowed whole, but Remeron SolTabs should be allowed to dissolve in the mouth and should not be split. No water is needed when taking the SolTabs, since these tablets disintegrate in saliva and are not swallowed whole.

Origins

Mirtazapine was approved by the U.S. Food and Drug Administration (FDA) in 1996.

Recommended dosage

The recommended initial dose of mirtazapine is 15 mg taken at bedtime. The dose may be increased in 15 mg increments every one or two weeks as needed until symptoms of depression or anxiety resolve. Typical doses range between 15 and 45 mg. Dosages above 45 mg per day are not recommended.

Other conditions and allergies

People with liver or kidney disease should use mirtazapine with caution and may require a reduced dosage.

Precautions

Mirtazapine may cause weight gain and increase cholesterol levels, so it should be used carefully in overweight individuals and those with high cholesterol. If symptoms of fever, sore throat, or irritation in the mouth occur, a healthcare provider should be notified. Rarely, mirtazapine may lower blood counts, causing people to be at an increased risk of serious complications, including infections. In theory, mirtazapine may increase the tendency for seizures. As a result, it should be used carefully in people with epilepsy or other seizure disorders. Mirtazapine may alter moods or cause mania and should be used carefully in people with a history of mania. Mirtazapine may alter liver function and should be used cautiously by those with a history of liver disease. If abdominal pain, yellowing of the skin or eyes,

KEY TERMS

Anxiety—An emotion that can be experienced as a troubled feeling, sense of dread, fear of the future, or distress over a possible threat to a person's physical or mental well-being.

Depression—A mental state characterized by feelings of sadness, despair, discouragement, and low energy, often with oversleeping and/or overeating.

Monoamine oxidase inhibitors (MAOIs)—A class of antidepressants used to treat certain types of depression. Monoamine oxidase inhibitors are especially useful in treating people whose depression is combined with other problems such as anxiety, panic attacks, phobias, or the desire to sleep too much.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

darkening of urine, or itching occurs, a healthcare provider should be notified immediately.

More than 50% of individuals using mirtazapine report feeling sleepier than normal and 7% feel dizzy. As a result, people taking mirtazapine should not participate in activities that require mental alertness, such as driving, until they know how the drug will affect them. Because there is an increased likelihood of suicide in depressed individuals, close supervision of those at high risk for suicide attempts using this drug is recommended. Children and young people up to age 24 are particularly affected, especially during the early stages of treatment. Use of the medicine should not be abruptly stopped, as withdrawal symptoms may occur.

Geriatric

Elderly patients may be more sensitive to some of the drug's side effects.

Pregnant or breastfeeding

Mirtazapine is not recommended in pregnant or breastfeeding women.

Side effects

The most common side effects that cause people to stop taking mirtazapine are sleepiness and nausea. Other common side effects include dizziness, increased appetite, and weight gain. Less common adverse effects include weakness and muscle aches, flu-like symptoms, low blood-cell counts, high cholesterol, back pain, chest

pain, rapid heartbeat, dry mouth, constipation, water retention, difficulty sleeping, nightmares, abnormal thoughts, vision disturbances, ringing in the ears, abnormal taste in the mouth, tremor, confusion, upset stomach, and increased urination.

Interactions

Individuals should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs and supplements, to avoid potential interactions.

Drugs

Use of mirtazapine with monoamine oxidase inhibitors (MAOIs), such as Parnate (tranylcypromine) and Nardil (phenelzine), is prohibited due to the potential for high fever, muscle stiffness, sudden muscle spasms, rapid changes in heart rate and blood pressure, and the possibility of death. In fact, there should be a lapse of at least 14 days between taking an MAOI and taking mirtazapine (and vice versa).

Because mirtazapine may cause drowsiness, it should be used carefully with other medications that also make people prone to sleepiness, such as antidepressants, antipsychotics, antihistamines, and antianxiety drugs.

Food and other substances

Alcohol use may increase the sedative effects of mirtazapine.

Resources

BOOKS

- Albers, Lawrence J., Rhoda K. Hahn, and Christopher Reist. *Handbook of Psychiatric Drugs*. Laguna Hills, CA: Current Clinical Strategies, 2010.
- American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda, MD: ASHP, 2015.
- North, Carol, and Sean Yutzy. *Goodwin and Guze's Psychiatric Diagnosis*. New York: Oxford University Press, 2010.
- Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger, 2013.

PERIODICALS

- Alam, A., Z. Voronovich, and J. A. Carley. "A Review of Therapeutic Uses of Mirtazapine in Psychiatric and Medical Conditions." *Primary Care Companion for CNS Disorders* 15, no. 5 (2013). <http://dx.doi.org/10.4088/PCC.13r01525> (accessed February 26, 2015).
- Jeong, J. H., and W. M. Bahk. "Sleep-Related Eating Disorder Associated with Mirtazapine." *Journal of Clinical Psychopharmacology* 34, no. 6 (2014): 752–53.
- Smith, J. H. "Mirtazapine for New Daily Persistent Headache-Associated Chronic Nausea." *Headache* 55, no. 1 (2015): 176–77.

WEBSITES

- AHFS Consumer Medication Information. "Mirtazapine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682022.html> (accessed February 26, 2015).
- Lexi-Comp. "Mirtazapine." Merck Manual Professional Edition. <http://www.merckmanuals.com/professional/lexicomp/mirtazapine.html> (accessed February 26, 2015).
- National Alliance on Mental Illness. "Remeron® (Mirtazapine)." http://www2.nami.org/Template.cfm?Section=About_Medications&template=/ContentManagement/ContentDisplay.cfm&ContentID=7396 (accessed February 26, 2015).
- U.S. Food and Drug Administration. "Mirtazapine (Marketed as Remeron) Information." <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm109344.htm> (accessed February 26, 2015).

ORGANIZATIONS

- American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.
- Depression and Bipolar Support Alliance, 55 E. Jackson Boulevard, Suite 490, Chicago, IL 60604, (800) 826-3632, (312) 642-7243, <http://www.dbsalliance.org/>.
- National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.
- National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Kelly Karpa, RPh, PhD.

Revised by Laura Jean Cataldo, RN, EdD

REVIEWED BY GREGORY A. PRATT, RPh

Mobic see **Meloxicam**

Modafinil

Definition

Modafinil is a type of medication called a central nervous system (CNS) stimulant. The CNS is the brain, spinal cord, and nerves. The drug can affect wakefulness and treat other conditions by stimulating the CNS and affecting certain substances in the brain.



Modafinil, 200 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

A number of conditions can cause people to have trouble sleeping at night and especially staying awake during the day. The nighttime wakefulness and daytime sleepiness may be caused by shift work that keeps a person's internal sleep and wake clock out of sync with their work schedule (shift work disorder) or result from medical conditions such as narcolepsy. Narcolepsy is noted by brief periods of sudden, deep sleep that can be associated with hallucinations and loss of muscle control. Another cause of daytime sleepiness is a sleep disturbance called obstructive sleep apnea, which is repeated moments in which the upper airways are blocked during sleep. The use of modafinil can help ease daytime sleepiness that comes with these disorders.

Some studies have shown that modafinil also may help adults who have attention deficit hyperactivity disorder (ADHD).

Description

Modafinil is a tablet taken by mouth, and the timing of the medication dose is based on its purpose. For example, people taking the drug for daytime sleepiness associated with sleep apnea usually take modafinil in the morning. In general, the medication has been evaluated as effective for short-term use (up to 9 to 12 weeks). Beyond that, it is up to the patient and doctor to continue to monitor whether the drug is effective.

KEY TERMS

Angina—Chest pain and pressure that occurs when not enough blood flows to the heart muscle.

Narcolepsy—A problem with the nervous system that causes attacks of daytime sleep and extreme sleepiness.

Stevens-Johnson syndrome—A rare but severe disorder that affects the skin and mucous membranes (thin layers that line organs such as the nose). It usually occurs as a reaction to a drug or infection and starts with flulike symptoms, followed by purplish bumps that spread and blister. It is a medical emergency requiring hospitalization.

U.S. brand names

In the United States, modafinil is sold under the brand name Provigil.

Recommended dosage

Modafinil comes in 100 and 200 milligram (mg) tablets. The recommended adult dose of modafinil is 200 mg taken by mouth once a day. Patients who have narcolepsy or obstructive sleep apnea should take their tablet of modafinil in the morning. If taking modafinil for shift work disorder, the tablet should be taken about one hour before the start of the work shift.

Geriatric

Modafinil may not be eliminated from the body as effectively in older adults as in other adults, so doctors usually recommend lowering the dose of modafinil in seniors.

Other conditions and allergies

People who have liver disease or impairment should receive a reduced dose of modafinil, usually one-half of the normally recommended dose.

Precautions

Some people are allergic to modafinil. It is important to inform the doctor of any known drug allergies, especially reactions to other CNS stimulants. A severe rash, including one called Stevens-Johnson syndrome, has occurred in adults and children who have taken modafinil and has required hospitalization for treatment.

People taking modafinil should use extreme caution when operating an automobile or heavy or hazardous equipment, because the medicine can affect their thinking or motor skills. Some people who take modafinil have reported hallucinations, delusions, and other psychiatric events severe enough to require inpatient treatment.

Taking modafinil can increase likelihood of high blood pressure in some people.

Pediatric

Severe skin rashes, including Stevens-Johnson syndrome, have been reported in children using modafinil. The drug is not approved by the FDA for use in children.

Pregnant or breastfeeding

Modafinil is a pregnancy category C drug. It has not been adequately tested in pregnant women, but studies in animals have shown that it could be harmful to a fetus. A woman who is pregnant should only continue using modafinil if she and her doctor decide that the benefits of the medication outweigh potential risks to her unborn child. It is not known whether modafinil is passed from a mother through breast milk. Women who are nursing should use caution and discuss use of modafinil with their doctors if they choose to breastfeed their infant.

Other conditions and allergies

Anyone who has a history of certain cardiovascular diseases, including heart attacks or unstable angina, should use modafinil with caution. The drug should not be taken by people who have heart valve disease.

Side effects

Modafinil can cause side effects, including:

- dizziness
- confusion
- headache
- nausea
- diarrhea
- gas and heartburn
- loss of appetite and unusual tastes
- excessive thirst
- nosebleeds
- flushing of the skin or sweating

Some side effects of modafinil use are considered severe and should be reported to a doctor immediately. These include:

- rash and hives
- blisters or peeling skin
- sores in the mouth
- itching
- problems breathing or swallowing
- swelling of the throat, tongue, lips, face, hands, or lower limbs
- chest pain
- rapid or irregular heartbeat
- anxiety and hallucinations

Interactions

Modafinil can cause interactions with other drugs and substances that may affect how well the modafinil or another drug works. It is important to tell the doctor about any drugs, herbal remedies, or supplements being taken when starting modafinil.

Drugs

Modafinil may interact with other CNS stimulants, so patients should discuss use of these medications with their doctor. Modafinil also can interact with:

- **citalopram** (Celexa), increasing side effects such as irregular heartbeat
- **clopidogrel** (Plavix), a drug used to help prevent blood clots or other heart and blood vessel problems; may become less effective
- **ranolazine** (Ranexa), which is used to treat angina; may become less effective
- certain birth control methods

Food and other substances

Modafinil can be taken with or without food.

Resources

PERIODICALS

- Arnold, Valerie K., et al. "A 9-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Finding Study to Evaluate the Efficacy and Safety of Modafinil as Treatment for Adults with ADHD." *Journal of Attention Disorders* 18, no. 2 (2014): 133–44.
- Chapman, Julia L., et al. "Modafinil Improves Daytime Sleepiness in Patients with Mild to Moderate Obstructive Sleep Apnoea not Using Standard Treatments: A

Randomised Placebo-Controlled Crossover Trial." *Thorax* 6, no. 9 (2014): 274–9.

Tryner, C., A. J. Belyavin, and A. N. Nicholson. "Duration of Activity and Mode of Action of Modafinil: Studies on Sleep and Wakefulness in Humans." *Journal of Psychopharmacology* 28, no. 7 (2014): 643–54.

Resources

WEBSITES

- MedlinePlus. "Modafinil." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a602016.html> (accessed February 7, 2015).
- "Modafinil." Drugs.com. <http://www.drugs.com/cdi/modafinil.html> (accessed February 7, 2015).
- "Provigil." RxList.com. <http://www.rxlist.com/provigil-drug.htm> (accessed February 7, 2015).
- Teva Pharmaceutical Industries. Provigil.com. <http://www.provigil.com/Default.aspx> (accessed February 7, 2015).

ORGANIZATIONS

- National Heart, Lung, and Blood Institute, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbiinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov/>.
- National Sleep Foundation, 1010 N. Globe, Suite 310, Arlington, VA 22201, (703) 243-1687, nsf@sleepfoundation.org, <http://sleepfoundation.org/>.

Teresa G. Odle, BA, ELS

REVIEWED BY KEVIN GLAZA, RPh

Mometasone

Definition

Mometasone is a type of drug called a corticosteroid. Its full name is mometasone furoate. It is inhaled to help relieve swelling and irritation of airways and to help people with asthma breathe more easily and have fewer symptoms.

Purpose

Asthma is a chronic disease that causes the airways leading to the lungs to become inflamed, or swollen, and narrowed. This makes it difficult to breathe and can cause other symptoms, including coughing, wheezing, and a tight feeling in the chest. Regular use of inhaled corticosteroids such as mometasone can help keep the inflammation in airways under control and/or lessen the severity of symptoms. Mometasone is intended to prevent asthma attacks, not as a medicine to take when someone has an asthma attack. The combination of



Asmanex (mometasone). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

mometasone and a drug called formoterol has been shown to reduce asthma symptoms and improve lung function in some patients.

Description

Although mometasone is a steroid, it is not the same type as the anabolic steroids abused by athletes. Mometasone is a corticosteroid, which is not habit-forming. The drug comes in a powder form that the person with asthma inhales by mouth. Because the medicine is inhaled, it targets the airways and lungs to work better at treating airway inflammation than if the drug were taken in a tablet or liquid form.

U.S. brand names

In the United States, mometasone is sold as Asmanex (Asmanex Twisthaler). A product that combines mometasone with formoterol, a long-acting beta-agonist, may be used temporarily to treat severe asthma in people age 12 years and older. It is sold under the brand name Dulera.

Canadian brand names

In Canada, mometasone inhaler is sold as Asmanex Twisthaler and Asmanex Twisthaler.

Recommended dosage

The inhaler that holds mometasone delivers the powder in measured doses of either 220 or 110 micrograms (mcg) of the drug by oral inhalation. Dosages of mometasone inhalers should be taken at the same time each day. When the user removes the inhaler's cap, the Asmanex Twisthaler counts down one dose and shows how many remain in the container.

Adults and children age 12 years and older who have previously had therapy with only bronchodilators or inhaled corticosteroids should have one inhalation (220 mcg) each evening and should not exceed a total of 440 mcg each day. If a person age 12 or older had previous therapy that consisted of corticosteroids taken by mouth (orally), the dose is 440 mcg twice a day, not to exceed 880 mcg in a day.

Pediatric

Children ages 4 to 11 should receive one dose of 110 mcg of mometasone each evening and should not exceed 110 mcg in a 24-hour period.

Precautions

People who use Asmanex Twisthalers should replace the cap after each use. This helps prevent moisture from entering the container.

Anyone who is taking corticosteroids for other medical conditions should be sure to tell their doctors before taking mometasone. Use of the drug can cause a fungal infection in the mouth called thrush, and the risk of the infection is higher in people who use inhaled mometasone along with other corticosteroids.

Pediatric

Mometasone and other orally inhaled corticosteroids can affect the growth of children. Doctors should slowly lower a child's dosage as symptoms improve to minimize the amount of mometasone the child inhales.

Geriatric

Older people often are more sensitive to drug effects, but no clinical trials have found extra precautions for seniors taking mometasone, unless they have some of the conditions or take other medications that cause interactions or more severe side effects.

Pregnant or breastfeeding

Mometasone is pregnancy category C, meaning that tests have been performed only on animals, not on pregnant women and their unborn children. In animal

tests, the drug caused some problems such as decreased growth of the fetus in the womb and malformations of the fetus. Orally inhaled mometasone should be used only if its benefits are expected to outweigh potential harm to a fetus. The effects of mometasone to breastfed babies are unknown, but other corticosteroids have been found to appear in breast milk of a mother using the drugs, so women who are breastfeeding should only use mometasone with caution.

Other conditions and allergies

People who have osteoporosis or who have a family member with the condition should tell their doctor before taking mometasone. Other conditions that might cause problems with the drug include:

- current or past tuberculosis
- cataracts or glaucoma
- liver disease
- herpes
- current untreated infection
- never having measles or chickenpox and never being vaccinated for the diseases

Side effects

Mometasone can cause several side effects, such as:

- headache
- irritated or bloody nose
- bone and muscle pain
- stomach pain
- dry throat
- nausea and vomiting
- painful urination or painful menstrual periods

Some side effects can be more serious. Symptoms such as difficulty breathing or swallowing, hives, facial or arm swelling, and tightness in the throat could indicate a serious reaction, and the patient should call the doctor immediately. Other serious side effects that have been reported are extreme tiredness or weak muscles, upper body or facial weight gain, thinning of arms and legs, and skin that becomes fragile and bruises easily.

Interactions

Mometasone is not known to interact with other medicines used to treat asthma, but it can interact with some drugs. Individuals who are already taking medication for any condition should discuss the drugs with their doctor before taking mometasone.

KEY TERMS

Bronchodilator—A medicine that relaxes the muscles around the airways, or bronchi, making it easier to breathe.

Long-acting beta-agonist—A medicine that eases irritation around the airways and lasts for at least 12 hours.

Osteoporosis—A condition in which the bones become brittle and weak.

Drugs

Mometasone interacts with the drug mifepristone (Korlym, Mifeprex), which is used to treat hyperglycemia, or high blood sugar. There are other drugs that might cause moderate reactions, including other drugs related to diabetes and blood sugar.

Resources

PERIODICALS

Meltzer, E. O., et al. "Mometasone Furoate/Formoterol Reduces Asthma Deteriorations and Improves Lung Function." *European Respiratory Journal* 39, no. 2 (2012): 279–89.

WEBSITES

American Society of Health System Pharmacists, Inc. "Mometasone Oral Inhalation." MedlinePlus. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a608035.html> (accessed December 18, 2014).

Asthma Society of Canada. "All About Inhaled Steroids." Asthma Society of Canada. <http://asthma.ca/adults/treatment/steroids.php> (accessed December 18, 2014).

Drugs.com. "Asmanex Twisthaler." <http://www.drugs.com/asmanex.html> (accessed December 18, 2014).

Merck & Co., Inc. "Asmanex Twisthaler." Merck Asmanex. <http://www.asmanex.com/asmanex/index.xhtml> (accessed December 18, 2014).

National Heart, Lung, and Blood Institute. "How Is Asthma Treated and Controlled?" <http://www.nhlbi.nih.gov/health/health-topics/topics/asthma/treatment.html> (accessed December 18, 2014).

ORGANIZATIONS

American Academy of Allergy, Asthma & Immunology, 555 E. Wells Street, Suite 1100, Milwaukee, WI 53202-3823, (414) 272-6071, <http://www.aaaai.org/home.aspx>.

American Lung Association, 55 W. Wacker Drive, Suite 1150, Chicago, IL 60601, (202) 452-1805, (800) 856-4872, <http://www.lung.org/>.

Teresa G. Odle, BA, ELS

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Monodox see **Doxycycline**

Monoket see **Isosorbide**

Monopril see **Fosinopril**

Montelukast

Definition

Montelukast is a leukotriene receptor agonist, a type of drug that blocks the action of leukotriene, a chemical that the body releases in response to an allergen. Montelukast is sold by prescription only and is used to manage symptoms such as wheezing in people with asthma and allergies.

Purpose

Asthma causes several symptoms related to inflammation or swelling of the airways. Montelukast helps prevent some of these symptoms, especially wheezing, chest tightness, difficult breathing, and coughing. Some people who have exercise-induced asthma may take montelukast to prevent difficult breathing and asthma symptoms that occur during exertion or exercise. People who have seasonal allergies may also use montelukast to ease the stuffiness, itching, and running of the nose—all symptoms that are associated with allergies.



Montelukast, 10 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

The active ingredient in montelukast is montelukast sodium. It controls a leukotriene receptor that leads to the airway and nasal symptoms of asthma and allergic rhinitis. Montelukast typically comes in tablet, chewable tablet, or granule form and is taken orally (by mouth).

U.S. brand names

In the United States, montelukast is sold as Singlair. The medication is sold by Merck & Co., Inc.

Recommended dosage

Dosages vary based on age. For most uses, patients take one tablet once each day in the evening. For asthma, adults and teens age 15 and older can take one 10 milligram (mg) tablet each evening. If taking montelukast to prevent exercise-induced asthma, the pill should be taken at least two hours before beginning exercise, with a maximum dose of one tablet per day.

Pediatric

Teens and children with asthma who are between 6 and 14 years should take one 5 mg chewable montelukast tablet each evening. Children between 2 and 5 years should take a single 4 mg chewable tablet or one packet of 4 mg oral granules, and children 12 months to 23 months old can take a single packet of 4 mg granules each day.

Oral granules can be dissolved in a teaspoonful of cold or room temperature breast milk, formula, or certain soft or baby foods (applesauce, carrots, rice, or ice cream). The granules can also be placed directly into a child's mouth.

Precautions

Montelukast is not intended as a medication to stop asthma attacks. Anyone who has asthma should have rescue medicines available to relieve acute symptoms. If a doctor prescribes montelukast after a person with asthma has been receiving treatment with inhaled corticosteroids, the corticosteroid treatment should be gradually reduced before beginning montelukast, not stopped abruptly. Only one dose of montelukast should be taken in a 24-hour period, even if a dose is missed.

Montelukast can cause people to feel drowsy or dizzy and should be taken in the evening when possible. People should not drive or perform other tasks that could be unsafe until they know how they react to the medication, and they should be aware that alcohol and some other medications can worsen the drowsiness.

Pediatric

Generally, children tolerate montelukast well, with fewer risks than inhaled corticosteroids. Studies have not demonstrated the safety of using montelukast to manage asthma in children younger than 12 months, or younger than 6 years for exercise-induced asthma. Use of montelukast also has not been proven effective for treatment of allergic rhinitis in children younger than age 2.

Geriatric

Clinical trials have shown that patients age 65 years and older experience no different effects from montelukast than younger adults and need no dosage adjustments.

Pregnant or breastfeeding

Montelukast is pregnancy category B, which means that the drug is thought to be safe during pregnancy but there are not enough effective studies in pregnant women. Because the risks are not known, the medication should only be used by pregnant women if the drug is clearly needed.

Other conditions and allergies

Some people are allergic to montelukast, and anyone who begins taking the medication and shows signs of an allergic reaction should stop taking the drug and contact a doctor immediately. Other conditions can cause problems in people who take montelukast, including:

- sensitivity to **aspirin**
- phenylketonuria
- current or past liver disease

Side effects

Montelukast can cause several side effects, including:

- stomach pain or heartburn
- headache
- fatigue
- dizziness
- drowsiness

Some side effects could indicate a more severe reaction to montelukast. If any of these occur, it is advised to stop taking montelukast and contact a doctor immediately:

- change in behavior, especially agitation, irritability, or hallucinations
- trouble breathing
- difficulty swallowing
- itching, rash, or hives
- numbness or tingling in the limbs
- fever or flu-like symptoms

KEY TERMS

Allergic rhinitis—Also called hay fever or allergies; the immune system's overreaction to allergens, usually particles in the air such as pollen. The person experiences a runny nose; sneezing; and itchy, watery eyes and throat.

Allergen—Any food, particle, or other substance that the immune system reacts to, causing an allergic reaction.

Corticosteroid—Drugs used to reduce inflammation in the body and made from artificial versions of hormones produced in the body, usually those in the adrenal glands.

Leukotriene receptor agonist—Also called a leukotriene modifier, a type of medication that treats allergy and asthma symptoms by blocking or altering leukotriene action. Leukotrienes are chemicals released in the body after exposure to an allergen that cause the airways to contract, or tighten, along with other symptoms.

Phenylketonuria—An inherited disorder that causes a defect in the enzyme that breaks down phenylalanine, an amino acid that is found in certain foods.

Interactions

Although there are no known severe interactions between montelukast and other drugs, use of the medication can cause a moderate interaction with a number of other drugs. When taking montelukast, patients should notify their doctor and pharmacist of all other medications (prescription and over-the-counter), vitamins, supplements, or herbal preparations that they are taking.

Food and other substances

There are no known food restrictions while taking montelukast, and the medication is equally effective when taken with or without food. When giving oral granules to young children, parents should be aware of the foods that the granules can be dissolved in or check with a doctor or pharmacist for instructions.

Resources

PERIODICALS

- Bush, Andrew. "Managing Wheeze in Preschool Children." *British Medical Journal* (February 2014): g15.
- Link, Holger W. "Pediatric Asthma in a Nutshell." *Pediatrics in Review* 35, no. 7 (2014): 287–97.

WEBSITES

American Society of Health-System Pharmacists, Inc. "Montelukast." MedlinePlus. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a600014.html> (accessed January 23, 2015).

Drugs.com. "Montelukast." <http://www.drugs.com/cdi/montelukast.html> (accessed January 23, 2015).

Merck. "Singulair (Montelukast Sodium)." http://www.merck.com/product/usa/pi_circulars/s/singulair/singulair.html (accessed January 23, 2015).

ORGANIZATIONS

American Academy of Allergy, Asthma & Immunology, 555 E. Wells Street, Suite 1100, Milwaukee, WI 53202-3823, (414) 272-6071, <http://www.aaaai.org/home.aspx>.

American Lung Association, 55 W. Wacker Drive, Suite 1150, Chicago, IL 60601, (202) 452-1805, (800) 856-4872, <http://www.lung.org/>.

Teresa G. Odle, BA, ELS

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Morphine

Definition

Morphine sulfate ER is an extended-release form of morphine used for the management of significant, long-term, or chronic pain.

Purpose

Morphine sulfate ER is an opioid medication used to treat serious, long-lasting, or chronic pain. It is not used for the treatment of mild or occasional pain. This drug is an extended-release medication, meaning that after it is taken, it is released into the body gradually over time. In some cases, morphine sulfate ER is used to control background, constant pain, and other, immediate-release drugs are used to treat "breakthrough" or occasional spikes in pain (acute pain).

Description

Morphine sulfate ER is an extended-release pain medication. Extended-release formulations control the release of the drug into the system so that instead of having a short spike of relief, the medication provides a more consistent experience of relief over a longer time. This drug works by binding to pain receptors in both the brain and in the spinal cord. This reduces the experience of pain.



Morphine ER (extended release), 15 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Morphine sulfate ER is available as a tablet, a capsule, and an injection.

U.S. brand names

Morphine sulfate ER is sold under the brand names Avinza and Kadian, and as MS Contin as a controlled-release tablet. The injectable form is sold under the brand name DepoDur. It is also sold as a generic produced by a wide variety of manufacturers.

Recommended dosage

This medication has many possible side effects, and dosing should be done to balance pain management with the minimization of adverse effects. Initial dosage depends on a variety of factors, including the patient's pain level, weight, and previous experience with opioids. For patients with no history of opioid use, the generally recommended starting dosage is 15 milligrams (mg) every 8 to 12 hours if given in tablet form, or 30 mg once daily if given as a capsule. For individuals who have a history of opioid use, conversion from the previously used opioid to morphine sulfate ER requires careful monitoring and specific calculations based on the patient's previous opioid dosage.

Morphine sulfate ER given as an injection is typically given only once, either before or after events that will cause serious pain. For surgery to the lower limbs, abdomen, or pelvis, a single injection of 10–15 mg

KEY TERMS

Anaphylaxis—Also called anaphylactic shock; a severe allergic reaction characterized by airway constriction, tissue swelling, and lowered blood pressure.

Cesarean section—Also called a C-section; delivery of a baby through an incision in the mother's abdomen instead of through the vagina.

Chronic—A disease or condition that progresses slowly but persists or reoccurs over time.

Epidural—A method of pain relief in which local anesthetic or analgesic (pain reliever) is injected into the epidural space in the middle and lower back.

Respiratory depression—A life-threatening situation in which the lungs do not take in enough air to provide the body with sufficient oxygen.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

is given before the procedure. For a cesarean section, a single 10 mg injection is given after delivery of the baby. Morphine sulfate ER is administered as a lumbar (spinal) epidural injection.

Pediatric

Morphine sulfate ER is not typically used to treat children. Children who have serious or chronic pain are generally treated using a continuous intravenous (IV) drip. If a child is to receive this medication, dosing is done based on the child's weight, level of pain, and experience with opioids.

Geriatric

Dosing should be done conservatively in seniors. As the body ages, it becomes less efficient at eliminating drugs, which can lead to increased risk of side effects and an increased risk of overdose. Seniors should be monitored closely and given the lowest effective dosage.

Precautions

Morphine sulfate can lead to opioid addiction or dependence. Dosing should be done as conservatively as possible. Morphine sulfate ER should not be used on an as-needed basis or for the treatment of occasional pain.

Individuals should not consume alcohol while taking this medication, as it can lead to an increased risk of side effects, respiratory depression, and overdose. This drug should be kept in a secure place, as even a single dose taken by an individual for whom it was not prescribed, especially a child, can result in fatal overdose.

Morphine sulfate ER tablets and capsules should be taken whole, not crushed, broken, or chewed. Breaking down the pills can result in too much morphine entering the bloodstream at one time, which can lead to fatal overdose.

All patients taking morphine sulfate ER should be monitored closely, and the dosage should be re-evaluated regularly. Morphine treatment should not be discontinued all at once. Instead, the dose should be slowly reduced over time (tapered) to reduce the risk of serious withdrawal symptoms.

Pediatric

Morphine sulfate ER is not typically used in the pediatric population. No studies have demonstrated the safety of its use in this population; however, there are also no studies that demonstrate significant increased risks in this population. Since the long-term effects of morphine sulfate ER use in children have not been demonstrated, it should be used with significant caution.

Geriatric

Seniors are at an increased risk of side effects from morphine sulfate ER and should be monitored closely. Opioid dependence and addiction are problems in the senior population, as they are in all populations, but may be underdiagnosed in this group.

Pregnant or breastfeeding

Morphine sulfate ER is a pregnancy class C drug, and it may be considered a class D drug if used near to the birth of the baby. Class C drugs should only be used if there are significant benefits that outweigh the risks, and even then, a class C drug should be used with caution. Class D drugs are those for which evidence of serious risk to a fetus exists. Class D drugs should only be used in life-threatening emergencies if there are no safer alternatives.

Side effects

In some very rare cases, anaphylactic allergic reactions to morphine sulfate ER have occurred. Any patient who experiences symptoms of an allergic reaction—including swelling of the lips, throat, mouth, or face; difficulty breathing; hives; or rash—should seek emergency medical attention.

Morphine sulfate ER can cause respiratory depression, especially within the first 72 hours after being taken for the first time or in the period following an increase in dosage. Patients should seek emergency medical assistance if any of the following symptoms occur:

- slowed or difficult breathing
- abnormal breathing noise, including wheezing, whistling, or crackling
- confusion
- agitation or extreme restlessness
- increased or decreased heart rate

Common but less serious side effects include:

- nausea
- vomiting
- constipation
- diarrhea
- itching
- anxiety
- dizziness
- drowsiness
- headache

Interactions

Many medications may cause serious interactions with morphine sulfate ER. Patients should tell their doctor and pharmacist about all prescription medications, over-the-counter medications, vitamins, herbs, and supplements that are being taken. It may be necessary to stop taking some medications or change to different medications to reduce the chance of serious or life-threatening interactions with morphine sulfate ER.

Drugs

Morphine sulfate ER should not be used in combination with naltrexone (Revia), a drug used to treat opioid dependence. It should also not be taken together with alvimopan (Entereg), a drug that works to block the action of opioid medications in the bowel. There are a wide variety of other drugs that may cause serious interactions with morphine sulfate ER, including **fluoxetine** (Prozac, Sarafem), quinidine, **paroxetine** (Paxil), and **linezolid** (Zyvox).

Food and other substances

Patients taking morphine sulfate ER should not consume alcohol. Alcohol may increase the amount of the medication active in the blood, which increases the risk of overdose and serious side effects. Alcohol also increases the risk of respiratory depression, which can be fatal.

Resources

BOOKS

- Deer, Timothy R., et al, eds. *Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches*. New York: Springer, 2013.
- Gerald, Michael C. *The Drug Book: From Arsenic to Xanax, 250 Milestones in the History of Drugs*. New York: Sterling, 2013.
- Smith, Howard S. *Opioid Risk Management: Tools and Tips*. 2nd ed. New York: Oxford University Press, 2014.

PERIODICALS

- Argoff, Charles E. and Eugene R. Viscusi. "The Use of Opioid Analgesics for Chronic Pain: Minimizing the Risk for Harm." *American Journal of Gastroenterology Supplements* 2, no. 1 (2014): 3–8.
- Michna, Edward, et al. "Systematic Literature Review and Meta-Analysis of the Efficacy and Safety of Prescription Opioids, Including Abuse-Deterrent Formulations, in Non-Cancer Pain Management." *Pain Medicine* 15, no. 1 (2014): 79–92.
- Sloan, Paul. "Update on Extended-Release Opioids in Pain Management." *Expert Opinion on Drug Delivery* 11, no. 2 (2014): 155–58.

WEBSITES

- Mayo Clinic staff. "Morphine (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/morphine-oral-route/description/drg-20074216> (accessed February 22, 2015).
- U.S. National Library of Medicine. "Morphine Sulfate Morphine Sulfate Tablet, Extended Release." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a07378f9-607a-49c6-bdb8-5c8b4ce91a49> (accessed February 22, 2015).
- World Health Organization (WHO). "Treatment of Opioid Dependence." http://www.who.int/substance_abuse/activities/treatment_opioid_dependence/en (accessed February 22, 2015).

ORGANIZATIONS

- American Association for the Treatment of Opioid Dependence, 225 Varick Street, Suite 402, New York, NY 10014, (212) 566-5555, Fax: (212) 366-4647, info@aatod.org, <http://www.aatod.org/>.
- American Chronic Pain Association, PO Box 850, Rocklin, CA 95677, (800) 533-3231, (916) 632-3208, ACPA@theacpa.org, <http://www.theacpa.org/>.
- American Society of Addiction Medicine, 4601 N. Park Avenue, Upper Arcade #101, Chevy Chase, MD 20815, (301) 656-3920, (301) 656-3815, email@asam.org, <http://www.asam.org/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Tish Davidson

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Motrin see **Ibuprofen**

Moxifloxacin

Definition

Moxifloxacin is an antibiotic drug in the family of fluoroquinolone drugs.

Purpose

Moxifloxacin treats a variety of infections, including bronchitis, pneumonia, and infections of the sinuses, skin, and abdominal cavity. Some of the organisms it is effective against include *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Proteus mirabilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Clostridium perfringens*, and *Bacteroides fragilis*.

Description

Systemic moxifloxacin is available in tablet, liquid suspension, and injectable (intravenous) forms, as well as in eyedrops. The medication is taken by mouth, through an intravenous (IV) line, or as eyedrops and must be prescribed by a physician. Moxifloxacin is used internationally. It is also occasionally used in veterinary medicine.



Avelox (moxifloxacin), 400 mg. (© Cengage Learning®.)

Moxifloxacin is available in the following forms and strengths:

- Tablets are oval shaped and red and contain 400 milligrams (mg) of active drug. The imprint on tablets depends on manufacturer.
- Moxifloxacin for injection contains 400 mg of active drug in 250 milliliters (mL) of a yellowish, sodium chloride-containing aqueous solution.

Moxifloxacin ophthalmic (eye) drops are light yellow.

U.S. brand names

Moxifloxacin for oral or IV administration is sold under the brand name Avelox. It is also manufactured as a generic by many different companies.

Moxifloxacin for ophthalmic use is sold under the brand name Vigamox.

Canadian brand names

In Canada, moxifloxacin is sold as Avelox. It is also manufactured as a generic by many different companies.

International brand names

Moxifloxacin is sold under a large variety of brand names internationally, including Moxof in Peru, Megaxin in Israel, Moxif in India, Omnimox in Ecuador, Pitoxil in Turkey, Avebact in South Africa, and Moxivig in the United Kingdom.

Recommended dosage

Systemic moxifloxacin (oral tablets or IV) is dosed at 400 mg, administered once per 24 hours. Duration of treatment depends on the site of the infection and may include 5 days for bronchitis, 5–14 days for an abdominal infection, 7–14 days for pneumonia, 10 days for sinusitis, and 7–21 days for skin/soft tissue/skin structure infections.

Moxifloxacin eyedrops are usually administered four times a day for at least a week.

It is important to read and follow the prescription instructions.

Precautions

The following precautions apply to all individuals. These precautions apply primarily to the systemic forms of moxifloxacin, as the eyedrops only act locally.

- This drug should be taken for the entire length of the prescription, even when symptoms cease. Failure to take a complete course of the medication can result in the return of symptoms.
- It is important to take all doses of the medication; doses should not be missed.

- Moxifloxacin can be taken with or without food.
- Moxifloxacin and other fluoroquinolones have been associated with tendinitis and tendon rupture. This risk is increased in individuals who are older than 60 years; have had kidney, heart, or liver transplants; or are taking steroid medications.
- Moxifloxacin use has been associated with blood disorders.
- Moxifloxacin increases the risk of heart arrhythmias, especially in individuals with known electrocardiogram (EKG) abnormalities (particularly prolonged QT intervals), low potassium levels, or on medications known to increase the QT interval.
- Moxifloxacin can cause numbness, tingling, and/or pain in the extremities (peripheral neuropathy), which can become permanent if the drug is continued.
- Use over a long period of time can increase the risk of developing another fungal or bacterial infection (secondary infection).
- *C. difficile*-associated diarrhea and pseudomembranous colitis have both been associated with long-term use of moxifloxacin, even months after the drug has been discontinued.
- It is important to drink plenty of water/fluids while using moxifloxacin.
- Moxifloxacin may make the skin more sensitive to sun exposure and tanning lights, resulting in more easily (and potentially severely) burned skin.

Pediatric

Moxifloxacin is not currently used for pediatric patients.

Geriatric

The risk of moxifloxacin-induced heart, liver, and tendon side effects may be increased in the elderly.

Pregnant or breastfeeding

Systemic moxifloxacin is a pregnancy category C drug, meaning that there are potential adverse effects on a developing fetus. It has not been well studied in pregnant women. Women who are pregnant or breastfeeding should tell their doctor before taking moxifloxacin. In most cases, an alternative drug will be prescribed unless the benefit is determined to outweigh the risk. This drug is considered safe for lactating mothers to use, although some practitioners recommend avoiding breastfeeding for four to six hours directly following a dose.

Moxifloxacin eyedrops are considered safe for pregnant or breastfeeding women.

KEY TERMS

Anaphylaxis—A severe, systemic allergic reaction that can be potentially life threatening.

Electrocardiogram (EKG)—A test of a patient's heartbeat.

Peripheral neuropathy—Damage to the peripheral nerves (in the extremities of the body) causing numbness, tingling, or pain.

QT interval—A segment of an electrocardiogram that represents the electrical conduction that occurs during the beating and relaxing of the ventricles (pumping chambers of the heart).

Secondary infection—An infection by a microbe that occurs because the body is weakened by a primary infection caused by a different kind of microbe; also called an opportunistic infection.

Systemic—A term used to describe a medicine that has effects throughout the body, as opposed to topical drugs that work on the skin. Most medicines that are taken by mouth or by injection are systemic drugs.

Other conditions and allergies

Individuals should not take moxifloxacin if they are allergic to moxifloxacin or other fluoroquinolone-type drugs (e.g., **ciprofloxacin** or **levofloxacin**) or have developed jaundice and liver problems when taking moxifloxacin in the past.

Individuals with a history of severe allergies, asthma, or prior reactions involving anaphylaxis, hives, or the severe swelling called angioedema are at higher risk for serious reactions to moxifloxacin.

Individuals who have had seizures should take moxifloxacin with great care, as the seizure threshold is lowered during its use.

Individuals who have myasthenia gravis may have worsened symptoms when taking moxifloxacin.

Individuals with a history of kidney or liver problems or on dialysis should tell their doctor before taking this drug.

Side effects

Serious and sometimes fatal reactions can occur in individuals who are allergic to fluoroquinolone drugs. Anyone who has had a severe reaction to any drug should alert the physician before taking this drug.

The most common adverse side effects of moxifloxacin for all age groups tend to be mild. They include:

- upset stomach
- loose stools or diarrhea
- nausea and vomiting
- heartburn

These side effects should be brought to the doctor's attention if they do not go away within a few days.

Whitish vaginal discharge or white coating of the tongue and inside of the mouth should also be reported to the doctor.

A doctor should be notified immediately if any of these less common but more serious side effects occur:

- wheezing, difficulty breathing or swallowing (may indicate a severe allergic reaction and require immediate medical attention)
- hoarse voice
- severe skin rash, itching, or hives; blistering or separating skin
- swelling
- yellowing of the skin or the whites of the eyes
- vaginal itching or discharge
- seizures
- abdominal pain with fever
- sensation of an extra, skipped, or fast heartbeat
- dizziness, fainting
- confusion
- anxiety
- mood changes
- insomnia
- hallucinations
- thoughts of injuring oneself or others
- severe, watery, and/or bloody diarrhea, even if it occurs two months after ending moxifloxacin treatment
- easy bruising or bleeding
- very dark urine
- severe muscle weakness or unusual loss of muscle control
- joint pain or any popping sensation in a joint

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including

nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Moxifloxacin is known to interact with the following pharmaceutical drugs. Other interactions are possible. An individual who develops any unusual or unexpected symptoms should contact a physician.

- Due to increased risk of cardiovascular complications, avoid using moxifloxacin in conjunction with all antiarrhythmic medications, such as amiodarone, dofetilide, procainamide, quinidine, and **sotalol**.
- Moxifloxacin taken with the following drugs may increase the risk of serious cardiovascular side effects: arsenic, asenapine, bepridil, chloroquine, cisapride, **citalopram**, **clozapine**, crizotinib, dolasetron, droperidol, halofantrine, **haloperidol**, iloperidone, imidazoles (e.g., **fluconazole**, **ketoconazole**), macrolides (e.g., erythromycin), maprotiline, **methadone**, nilotinib, **ondansetron**, paliperidone, pentamidine, phenothiazines (e.g., chlorpromazine), pimozide, **quetiapine**, romidepsin, **tacrolimus**, telithromycin, tetrabenazine, toremifene, tricyclic antidepressants (e.g., **nortriptyline**), tyrosine kinase inhibitors (e.g., sunitinib), vandetanib, or **ziprasidone**
- Using moxifloxacin while taking insulin or oral antidiabetic drugs may increase the risk of high or low blood sugar.
- Using moxifloxacin while taking anticoagulant drugs may increase the risk of bleeding.
- Using moxifloxacin while taking nonsteroidal anti-inflammatory drugs (NSAIDs) or theophylline may increase the risk of seizures and other severe adverse effects.
- Moxifloxacin should be taken either four hours before or eight hours after taking sucralfate or didanosine.

Herbs and supplements

Moxifloxacin should be taken either four hours before or eight hours after taking any products containing aluminum, magnesium, iron, or zinc.

Resources

BOOKS

- Bennett, John E., Raphael Dolin, and Martin J. Blaser. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia: Saunders, 2014.
- Cherry, James, et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Saunders, 2014.

Lexicomp. *Drug Information Handbook*. 23rd ed. Hudson, OH: Lexicomp Inc., 2014.

Magill, Alan, et al. *Hunter's Tropical Medicine and Emerging Infectious Diseases*. Philadelphia: Saunders, 2013.

Rang, Humphrey, et al. *Rang and Dale's Pharmacology*. 7th ed. London: Churchill Livingstone, 2012.

WEBSITES

MedlinePlus. "Moxifloxacin." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a600002.html> (accessed February 23, 2015).

"Moxifloxacin." Drugs.com. <http://www.drugs.com/cdi/moxifloxacin.html> (accessed February 23, 2015).

U.S. National Library of Medicine. "LactMed: Moxifloxacin." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+191> (accessed February 23, 2015).

ORGANIZATIONS

Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, Atlanta, GA 30329, (404) 639-3534, (800) CDC-INFO (800-232-4636), TTY: (888) 232-6348, inquiry@cdc.gov, <http://www.cdc.gov/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rosalyn Carson-DeWitt, MD

REVIEWED BY KEVIN GLAZA, RPh

MS Contin see **Morphine**

Mupirocin

Definition

Mupirocin is a topical antibiotic drug.

Purpose

Mupirocin is used to treat primary and secondary skin infections with *Staphylococcus aureus* and *Staphylococcus pyogenes*. Primary skin infections occur in healthy skin. Secondary skin infections affect skin that has been injured or burned or occur within a surgical incision. *S. aureus* and *S. pyogenes* skin infections are called impetigo.

Mupirocin is also used intranasally (in the nose) to eliminate the presence of methicillin-resistant *Staphylococcus aureus* (MRSA). This organism can live in the nose without causing symptoms but can be passed to other vulnerable people who may develop an infection from the bacteria.



Mupirocin ointment. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Off-label uses

Mupirocin has been used intranasally in an effort to prevent surgical incision infections in surgical patients who may have MRSA growing in their nostrils.

Description

Mupirocin is available as a cream, an ointment, and an intranasal ointment.

U.S. brand names

Mupirocin is sold under the brand names Bactroban, Bactroban Nasal, Centany, and Centany AT. It is also manufactured as a generic by many different companies.

Canadian brand names

Mupirocin is sold under the brand name Bactroban in Canada.

International brand names

Mupirocin is sold under a variety of brand names internationally. For example, it is sold as Bacidal in Thailand, Bactifree in the Philippines, Dimsa in Argentina, Hevronaz in Greece, Pirocin in India, Sinpebac in Mexico, and Trego in Bangladesh.

Recommended dosage

Dosage recommendations apply to adults, pediatric patients, and geriatric patients:

KEY TERMS

Anaphylaxis—A severe, systemic allergic reaction that can be potentially life-threatening.

MRSA—Methicillin-resistant *Staphylococcus aureus*, a staphylococcal organism that has developed the ability to resist killing by many conventional antibiotics.

Resistance—A characteristic developed by some organisms that allows them to escape the effects of certain antibiotics.

Secondary infection—An infection by a microbe that occurs because the body is weakened by a primary infection caused by a different kind of microbe; also called an opportunistic infection.

Systemic—A term used to describe a medicine that has effects throughout the body as opposed to topical drugs that work on the skin. Most medicines that are taken by mouth or by injection are systemic drugs.

- For primary skin infections (impetigo), apply ointment to lesions three times a day. Improvement should be noted within three to five days; if none is noted, the treatment plan should be reassessed.
- For secondary skin infections (e.g., infections within wounds, lacerations, burns, surgical incisions), apply cream to the infected area three times a day for ten days. Improvement should be noted within three to five days; if none is noted, the treatment plan should be reassessed.
- For eradicating intranasal MRSA, single-use tubes are dispensed. Half should be used in each nostril twice a day for five days.

Precautions

The following precautions apply to all individuals:

- This drug should be taken for the entire length of the prescription. Failure to take a complete course of the medication can result in the return of symptoms.
- Use over a long period of time can increase the risk of developing another fungal or bacterial infection (secondary infection).
- *C. difficile*-associated diarrhea and pseudomembranous colitis have both been associated with the long-term use of mupirocin, even months after the drug has been discontinued.

Pregnant or breastfeeding

Mupirocin carries the FDA pregnancy category B, meaning that studies in animals have found no risk to the developing fetus. Women who are pregnant or breastfeeding should tell their doctor before taking mupirocin.

Other conditions and allergies

Individuals who are allergic or who have had reactions to mupirocin should not use this drug.

Individuals with a history of severe allergies, asthma, or prior reactions involving anaphylaxis, hives, or the severe swelling called angioedema are at higher risk of serious reactions to mupirocin.

Side effects

Serious and sometimes fatal reactions can occur in individuals who are allergic to penicillin and penicillin-like drugs. Anyone who has had a severe reaction to any drug should alert the physician before taking this drug.

The most common adverse side effects of mupirocin for all age groups tend to be mild. They include:

- headache
- burning, stinging, or pain in the affected area being treated
- burning and/or tearing of the eyes
- itching
- rash
- nausea
- changes in the sensation of taste during use of the drug
- congested or runny nose
- sore throat
- cough

These side effects should be brought to the doctor's attention if they do not go away within a few days.

A doctor should be notified immediately if any of these less common but more serious side effects occur:

- wheezing, difficulty breathing or swallowing; may indicate a severe allergic reaction and require immediate medical attention
- severe skin rash, itching, or hives
- swelling

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all

the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Because mupirocin is not systemic, there have been few reported drug interactions. However, antibiotics are known to decrease the therapeutic effect of the BCG vaccine, typhoid vaccine, and actions of sodium picosulfate. It is advisable to delay immunization until at least 24 hours after the last use of an antibiotic.

Resources

BOOKS

- Bennett, John E., Raphael Dolin, and Martin J. Blaser. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia: Saunders, 2014.
- Cherry, James, et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Saunders, 2014.
- Lexicomp. *Drug Information Handbook*. 23rd ed. Hudson, OH: Lexicomp Inc., 2014.
- Magill, Alan, et al. *Hunter's Tropical Medicine and Emerging Infectious Diseases*. Philadelphia: Saunders, 2013.
- Rang, Humphrey, et al. *Rang and Dale's Pharmacology*. 7th ed. London: Churchill Livingstone, 2012.

WEBSITES

- MedlinePlus. "Mupirocin." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a688004.html> (accessed February 23, 2015).
- "Mupirocin Nasal." Drugs.com. <http://www.drugs.com/mtm/mupirocin-nasal.html> (accessed February 23, 2015).
- U.S. National Library of Medicine. "LactMed: Mupirocin." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+548> (accessed February 23, 2015).

ORGANIZATIONS

- Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, Atlanta, GA 30329, (404) 639-3534, (800) CDC-INFO (800-232-4636), TTY: (888) 232-6348, inquiry@cdc.gov, <http://www.cdc.gov/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Myambutol see **Ethambutol**

Mycostatin see **Nystatin**



Nabumetone

Definition

Nabumetone is a type of medication called a nonsteroidal anti-inflammatory drug (NSAID). It helps relieve the swelling, pain, and stiffness of arthritis and can help ease moderate pain for people with certain conditions or diseases.

Purpose

Because NSAIDs such as nabumetone help ease inflammation, the medication can relieve the symptoms of rheumatoid arthritis and osteoarthritis. Nabumetone doesn't cure these diseases but can help ease symptoms by blocking substances or chemicals in the body that cause joints to swell and become irritated, stiff, and painful. Nabumetone can also relieve pain, fever, and inflammation from other conditions.

Description

NSAIDs such as nabumetone are prescribed more often by doctors for people with arthritis than any other medications. Although some NSAIDs, such as **aspirin** and **ibuprofen**, are available without a prescription, nabumetone requires a doctor's prescription. The medication comes in a tablet that is taken by mouth.

U.S. brand names

Nabumetone is only available in the United States in the generic, or non-brand, form. The drug was previously available under the brand name Relafen.

Recommended dosage

Nabumetone tablets typically come in 500 or 750 milligram (mg) formulas. Adults who have osteoarthritis or rheumatoid arthritis usually take 1,000 mg of nabumetone once a day at bedtime when they begin use of the medication, and may later increase the dosage to

1,500 or 2,000 mg each day, divided into two doses. The daily dose should not exceed 2,000 mg.

Other conditions and allergies

Doctors try to relieve a patient's symptoms using the lowest dose that is effective. Some patients need to have lower doses than those typically used because they weigh less than the average adult, or because they have kidney disease or problems with liver function.

Precautions

Use of nabumetone and some other NSAIDs is associated with significant warnings about increased risk of heart attack or stroke. The risk is higher for people who use nabumetone for a long period of time to treat chronic conditions such as arthritis. Studies have shown



Nabumetone, 500 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

that risk of heart attack and stroke with use of nabumetone is slightly lower than risk with some other NSAIDs used to manage arthritis symptoms. Still, anyone who has certain other diseases or participates in behaviors that increase risk of heart attack or stroke should inform their doctor of these facts before taking nabumetone. Examples are smoking or having high cholesterol, high blood pressure, or diabetes.

Nabumetone can cause ulcers in the stomach or intestine of people who use the medication, and the ulcers can develop after short-term or long-term use with little or no warning. Ulcers can lead to internal bleeding and even death. It is important for people who take nabumetone to keep their doctor informed of how the drug is working so that the doctor can prescribe the lowest dose possible to relieve symptoms effectively or stop use of the drug when symptoms are under control. Patients should keep all scheduled appointments so that their doctor can monitor their response to medications and potential side effects.

Use of nabumetone can make people more sensitive to sunlight. Anyone taking the medication who plans to be in the sun for an extended period should wear sunscreen and sunglasses, a hat, or other protective clothing.

Pediatric

Safety of nabumetone has not been established in children.

Geriatric

Older patients should be careful about the use of nabumetone and other NSAIDs and may be more sensitive to the effects of the medication. Studies have not shown that nabumetone is any less effective or safe in geriatric patients than in older adults.

Pregnant or breastfeeding

Nabumetone is a pregnancy category C medication. Pregnant women should only use the drug if the potential benefits outweigh the risks. The medicine's effects on unborn children have only been tested in animals, not in humans. Nabumetone may pass from a nursing mother to an infant, but it is not known what effects it might have, so a woman who wants to breastfeed her infant may wish to either discontinue use of nabumetone or choose not to breastfeed while taking the medication.

Other conditions and allergies

People who have asthma or swelling of the lower limbs or who are at risk for heart attack or stroke should talk to their doctors before taking nabumetone. Anyone who is on the medication and plans to have dental

KEY TERMS

Inflammation—The body's reaction to invasion by foreign matter, particularly infection. The result is swelling, redness, and pain.

Osteoarthritis—The most common type of arthritis. This chronic condition affects the cartilage that cushions the joints and causes bones to rub against each other.

Rheumatoid arthritis—A chronic disease of the immune system that causes the body to attack the joints by mistake. The joints swell, or become inflamed, and joints and organs become damaged.

Ulcer—A small sore, or hole, in the lining of the stomach or intestine that can become painful and bleed into the stomach.

surgery should inform the doctor or dentist about use of nabumetone. Additionally, anyone who has developed hives or any other allergic-type reactions after taking NSAIDs (including aspirin) should not take nabumetone.

Side effects

Nabumetone can cause several side effects, in addition to the increased risk of stroke, heart attack, and ulcers. Less serious side effects may include:

- diarrhea
- gas
- constipation
- headache
- dizziness
- sores in the mouth or dry mouth
- ringing in the ears

If any of the following symptoms occur after taking nabumetone, it is best to contact a doctor immediately:

- yellowing of the eyes or skin
- loss of appetite and energy
- nausea
- pain in the upper right area of the stomach
- unexpected weight gain
- fever and flulike symptoms
- rash or hives and itching
- blisters

Interactions

Nabumetone can interact with other drugs, affecting how well one of the drugs works.

Drugs

Nabumetone can interact with several drugs, including:

- ACE inhibitors, which are drugs taken to manage high blood pressure and which may become less effective if taken with nabumetone
- diuretics, also known as water pills, which can lead to kidney failure
- aspirin, which can reduce the effects of the medicine and increase the risk of side effects
- **warfarin** (Coumadin), a blood thinner that also increases risk of GI bleeding; patients using both warfarin and nabumetone should be watched closely

Food and other substances

Drinking alcohol while taking nabumetone could increase the risk of bleeding in the stomach and intestines.

Resources

PERIODICALS

Hussain, Jamilla, Karen Neoh, and Adam Hurlow. "Managing Pain in Advanced Illness." *Clinical Medicine* 14, no. 3 (2014): 303–7.

Patrono, Carlo, and Colin Baignet. "Nonsteroidal Anti-inflammatory Drugs and the Heart." *Circulation* 129, no. 8 (2014): 907–16.

OTHER

GlaxoSmithKline. "Relafen (Nabumetone)." FDA.gov. http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/019583s0251bl.pdf (accessed February 7, 2015).

WEBSITES

American Academy of Orthopaedic Surgeons. "What Are NSAIDs?" <http://orthoinfo.aaos.org/topic.cfm?topic=a00284> (accessed February 7, 2015).

MedlinePlus. "Nabumetone." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a692022.html> (accessed February 7, 2015).

Meland, Marius. "Glaxo Pays \$175 Million To Settle Antitrust Suit Over Relafen Patent." <http://www.law360.com/articles/913/glaxo-pays-175-million-to-settle-antitrust-suit-over-relafen-patent> (accessed February 7, 2015).

"Nabumetone." Drugs.com. <http://www.drugs.com/cdi/nabumetone.html> (accessed February 7, 2015).

ORGANIZATIONS

American College of Rheumatology, 2200 Lake Blvd NE, Atlanta, GA 30319, (404) 633-3777, (404) 633-1870, acr@rheumatology.org, <https://www.rheumatology.org/>.

Arthritis Foundation, 1330 West Peachtree Street, Suite 100, Atlanta, GA 30309, (404) 872-7100, <http://www.arthritis.org/>.

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REVIEWED BY CHRISTY McDONALD LENAHA, DNP, MSN, APRN, FNP-BC

Naloxone/buprenorphine see **Buprenorphine/naloxone**

Namenda see **Memantine**

Nasacort see **Triamcinolone**

Nebivolol

Definition

Nebivolol is an oral drug for treating hypertension (high blood pressure). It is in the drug class of beta blockers or beta-adrenergic-receptor antagonists, specifically beta-1 selective or cardioselective beta blockers.



Bystolic (nebivolol), 5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Nebivolol is used alone or in combination with other drugs to control high blood pressure. Nebivolol does not cure hypertension, but lowering blood pressure can help prevent strokes, heart attacks, and kidney problems. Lifestyle changes, including diet, exercise, and stress reduction, may increase the effectiveness of nebivolol.

Off-label uses

Nebivolol is used off label for purposes not specifically approved by the U.S. Food and Drug Administration (FDA). These include prevention of angina (chest pain), improving survival after a heart attack, as an adjunct treatment for heart failure, and for mitral valve prolapse, a condition in which the valve separating the upper and lower chambers of the heart does not close properly.

Description

Nebivolol binds competitively and selectively to beta-1-adrenergic receptors (adrenoreceptors or adrenoceptors) in the heart and blood vessels. Nebivolol blocks the binding of endogenous substances such as **epinephrine** (adrenaline) and norepinephrine, thereby slowing the heart rate, dilating (relaxing) blood vessels to improve blood flow and decrease blood pressure, and reducing strain on the heart. Nebivolol is a considered a selective beta blocker because at doses below 10 milligrams (mg), it has little or no effect on beta-2 receptors.

Nebivolol is supplied as heart-shaped oral tablets debossed with “FL” (for Forest Labs) on one side and the dose on the other side. Different forms include:

- 2.5 mg dark blue tablets debossed with “2 1/2”
- 5 mg brown tablets debossed with “5”
- 10 mg pink tablets debossed with “10”
- 20 mg light blue tablets debossed with “20”

Nebivolol is also available in combination medications with drugs such as diuretics. Nebivolol is usually taken once a day, at about the same time each day, with or without food. It is stored in the tightly closed container it is supplied in, at room temperature and away from excess heat and moisture (not in the bathroom).

U.S. brand names

The U.S. brand name for nebivolol is Bystolic.

Canadian brand names

The Canadian brand name for nebivolol is Bystolic.

International brand names

Nebilet and Nebivolol are the most common international brand names. Other more common brand names include:

- Hypoloc
- Lobivon
- Lovispes
- Nebicard
- Nebilox
- Nebinorm
- Nebisam
- Nebiscop
- Nebispes
- Nebiten
- Nebitrix
- Nemirostad
- Nepiphar

Origins

Nebivolol hydrochloride was approved by the FDA in 2007.

Recommended dosage

Nebivolol dosage is based on the condition being treated and the patient's response to treatment. The initial dosage is usually low and may be gradually increased at intervals of at least two weeks. The initial dosage for treating hypertension is usually 5 mg per day, increased at two-week intervals to a maximum of 40 mg per day. A missed dose should be taken as soon as possible, unless it is almost time for the next dose, in which case the dose should be skipped and the regular dosing schedule resumed.

Geriatric

For treating hypertension in elderly patients, the initial dose is 5 mg per day, which may be increased every two weeks to a maximum of 40 mg per day. For heart failure in patients over age 70, the initial dose is 1.25 mg per day. This may be increased by 2.5 mg every one or two weeks, for a maximum of 10 mg per day. The dosage for heart failure in patients under age 70 has not been established.

Other conditions and allergies

For patients with liver impairment or kidney impairment with creatinine clearance of less than 30 milliliters (mL) per minute, the initial dosage is 2.5 mg per day, which may be cautiously increased. Creatinine is

KEY TERMS

Angina—Chest pain from diseased blood vessels that restrict blood flow to the heart.

Antagonist—A drug, such as nebivolol, that blocks the action of a substance, such as epinephrine, by binding to its receptor.

Beta blocker—Beta-adrenergic-receptor (-adrenoceptor) antagonist; a drug, such as nebivolol, that slows heart rate and lowers blood pressure by blocking beta receptors for the hormones epinephrine and norepinephrine.

Diuretic—"Water pill"; a medication that increases urine excretion and removes water and salt from the body, which helps lower blood pressure.

Epinephrine—Adrenaline; a hormone released into the bloodstream in response to stress that stimulates the heart and increases blood pressure, metabolic rate, and blood glucose concentration; blocked by nebivolol.

Hypertension—High blood pressure.

Norepinephrine—A hormone released by nerve cells and the adrenal medulla that causes constriction of blood vessels. Norepinephrine also functions as a neurotransmitter.

Receptor—A molecule, usually a protein, inside or on the surface of a cell, that binds to a specific substance to initiate a series of events, such as raising blood pressure.

a waste material that is filtered out of the body by the kidneys. Measuring the amount of creatinine in a patient's urine helps determine kidney function.

Precautions

Nebivolol should be taken regularly, exactly as prescribed, to obtain the most benefit. It may take several weeks before the full blood pressure-lowering effects of the drug are realized. Patients should routinely check their blood pressure and pulse (heart rate) while taking nebivolol. The patient's healthcare provider should be notified if blood pressure remains high or increases or if the pulse is fast or slow.

Additional precautions include:

- Nebivolol may cause drowsiness or dizziness, so patients should not drive, operate machinery, or

perform activities that require alertness until they know how the drug affects them.

- Patients should rise slowly from sitting or lying down to reduce the risk of dizziness and light-headedness.
- All healthcare providers, including dentists, should be told about nebivolol use (and any other prescription and nonprescription drugs and herbal supplements) before the patient undergoes any type of surgical procedure.
- The healthcare provider and laboratory personnel should be notified of nebivolol use before having any type of laboratory testing.
- High doses cause nebivolol to lose its receptor selectivity and to block beta-2 receptors.
- Nebivolol increases the risk of stroke following surgery.

Nebivolol should not be stopped without consulting the treating physician. The dose must be gradually decreased over one to two weeks. Patients should temporarily limit physical activity during this period to reduce strain on the heart. Stopping nebivolol suddenly can cause angina, irregular heartbeat, or a heart attack. Medical assistance should be obtained immediately if any of the following symptoms occur:

- chest tightness, pressure, or pain
- chest pain that spreads to the neck, jaw, or arm
- unusual sweating
- difficulty breathing
- fast or irregular heartbeat

Symptoms of nebivolol overdose can include:

- slow heart rate
- dizziness or fainting
- shakiness
- clumsy or jerky movements
- sweating
- confusion
- nervousness, irritability, or sudden changes in behavior or mood
- headache
- numbness or tingling around the mouth
- weakness
- pale skin
- sudden hunger
- difficulty breathing
- fatigue
- vomiting
- seizures

Pediatric

The safety and effectiveness of nebivolol have not been established for patients under age 18.

Pregnant or breastfeeding

Nebivolol is in the FDA pregnancy category C. Women should contact their healthcare provider if they become pregnant while taking nebivolol. It should only be used during pregnancy if it is clearly needed. It may cause low birth weight, and infants may require monitoring for problems such as low blood pressure or slow heartbeat. It is not known whether nebivolol is excreted in breast milk, but breastfeeding while taking the drug is not recommended.

Other conditions and allergies

Patients with allergies to various substances may have worse reactions while taking nebivolol, and allergic reactions may not respond to usual epinephrine injection doses. Before taking nebivolol, patients should tell their healthcare provider and pharmacist if they are allergic to:

- nebivolol
- any ingredients in nebivolol tablets
- acebutolol (Sectral)
- **atenolol** (Tenormin, in Tenoretic)
- betaxolol (Kerlone)
- bisoprolol (Zebeta, in Ziac)
- **carvedilol** (Coreg)
- labetalol (Trandate)
- **metoprolol** (Lopressor, Toprol XL)
- nadolol (Corgard, in Corzide)
- pindolol
- **propranolol** (Inderal, InnoPran XL, in Inderide)
- **sotalol** (Betapace, Betapace AF, Sorine)
- **timolol** (Blocadren, in Timolide)
- any other medications

In addition to hypersensitivity reactions, nebivolol may be contraindicated for patients with:

- slow heart rate (below 50 beats per minute)
- heart disease
- uncontrolled heart failure
- severe liver impairment
- chronic obstructive pulmonary disease (COPD)
- hypotension (low blood pressure)

The healthcare provider should be informed of the patient's complete medical history, especially:

- severe allergies

- heart problems such as previous heart failure, heart attack, heart rhythm problems, primary heart block, ischemic heart disease, or Prinzmetal angina
- asthma or other lung diseases such as chronic bronchitis or emphysema
- diabetes
- hyperthyroidism (overactive thyroid gland), since nebivolol may mask symptoms of hyperthyroidism
- blood circulation problems, such as Raynaud's disease or peripheral vascular disease
- kidney disease, since severe kidney impairment decreases nebivolol clearance from the body
- pheochromocytoma (a tumor on a gland near the kidneys that can cause high blood pressure and fast heart rate)
- liver problems, since moderate liver impairment decreases nebivolol metabolism, which causes it to lose receptor selectivity and block beta-2 receptors
- mood or mental disorders including depression
- myasthenia gravis (a muscle disorder)
- psoriasis

Patients with diabetes should check their blood glucose (sugar) levels regularly, because nebivolol can make blood glucose harder to control. Nebivolol may also prevent a fast or pounding heartbeat from low blood glucose (hypoglycemia), although other symptoms, such as sweating and dizziness, are unaffected by the drug. The treating physician should be contacted immediately if symptoms of high blood glucose, such as increased thirst and urination, occur. Diabetes medication, exercise programs, and/or diet may require adjustment.

Side effects

Many individuals do not experience serious side effects from nebivolol, but the healthcare provider should be notified if side effects are severe or persistent. Side effects occurring in 1%–10% of patients taking nebivolol include:

- headache
- fatigue
- dizziness
- diarrhea
- nausea
- increased triglyceride levels and insulin resistance and decreased high-density lipoprotein (HDL) levels
- insomnia
- peripheral edema (swelling)
- weakness

Side effects occurring in fewer than 1% of patients are:

- slow heart rate (bradycardia)
- chest pain
- difficult or labored breathing (dyspnea)

Nebivolol can reduce blood flow to the hands and feet, causing them to feel cold. Smoking worsens this effect. Patients should dress warmly and avoid tobacco. The healthcare provider should be contacted immediately in case of serious side effects such as:

- asthma symptoms (chest tightness, shortness of breath, cough, wheezing)
- blue fingers or toes
- fainting
- very slow heartbeat
- new or worsening heart failure symptoms (swelling of ankles and feet, severe fatigue, shortness of breath, sudden unexplained weight gain)
- mental or mood changes such as depression, confusion, or mood swings
- chest pain
- swelling of the hands, feet, ankles, or lower legs

Other conditions and allergies

Although very serious allergic reactions are rare with nebivolol, symptoms include:

- rash
- itching or swelling, especially of the face, tongue, or throat
- severe dizziness
- difficulty breathing

Interactions

It is very important that the healthcare provider and pharmacist be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used or planning to be used by patients. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

Anesthetics may depress the heart rate in combination with nebivolol. Nebivolol should be used with caution in patients taking calcium channel blockers, such as **diltiazem** (e.g., Cardizem, Dilacor, Tiazac) and verapamil (e.g., Calan, Isoptin, Verelan), or cardiac glycosides or using inhaled anesthetics. Other drug

interactions that may require changing doses or careful monitoring for side effects include:

- amiodarone (Cordarone, Pacerone)
- other beta blockers such as acebutolol (Sectral), atenolol (Tenormin, in Tenoretic), betaxolol (Kerlone), bisoprolol (Zebeta, in Ziac), carvedilol (Coreg), labetalol (Trandate), metoprolol (Lopressor, Toprol XL), nadolol (Corgard, in Corzide), pindolol, propranolol (Inderal, InnoPran XL, in Inderide), sotalol (Betapace, Betapace AF, Sorine), and timolol (Blocadren, in Timolide)
- **bupropion** (Wellbutrin)
- chlorpheniramine, an antihistamine in allergy and cold medications
- cimetidine (Tagamet)
- clomipramine (Anafranil)
- **clonidine** (Catapres)
- **digoxin** (Digitek, Lanoxicaps, Lanoxin)
- disopyramide (Norpace)
- **duloxetine** (Cymbalta)
- **fluoxetine** (Prozac, Sarafem)
- **haloperidol** (Haldol)
- insulin
- oral diabetes medications
- **methadone** (Dolophine, Methadose)
- **paroxetine** (Paxil)
- propafenone (Rythmol)
- quinidine (Quinaglute, Quinidex)
- reserpine
- ritonavir (Norvir, in Kaletra)
- **sildenafil** (Revatio, Viagra)

Food and other substances

A low-salt or low-sodium diet may be prescribed. Alcoholic beverages should be limited while taking nebivolol.

Resources

PERIODICALS

Arnold, Suzanne V., et al. "Type of [Beta]-Blocker Use among Patients with versus without Diabetes after Myocardial Infarction." *American Heart Journal* 168, no. 3 (2014): 273–79.

"Drugs to Treat Hypertension." *Journal of Psychosocial Nursing & Mental Health Services* 52, no. 2 (2014): 11–12.

WEBSITES

Agency for Healthcare Research and Quality. "Medicines for Early Stage Chronic Kidney Disease: A Review of the Research for Adults with Kidney Disease and Diabetes or High Blood Pressure." <http://effectivehealthcare.ahrq.gov/>

search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1139 (accessed February 24, 2015).

“Nebivolol (Rx)—Bystolic.” Medscape.com. <http://reference.medscape.com/drug/bystolic-nebivolol-342363#91> (accessed February 24, 2015).

U.S. Food and Drug Administration. “High Blood Pressure—Medicines to Help You.” <http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118594.htm> (accessed February 24, 2015).

ORGANIZATIONS

Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, (301) 427-1364, <http://www.ahrq.gov/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Neoral see **Cyclosporine**

Neulasta see **Pegfilgrastim**

Neurontin see **Gabapentin**

Nexium see **Esomeprazole**

Nifedipine

Definition

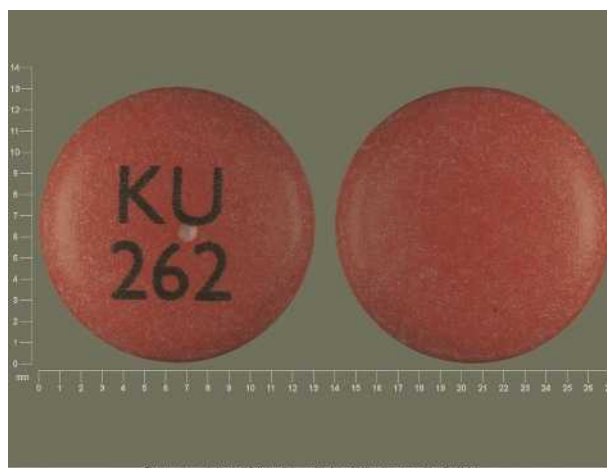
Nifedipine is a calcium channel blocker used to lower blood pressure and reduce chest pain.

Purpose

Nifedipine and nifedipine ER (extended release) are drugs used to lower blood pressure and reduce angina (chest pain caused by restricted blood flow to the heart). Nifedipine must be taken regularly; it is not for treating specific instances of chest pain when they occur.

Off-label uses

Nifedipine is sometimes used off label to treat Raynaud's disease, a condition in which circulation is impaired by spasms of the blood vessels. Off-label use means that the drug has not been specifically approved by the U.S. Food and Drug Administration (FDA) for this use. Nifedipine has also been used off label to prevent migraines in some patients. Another off-label, and sometimes controversial, use of nifedipine is to stop the contractions associated with preterm labor. Nifedipine



Nifedipine ER (extended release), 90 mg. (U.S. National Library of Medicine, Pillbox)

blocks the passage of calcium into uterine cells, which impairs the uterus's ability to contract, stopping the labor contractions.

Description

Nifedipine is a calcium channel blocker. It works by reducing the amount of calcium that can enter cells of the heart and blood vessels. This causes the blood vessels to relax and widen.

Nifedipine is often prescribed to lower blood pressure. Because the drug causes the walls of blood vessels to relax, the same amount of blood flowing through them has more space in which to flow, reducing the amount of pressure placed on the walls of the blood vessels. Nifedipine is also prescribed to help reduce chest pain caused by reduced blood flow to the heart. Wider blood vessels allow more blood to reach the heart, reducing the occurrence of pain.

U.S. brand names

Nifedipine is sold in the United States under the brand names Procardia and Adalat. The extended-release form is sold under the brand names Procardia XL, Nifedical XL, Adalat CC, Afeditab CR, and Nifediac CC.

Canadian brand names

Nifedipine is sold in Canada under the brand names Adalat, Adalat XL Plus, Apo-Nifed, Apo-Nifed PA, and Mylan-Nifedipine Extended Release.

International brand names

Nifedipine is sold under a wide variety of brand names in different countries.

KEY TERMS

Angina—Chest pain due to restricted blood flow to the heart.

Edema—Swelling of a body tissue due to collection of fluids.

Hypertension—Persistently high blood pressure.

Hypotension—Low blood pressure.

Raynaud's disease—A disease that causes decreased circulation to the hands and feet. Its cause is unknown.

Origins

Nifedipine was approved by the FDA in December 1981.

Recommended dosage

Dosage depends on the patient's history, the condition being treated, and whether the medication is given in immediate-release or extended-release form. For individuals with angina, the starting dosage is typically 10 milligrams (mg) of immediate-release medication taken three times daily or 30–60 mg of the extended-release formulation taken once daily.

The starting dosage for hypertension is typically 30–60 mg of the extended-release formulation once daily. For pulmonary hypertension, the starting dosage is typically 30 mg of the extended-release formulation taken twice daily. For treating Raynaud's disease, the recommended dose is 30–120 mg of the extended-release formulation taken once daily.

For patients with migraines, the typical dose is 10 mg of the immediate-release formulation taken three times a day or 30 mg of the extended-release formulation taken once daily.

There is no specific recommended dose of nifedipine for delaying premature labor during pregnancy, but typical amounts are a first dose of 10–40 mg of the immediate-release formulation followed by 10–20 mg taken three to four times daily.

Pediatric

Nifedipine has not been approved by the FDA for use in children and can be toxic in children under 6 at a dose as low as 2 mg per kilogram (kg, or 2.2 lb.) of body weight. In some cases, nifedipine is used to treat high blood pressure in children and is typically given in doses of 0.25–0.5 mg/kg/day of the extended-release formulation, taken once daily or split into two daily doses.

Geriatric

Dosing in elderly patients should be done conservatively. As the body ages, its ability to break down and eliminate medications can be reduced, leading to an increased risk of side effects. Elderly patients being treated for angina should begin with a recommended starting dose of 10 mg of immediate-release nifedipine taken three times a day, or 30–60 mg of the extended-release formulation taken once daily. For high blood pressure, the recommended starting dose is 30–60 mg of the extended-release formulation taken once daily.

Precautions

In some cases, nifedipine has caused patients to have a worsening of their angina symptoms or to have a heart attack. This is more common in patients who have severe coronary artery disease and is most likely to occur just after beginning treatment with nifedipine or after the patient's dose has been increased.

Nifedipine should be taken on an empty stomach. It should not be broken, crushed, or chewed.

Pediatric

If nifedipine is used in children, it should be done so with extreme caution and while the child is under close medical supervision. There have been no adequate studies to determine the effects of long-term nifedipine use in children, so it should be used only when better alternatives are not available.

Geriatric

Nifedipine can cause dizziness, which can be especially dangerous for elderly patients. It is recommended that elderly patients be prescribed extended-release nifedipine instead of immediate-release formulations in order to decrease the risk of hypotension and falls.

Pregnant or breastfeeding

Nifedipine is a class C pregnancy drug, meaning that it is recommended for use during pregnancy with caution and only when the benefits clearly outweigh the risks. Nifedipine passes through breast milk to a nursing baby, and whether it is safe for use by nursing mothers is somewhat controversial.

Other conditions and allergies

Individuals who have recently had a heart attack, who have congestive heart failure, or who have edema should only be prescribed nifedipine with caution and under the close supervision of a healthcare provider. Individuals who have renal (kidney) or liver problems

should be monitored closely and may need a reduced dosage. Some brands of extended-release nifedipine may contain lactose and should not be taken by patients with severe lactose sensitivity.

Side effects

In rare cases, serious allergic reactions to nifedipine have been reported. Patients who experience swelling of the face, mouth, throat, or tongue; severe dizziness; rash or hives; or difficulty breathing should seek emergency medical treatment immediately.

Individuals who experience any of the following side effects should promptly call their healthcare provider:

- unusual weight gain
- bloating or swelling
- difficulty breathing
- tremors
- cramps
- headache
- cough
- tingling in the extremities
- chest tightness
- worsening of chest pain or any symptom of a heart attack

Common but less serious side effects include:

- indigestion
- mild redness of the skin
- burping
- constipation
- diarrhea
- decreased sexual interest or performance
- insomnia

Interactions

Many different over-the-counter medications, prescription medications, herbs, vitamins, and supplements may interact with nifedipine. Patients should be sure to tell their doctor and pharmacist about everything they are taking, even if it is a natural product. The doctor or pharmacist can check a complete and up-to-date list of substances known to interact with nifedipine. This can help prevent serious and even life-threatening interactions.

Drugs

Nifedipine may cause serious interactions with some medications. Patients taking **rifampin**, rifabutin, phenobarbital, **lovastatin**, idelalisib, **carbamazepine**, **phenytoin**, quinidine, or **tacrolimus** should not take nifedipine. Many

over-the-counter medications contain phenylephrine, caffeine, or pseudoephedrine, none of which should be used while taking nifedipine.

Herbs and supplements

Nifedipine can interact with herbs, supplements, vitamins, and natural remedies. Patients taking nifedipine should not take St. John's wort.

Food and other substances

Patients who are taking nifedipine should not drink grapefruit juice or eat grapefruit or products made from grapefruit. Grapefruit contains chemicals that can change the way nifedipine is released into the body, increasing the risk of serious side effects or overdose.

Resources

BOOKS

- Blush, Joel A. *Integrative Treatment of Hypertension: A Clinical and Mechanistic Approach*. Boca Raton, FL: CRC Press, 2014.
- Sheps, Sheldon O. *Mayo Clinic: 5 Steps to Controlling High Blood Pressure: Your Personal Guide to Preventing and Managing Hypertension*. 2nd ed. Rochester, MN: Mayo Clinic, 2015.

PERIODICALS

- Kjeldsen, Sverre E., et al. "Nifedipine Plus Candesartan Combination Increases Blood Pressure Control Regardless of Race and Improves the Side Effect Profile: Distinct Randomized Trial Results." *Journal of Hypertension* 32, no. 12 (2014): 2488–98.
- Shi, Qingguan, et al. "Oral Nifedipine versus Intravenous Labetalol for the Treatment of Severe Hypertension in Pregnancy." *International Journal of Cardiology* 178 (January 15, 2015): 162–64.
- Webb, Tennille N., Ibrahim F. Shatat, and Y. Miyashita. "Therapy of Acute Hypertension in Hospitalized Children and Adolescents." *Current Hypertension Reports* 16, no. 4 (2014): 424–32.

WEBSITES

- Mayo Clinic staff. "Nifedipine (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/nifedipine-oral-route/description/drg-20071680> (accessed February 24, 2015).
- MedlinePlus. "Nifedipine." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a684028.html> (accessed February 24, 2015).
- "Nifedipine." Drugs.com. <http://www.drugs.com/nifedipine.html> (accessed February 24, 2015).

ORGANIZATIONS

- American Heart Association National Center, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.

National Heart, Lung, and Blood Institute Health Information Center, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, (301) 592-8563, nhlbiinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Nitro-Dur see **Nitroglycerin**

Nitrofurantoin

Definition

Nitrofurantoin is an antibiotic drug used to treat urinary tract infections.

Purpose

Nitrofurantoin is used to treat urinary tract infections with susceptible bacteria, including *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus saprophyticus*, *Enterococcus*, *Klebsiella*, and *Enterobacter*. It can also be taken for up to a year as prophylaxis (prevention) of urinary tract infections in susceptible individuals.

Description

Nitrofurantoin is available in 25, 50, 75, and 100 milligram (mg) capsules, usually imprinted with the dosage and brand name. Nitrofurantoin capsules come in a variety of colors depending on the manufacturer. A liquid alternative is also available, containing 25 mg of active drug per 5 milliliters (mL) of suspension.

There are several formulations of nitrofurantoin, each differing in terms of the crystalline structure of the drug:

- Furadantin is the microcrystalline form and is more quickly absorbed.
- Macrochantin is the macrocrystalline form and is more slowly absorbed than the microcrystalline form, allowing it to be better tolerated by some individuals.
- Macrobid is a macrocrystalline form that can be taken just twice a day.

U.S. brand names

In the United States, nitrofurantoin is sold under the brand names Furadantin, Macrobid, and Macrochantin. It is also manufactured as a generic by many different companies.



Macrochantin (nitrofurantoin), 25 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Canadian brand names

In Canada, nitrofurantoin is sold under the brand names Apo-Nitrofurantoin, Macrobid, Macrochantin, Novo-Furantoin, and Teva-Nitrofurantoin.

International brand names

Nitrofurantoin is sold under a variety of brand names internationally. For example, it is sold as Aicol in Taiwan, Furabid in the Netherlands, Furadantina in Argentina, Furolin in Greece, Furedan in Italy, Nifurettin in Germany, and Tanding in China.

Recommended dosage

For the treatment of urinary tract infections with Furadantin or Macrochantin, 50–100 mg should be taken by mouth every six hours for seven days, or for at least three days after a urine test no longer reveals the presence of bacteria. For the treatment of urinary tract infections with Macrobid, 100 mg should be taken by mouth twice a day for seven days.

For prophylaxis of urinary tract infections with Furadantin or Macrochantin, 50–100 mg should be taken by mouth at bedtime.

Pediatric

Pediatric dosing is by weight. Children over 12 can be dosed as adults.

To treat urinary tract infections with Furadantin or Macrochantin, the recommended dose for children older than one month is 5–7 mg per kilogram (kg, or 2.2 lb.) of body weight per day, divided into four doses and taken every six hours. The maximum dose per day is 400 mg. This medication should be taken for seven days, or for at least three days after a urine test no longer reveals the presence of bacteria.

For prophylaxis of urinary tract infections with Furadantin or Macrochantin, the recommended dose for children older than one month is 1–2 mg/kg/day, divided into two doses given 12 hours apart, or given as a single dose once a day. The maximum dose per day is 100 mg.

The liquid may be mixed with water, milk, fruit juice, or infant formula prior to administering.

Precautions

The following precautions apply to all individuals.

- This drug should be taken for the entire length of the prescription. Failure to take a complete course of the medication can result in the return of symptoms.
- Nitrofurantoin should be taken with meals and with a full glass of water.
- Use of nitrofurantoin over a long period of time can increase the risk of developing another fungal or bacterial infection (secondary infection).
- *C. difficile*—associated diarrhea and pseudomembranous colitis have both been associated with the long-term use of nitrofurantoin, even months after the drug has been discontinued.
- Nitrofurantoin use can induce liver problems, including hepatitis. The drug should be immediately discontinued if signs or symptoms of liver impairment occur.
- The drug should be discontinued if vision problems occur, as inflammation of the optic nerve is a serious side effect.
- Pain, numbness, or tingling of the extremities may occur, particularly in individuals with a history of diabetes, low vitamin B, chronic illness, or chemical (electrolyte) imbalances.
- Nitrofurantoin can cause lung reactions, especially in the elderly, necessitating the immediate discontinuation of the drug. Signs include severe fatigue, shortness of breath, cough, fever, and lung changes visible by x-ray.
- While nitrofurantoin is appropriate for treating uncomplicated urinary tract infections, it is not appropriate for kidney infections.

Geriatric

Nitrofurantoin should be avoided in the geriatric population.

KEY TERMS

Anaphylaxis—A severe, systemic allergic reaction that can be potentially life threatening.

Cystitis—Inflammation of the bladder. When caused by an infection, this can also be called a urinary tract infection.

Jaundice—Yellowing of the skin and the whites of the eyes due to high blood levels of a substance called bilirubin.

Pregnancy category—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk but no human studies exist, or adverse effects have been seen in animals but not in well-controlled human studies. Category C: No adequate human or animal studies exist, or adverse fetal effects have occurred in animal studies but there is no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk, and risks outweigh any benefits.

Prophylaxis—Prevention.

Resistance—A characteristic that can be developed by some organisms that allows them to escape the effects of certain antibiotics.

Secondary infection—An infection by a microbe that occurs because the body is weakened by a primary infection caused by a different kind of microbe; also called an opportunistic infection.

Pregnant or breastfeeding

Nitrofurantoin is in the FDA pregnancy category B but has not been well studied in pregnant women. It should not be used at term (38–42 weeks of pregnancy) or during labor and delivery, as its use puts babies at higher risk of jaundice. It should only be used in the first trimester if other appropriate options are unavailable.

Nitrofurantoin passes into breast milk and cannot be used by women breastfeeding babies under a month old due to the possibility of inducing a form of anemia in the newborn. Women who are pregnant or breastfeeding should tell their doctor before taking nitrofurantoin.

Other conditions and allergies

Severe anemia can occur in people with a particular enzyme deficiency called G6PD deficiency. People with

this condition should use extreme caution when taking nitrofurantoin.

Nitrofurantoin may be used in patients with mild kidney impairment but should be avoided in patients with more severe kidney impairment. The measure of impairment is creatinine clearance, an indicator of kidney function. Normal creatinine clearance is about 125 milliliters (mL) per minute. Patients with creatinine clearance greater than 60 mL/min may still use nitrofurantoin, but those with creatinine clearance less than 60 mL/min should not.

Nitrofurantoin can be used in patients with liver impairment but should not be used in individuals who have previously experienced liver problems due to nitrofurantoin administration.

Individuals who are allergic or who have had reactions to nitrofurantoin should not use this drug. Individuals with a history of severe allergies, asthma, or prior reactions involving anaphylaxis, hives, or the severe swelling called angioedema are at higher risk for serious reactions to nitrofurantoin.

Side effects

Serious and sometimes fatal reactions can occur in individuals who are allergic to nitrofurantoin. Anyone who has had a severe reaction to any drug should alert the physician before taking this drug.

The most common adverse side effects of nitrofurantoin for all age groups tend to be mild. They include:

- nausea, vomiting
- decreased appetite
- dark brown urine

These side effects should be brought to the doctor's attention if they do not go away within a few days.

A doctor should be notified immediately if any of these less common but more serious side effects occur:

- wheezing, difficulty breathing or swallowing (may indicate a severe allergic reaction and require immediate medical attention)
- severe skin rash, itching, hives, skin blisters, skin peeling
- swelling
- extreme fatigue
- fever
- chest pain
- weak muscles
- cough
- numbness, tingling, burning, or pain in the extremities

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Nitrofurantoin is known to interact with the following pharmaceutical drugs. Other interactions are possible. An individual who develops any unusual or unexpected symptoms should contact a physician.

- Nitrofurantoin may decrease the effect of the bacillus Calmette–Guérin (BCG) vaccine, magnesium trisilicate, norfloxacin, sodium picosulfate, and the typhoid vaccine.
- Nitrofurantoin may increase the possible side effects of eplerenone, prilocaine, lidocaine, probenecid, sodium nitrate, and **spironolactone**.

Resources

BOOKS

- Bennett, John E., Raphael Dolin, and Martin J. Blaser. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia: Saunders, 2014.
- Cherry, James, et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Saunders, 2014.
- Lexicomp. *Drug Information Handbook*. 23rd ed. Hudson, OH: Lexicomp Inc., 2014.
- Magill, Alan, et al. *Hunter's Tropical Medicine and Emerging Infectious Diseases*. Philadelphia: Saunders, 2013.
- Rang, Humphrey, et al. *Rang and Dale's Pharmacology*. 7th ed. London: Churchill Livingstone, 2012.

WEBSITES

- MedlinePlus. "Nitrofurantoin." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682291.html> (accessed February 24, 2015).
- "Nitrofurantoin." Drugs.com. <http://www.drugs.com/nitrofurantoin.html> (accessed February 24, 2015).
- U.S. National Library of Medicine. "LactMed: Nitrofurantoin." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+202> (accessed February 24, 2015).

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ORGANIZATIONS

- American Society of Health-System Pharmacists (ASHP) 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, Atlanta, GA 30329, (404) 639-3534, (800) CDC-INFO (800-232-4636), TTY: (888) 232-6348, inquiry@cdc.gov, <http://www.cdc.gov/>.

U.S. Food and Drug Administration (FDA) 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Nitroglycerin

Definition

Nitroglycerin is a medication used to treat angina attacks. Angina is chest pain caused by a lack of blood supply to the heart when blood vessels narrow. Nitroglycerin is a nitrate and is in a class of drugs known as vasodilators. The medicine is also called an antianginal drug.

Purpose

Angina is more of a symptom than a disease, signaling that a problem exists within the coronary arteries that is keeping blood and oxygen from reaching the heart. People who have angina experience episodes of pain or discomfort in their chests and sometimes in their neck, shoulders, arms, back, or jaw. Nitroglycerin helps to relax blood vessels and increase blood and oxygen supply to the heart. Nitroglycerin is used to treat angina episodes, or attacks, when people have coronary artery disease and angina by relaxing the blood vessels and easing the work of the heart. Some forms of nitroglycerin help prevent angina episodes from occurring.

Description

Nitroglycerin comes in several different forms for preventing or relieving angina. Usually, when nitroglycerin is taken to relieve an angina attack, the individual uses a sublingual spray or tablet. Sublingual means that the spray is applied under the tongue or the tablet is held there while it is dissolved. Sublingual forms of nitroglycerin may also be used to prevent attacks if taken just before engaging in activities that typically trigger angina episodes, such as physical activity or emotional stress.

Transdermal patches with nitroglycerin, which are applied to the skin in an area of the upper body once a day, can help prevent angina episodes but do not help relieve symptoms of angina attacks once they occur.

U.S. brand names

In the United States, nitroglycerin sublingual tablets and sprays are sold under the brand names of:

- Nitrolingual
- Nitromist
- Nitrostat

Nitroglycerin in a transdermal patch is sold as:

- Minitran Patch
- Nitro-Dur Patch

Recommended dosage

For relief of an angina episode, it is recommended to take one to two sprays under the tongue every 3 to 5 minutes until pain subsides, for up to three sprays in 15 minutes. If pain continues after 15 minutes (and three sprays), the patient is advised to seek immediate medical attention. Each spray delivers 0.4 to 0.8 milligrams (mg) of nitroglycerin. A sublingual tablet for angina episodes should be dissolved under the tongue every five minutes as needed for symptom relief, taking up to three doses in 15 minutes and seeking immediate medical attention if the tablets do not relieve angina pain. Each sublingual tablet delivers between 0.3 and 0.6 mg of nitroglycerin. Sublingual nitroglycerin tablets should never be chewed or swallowed.



Nitroglycerin ER (extended release), 6.5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Angina—Severe chest pain caused by a lack of blood to the heart.

Coronary artery disease—The most common type of heart disease. Coronary artery disease occurs when the arteries supplying blood to the heart muscle harden and narrow, usually because of cholesterol buildup.

Sublingual—Under the tongue.

When using spray to prevent angina episodes, one to two sprays under the tongue within 5 to 10 minutes of participating in a triggering activity are recommended. Each spray delivers between 0.4 and 0.8 mg of nitroglycerin. The sublingual tablet delivers from 0.3 to 0.6 mg of the drug and should be dissolved under the tongue 5 to 10 minutes before an activity that might cause an angina episode.

The transdermal patch delivers a steady, measured dose of nitroglycerin throughout the course of the day. The starting dose for the prevention of angina is 0.2 mg of nitroglycerin per hour. The patch has been shown as effective and safe at up to 0.8 mg per hour, but the doctor should increase the amount slowly once it is determined whether the patch is working to prevent angina episodes at a lower level. The patch is not left in place all day—it requires an off time of about 10 to 12 hours per day, and individuals using the nitroglycerin transdermal patch should rotate its location on the upper body from day to day.

Precautions

It is recommended to use the smallest dose necessary to relieve an angina episode. If a person uses too much nitroglycerin, it can lead to tolerance for the drug, which means it could stop working. Some people who take nitroglycerin experience severe low blood pressure and should use caution to be sure they do not have problems with slow heart rate or falling as a result.

Some people are allergic to nitroglycerin or to the adhesives used in transdermal patches. Anyone using transdermal patches should carefully follow package and doctor or pharmacist instructions regarding patch application. Caution also should be taken when discarding used patches. There is enough nitroglycerin remaining in the patches to harm children and pets.

Pediatric

The safety and effectiveness of nitroglycerin use have not been established in children.

Geriatric

Doctors recommend starting older patients at the lowest dose possible until they determine how the drug affects them.

Pregnant or breastfeeding

Nitroglycerin is a pregnancy category C drug. There are no studies of the drug's effects in pregnant women, so the drug should only be given to a pregnant woman if the benefits of treatment outweigh the risk of possible harmful effects to her fetus. It is not known whether nitroglycerin is passed from a mother to her infant through breast milk, so women who are breastfeeding should use caution and discuss the use of nitroglycerin with their healthcare providers.

Side effects

Nitroglycerin can cause side effects, including:

- light-headedness
- flushing
- dizziness

In addition to these side effects, the nitroglycerin patch can cause red or irritated skin in the area where the patch was located.

Nitroglycerin can also cause severe side effects. These side effects should be reported to a doctor immediately and may include:

- worsening chest pain
- fainting
- dry mouth
- blurred vision
- rash and blistering, itching, or peeling skin
- problems with breathing or swallowing
- nausea and vomiting
- weakness
- changes in heartbeat

Geriatric

Older people may be more likely to experience low blood pressure when taking nitroglycerin and may be more likely to fall as a result of this side effect.

Interactions

Nitroglycerin can interact with some drugs and other substances. It is important for patients to list all medications, herbal remedies, and vitamin supplements being taken and give these to their doctor before using nitroglycerin.

Drugs

Several medicines interact with nitroglycerin. Patients should inform their doctors if they take beta blockers for high blood pressure or heart failure. Medicines called phosphodiesterase inhibitors (sildenafil, **tadalafil**, or **vardenafil**), which are used to treat erectile dysfunction and pulmonary arterial hypertension, should not be taken with nitroglycerin because of the risk of severe drops in blood pressure from the combined drugs. Nitroglycerin can cause a problem with the blood's ability to carry oxygen when taken together with **epinephrine**, a medicine typically given by injection to treat life-threatening allergic reactions.

Food and other substances

Drinking alcohol while taking nitroglycerin increases the drug's effects and should be avoided.

Resources

PERIODICALS

Beksey, Jonathan, et al. "Relative Efficacy of Antianginal Drugs Used as Add-On Therapy in Patients with Stable Angina: a Systematic Review and Meta-Analysis." *European Journal of Preventive Cardiology* (April 28, 2014): e-pub ahead of print. <http://dx.doi.org/10.1177/2047487314533217> (accessed February 11, 2015).

Munzel, Thomas, Andreas Daiber, and Tommaso Gori. "More Answers to the Still Unresolved Question of Nitrate Tolerance." *European Heart Journal* 34, no. 34 (2014): 2666–73.

Tarkin, Jason M., and Juan Carlos Kaski. "Pharmacological Treatment of Chronic Stable Angina Pectoris." *Clinical Medicine* 13, no. 1 (2013): 63–70.

OTHER

Merck & Co., Inc. "Nitro-Dur (Nitroglycerin) Transdermal Infusion System." Merck.com. http://www.merck.com/product/usa/pi_circulars/n/nitro-dur/nitrodur_pi.pdf (accessed February 7, 2015).

WEBSITES

MedlinePlus. "Nitroglycerin." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601086.html> (accessed February 7, 2015).

MedlinePlus. "Nitroglycerin Transdermal Patch." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601085.html> (accessed February 7, 2015).

National Heart, Lung, and Blood Institute. "How Is Angina Treated?" National Institutes of Health. <http://www.nhlbi.nih.gov/health/health-topics/topics/angina/treatment> (accessed February 11, 2015).

U.S. National Library of Medicine. "Nitrostat." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=79ba021e-183c-4b4d-822e-4ff5ef54ca61> (accessed February 7, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.

National Heart, Lung, and Blood Institute (NHLBI), PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbiinfo@nhlbi.org, <http://www.nhlbi.nih.gov/>.

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Nitrolingual see **Nitroglycerin**

Nitrostat see **Nitroglycerin**

Nizoral see **Ketoconazole**

Nolvadex see **Tamoxifen**

Norco see **Hydrocodone/acetaminophen**

Norelgestromin/ethinyl estradiol

Definition

Norelgestromin/ethinyl estradiol—also called norelgestromin plus ethinylestradiol or ethinyl estradiol and norelgestromin transdermal contraception—is a topical birth control patch for preventing pregnancy. It is in the drug class of estrogens/progestins or estrogen plus progestin (combination hormone) contraceptives.

Purpose

The norelgestromin/ethinyl estradiol transdermal system is very effective for preventing pregnancy. It does not prevent the transmission of HIV/AIDS or other sexually transmitted infections.

Description

Norelgestromin and ethinyl estradiol are synthetic versions of the female sex hormones progestin and estrogen, respectively. They are similar to the hormones in **oral contraceptives** (birth control pills) except that they are absorbed into the bloodstream through the skin. Like oral contraceptives, they override a woman's normal menstrual cycle. During a normal monthly cycle, changing hormone levels cause an egg to ripen and release from the ovaries (ovulation) and prepare the uterine lining for pregnancy. If a fertilized egg does not attach to the uterus, hormone levels drop, and the uterine lining is shed in menstruation.



Ortho Evra (norelgestromin/ethinyl estradiol) patch.
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The primary mechanism of combination-hormone contraception is the prevention of ovulation. The hormones signal the hypothalamus in the brain to inhibit the release of gonadotropins by the pituitary gland, and norelgestromin prevents the egg from ripening and being released. Combination hormones also thicken cervical mucus, which helps prevent sperm from crossing from the vagina to the uterus and reaching an egg even if ovulation occurs. Furthermore, the hormones change the quality of the uterine lining, making it more difficult for a fertilized egg to implant. Combination hormonal contraceptives may also alter transport of eggs from the ovaries through the fallopian tubes, and progestins may alter sperm fertility.

U.S. brand names

In the United States, norelgestromin/ethinyl estradiol is sold under the brand names Ortho Evra and Xulane (a generic version).

Canadian brand names

In Canada, norelgestromin/ethinyl estradiol is sold under the brand name Evra.

International brand names

Internationally, norelgestromin/ethinyl estradiol is sold under the brand name Evra.

Origins

Ortho Evra, produced by Janssen Pharmaceuticals, was approved by the U.S. Food and Drug Administration (FDA) in 2001. Xulane, produced by Mylan, was approved in 2014.

Recommended dosage

Transdermal drug-delivery systems or patches are typically composed of three layers: a backing film, an adhesive layer containing the active drugs, and a release liner. A one-week, extended-release combination-hormone contraceptive patch releases 150 micrograms (mcg) of norelgestromin and 35 mcg of ethinyl estradiol over 24 hours.

A single norelgestromin/ethinyl estradiol patch is applied each week for three weeks—days 1, 8, and 15 are patch-change days. The last patch is removed on day 22, and a patch is not used for one week before repeating the cycle. Menstruation should begin during this fourth week, but a patch is applied to start the new cycle after 7 days, even if menstruation has not started or ended.

- For initial treatment, a patch is applied on the first day of menstruation or the first Sunday after menstruation begins (day 1). If it is applied after the first day of menstruation, another form of contraception must be used for 7 days.
- When switching from oral contraceptives, a patch is applied on the first day of withdrawal bleeding (day 1). If it is applied after the first day, an additional form of contraception should be used for 7 days.
- After a first-trimester abortion, the patch is applied immediately. If it is not applied within 5 days, an additional form of contraception should be used for 7 days.
- After giving birth, women should wait at least three weeks following vaginal delivery and at least six weeks following cesarean delivery before initiating the patch. This is because of an increased risk for blood clots called venous thromboembolism (VTE) in postpartum women using combined-hormonal contraceptives. Risk declines rapidly after 21 days postpartum but does not return to normal until 42 days.
- If a patch is not applied at the start of a new cycle, the new application day becomes day 1, and additional contraception is used for 7 days.
- If a mid-cycle patch is changed within 48 hours of the correct change day, the next patch is applied on the usual change day.
- If a mid-cycle patch is not changed within 48 hours of the correct change day, a new patch is applied immediately, and that day becomes day 1 of a new cycle. An additional form of contraception is used for 7 days.

KEY TERMS

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Contraceptive—A method of birth control.

Estrogens—Various naturally occurring steroid hormones, such as estradiol, and synthetic or semisynthetic steroids, such as ethinyl estradiol, that promote the growth and maintenance of the female reproductive system.

Fallopian tubes—Part of the internal female anatomy that carries eggs from the ovaries to the uterus.

Gonadotropins—Protein hormones secreted by the pituitary gland that affect and stimulate the ovaries or testes.

Hormones—Substances, such as estrogens and progestins, that are produced in one area of the body and travel through the bloodstream to other parts of the body, where they exert their effects.

Jaundice—Yellowing of the eyes and skin due to accumulation in the blood of a heme breakdown product; an indication of liver dysfunction.

Ovulation—The monthly release of a mature egg from an ovary.

Progestins—Natural hormones, such as progesterone, and synthetic hormones, such as norelgestromin, that prepare the lining of the uterus for implantation with a fertilized egg and maintain pregnancy.

Venous thromboembolism (VTE)—A blood clot in a vein that can break off and block a blood vessel elsewhere in the body.

- If a patch is not removed at the end of the third week, it is removed as soon as possible, and the next cycle is started on the usual day (the day after day 28).
- If a patch has been partially or completely detached for less than 24 hours, it is immediately reapplied to the same site or replaced with a new patch.
- If a patch has been partially or completely detached for more than 24 hours, a new patch is applied immediately, and that day becomes day 1 of a new cycle.

- If a patch has been partially or completely detached for more than one week, pregnancy must first be ruled out. Another form of contraception must be used before and for 7 days after restarting treatment.

To apply a patch:

- The foil pouch is opened by tearing along the edge, peeling apart, and opening flat.
- Using a fingernail to lift one corner, the patch and its clear plastic liner are peeled off the foil.
- Half of the plastic liner is peeled away without touching the sticky surface.
- The sticky surface is applied to clean, dry, healthy skin on the buttock, abdomen, upper outer arm, or upper torso where it will not be rubbed by tight clothing. The other half of the plastic liner is removed.
- The patch is pressed firmly with the palm of the hand for ten seconds, ensuring that the edges stick.
- Used patches are folded in half to stick to themselves and discarded in the trash. They are not flushed down the toilet.
- The patches are stored in protective pouches at room temperature, away from light and moisture.

Hormone absorption is equivalent when the patch is applied to the abdomen, buttock, upper outer arm, or upper torso.

Precautions

Norelgestromin/ethinyl estradiol patches carry an FDA-issued boxed warning that states that hormonal contraceptives should not be used by women aged 35 or older who smoke because of increased risk of cardiovascular disease, including high blood pressure, heart attacks, blood clots, and strokes. Women using contraceptive patches should not use tobacco. There may also be an increased risk of venous thromboembolism (VTE) compared with oral contraceptives.

Additionally:

- Patches may not work well for women who weigh more than 198 pounds (90 kilograms).
- The healthcare provider should be informed of spotting or breakthrough bleeding, because this may indicate that the patches are not working effectively.
- Patches should not be applied to a breast or to red, irritated, or broken skin. Makeup, creams, lotions, powders, or other topical products should not be applied to the area of the patch. Each patch should be applied to a new spot to help avoid irritation.
- Patches should not be cut, decorated, or changed in any way or applied with extra material to hold them in place.

- The patch should be checked daily. A patch that is not sticky, has stuck to itself or another surface, or has loosened previously should not be reapplied.
- If skin under a patch becomes irritated, the patch should be removed and a new one applied to a different spot.
- Doctors and dentists must be informed of contraceptive patch use before scheduling any type of surgery, since it may be necessary to stop using the patch several weeks prior to surgery.
- It may be necessary to stop using hormonal contraception before a period of prolonged immobilization, including long plane flights.
- Women should undergo complete yearly physicals, including blood pressure measurements, breast and pelvic exams, and a Pap test.
- Laboratory personnel should be informed of patch use because the hormones can interfere with some tests, such as blood-clotting factors or thyroid activity, possibly yielding false results.
- Before undergoing magnetic resonance imaging (MRI), personnel should be informed of the patch, because some patches have metals that can cause serious burns during an MRI.
- Combination patches can cause blotchy, dark areas on the skin that may be worsened by sunlight. Prolonged sun exposure, sunlamps, and tanning booths should be avoided and sunscreen and protective clothing worn outdoors.
- Women who are nearsighted or wear contact lenses may develop vision problems or have trouble wearing their contact lenses.
- Because patches deliver more estrogen than most birth control pills, there may be increased risk of blood clots or other side effects.
- The norelgestromin/ethinyl estradiol patch may increase risks for endometrial and breast cancers, gallbladder disease, and liver tumors, as well as heart attack, stroke, and blood clots.

Pediatric

Norelgestromin/ethinyl estradiol patches are not recommended for pediatric patients.

Pregnant or breastfeeding

Norelgestromin/ethinyl estradiol is in the FDA pregnancy category X—it must not be used during pregnancy. Women should contact their healthcare provider immediately if they miss two consecutive periods or one period if the patch was not used properly.

Small amounts of steroid hormones are excreted in breast milk, and estrogens may reduce the quality or

quantity of the milk. Therefore, women may want to use other forms of birth control while breastfeeding, although the American Academy of Pediatrics states that contraceptive-patch use is compatible with nursing.

Other conditions and allergies

Women should tell their doctor and pharmacist if they are allergic to estrogens, progestins, or any other medications or have other allergies. Women should not use a norelgestromin/ethinyl estradiol patch if they have had recent surgery, are on bed rest, or have ever had:

- hypersensitivity to steroid hormones
- VTE risk factors other than postpartum
- cancer of the breast, lining of the uterus, cervix, or vagina
- estrogen-dependent tumor formation
- uncontrolled high blood pressure
- cardiovascular disease
- chest pain due to heart disease
- heart attack
- stroke
- blood clots in the legs, lungs, or eyes
- liver disease, impairment, or tumors or hepatitis
- jaundice (yellowing of the eyes or skin) during pregnancy or prior contraceptive use
- vaginal bleeding between menstrual periods
- headaches accompanied by symptoms such as weakness or difficulty seeing or moving
- diabetes with kidney, eye, nerve, or blood-vessel problems

Women with kidney impairment should use norelgestromin/ethinyl estradiol with caution and monitor their blood pressure. Women should tell their healthcare provider if they have recently given birth, had a miscarriage or abortion, have a family history of breast cancer or blood clots, or have ever had:

- breast lumps or fibrocystic breast disease
- an abnormal breast exam or mammogram
- high blood cholesterol and fats
- migraines or other headaches
- depression
- seizures
- scanty or irregular menstrual periods
- gallbladder or kidney disease
- blood clots
- blood-clotting disorders
- high blood pressure
- swelling (edema)

- thyroid problems
- endometriosis
- bone-mineral density changes
- bone metabolic disease
- conditions that are worsened by fluid retention, such as asthma or epilepsy
- systemic lupus erythematosus

Norelgestromin/ethinyl estradiol may make it harder for women with diabetes to control their blood glucose (sugar) levels. Blood glucose should be checked regularly, and diabetes medication, exercise programs, or diet may need adjusting.

Side effects

Many women do not experience serious side effects with norelgestromin/ethinyl estradiol. The treating physician should be contacted if any of the following potential side effects are severe or persistent:

- irritation, redness, or rash at the site of application
- breast tenderness, enlargement, or discharge
- nausea
- vomiting
- stomach cramps or bloating
- weight gain or loss
- change in appetite
- brown or black skin patches
- acne
- swelling of the hands, feet, ankles, or lower legs
- hair loss
- bleeding or spotting between periods
- changes in menstrual flow
- painful or missed periods
- vaginal itching or irritation
- white vaginal discharge
- difficulty wearing contact lenses
- headache

The doctor should be contacted immediately in case of any of the following symptoms:

- sudden severe headache or vomiting
- speech problems
- dizziness or faintness
- weakness or numbness of an arm or leg
- sudden partial or complete loss of vision
- calf pain
- double vision
- bulging eyes
- sharp or crushing chest pain

- chest tightness
- coughing up blood
- shortness of breath
- severe stomach pain
- sleep problems, mood changes, and other signs of depression
- unusual bleeding
- loss of appetite
- extreme tiredness, weakness, or lack of energy
- fever
- dark urine
- light-colored stool
- breast lumps
- unusual vaginal bleeding

Norelgestromin/ethinyl estradiol must be discontinued if any of the following develop:

- jaundice
- vision problems
- signs of VTE
- severe migraine
- significant blood pressure increase
- severe depression

Other conditions and allergies

Serious allergic reactions are rare. Symptoms that require emergency assistance include:

- rash
- itching or swelling, especially of the face, tongue, or throat
- severe dizziness
- difficulty breathing

Interactions

It is very important that the doctor and pharmacist be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used or initiated. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Drugs

Women must not use any other type of hormonal contraception while using the patch. Ombitasvir, paritaprevir, ritonavir, dasabuvir, and oral **tranexamic acid** should never be used in combination with ethinyl estradiol.

Drugs that may decrease the amounts of contraceptive hormones in the body, which could result in pregnancy, include:

- antiseizure drugs such as barbiturates, **carbamazepine**, felbamate, **phenytoin**, primidone, and **topiramate**
- **griseofulvin**
- HIV drugs such as nelfinavir and nevirapine
- **modafinil**
- rifamycins such as **rifampin** and rifabutin
- **tetracycline** antibiotics

More than 100 other drugs have known interactions with norelgestromin/ethinyl estradiol. Patients should be sure to tell their healthcare provider if they take:

- acetaminophen
- antibiotics such as ampicillin
- anticoagulants such as **warfarin**
- antifungals such as itraconazole and **ketoconazole**
- the antiseizure drugs phenobarbital and **oxcarbazepine**
- aromatase inhibitors such as anastrozole and exemestane
- **atorvastatin** (Lipitor)
- clofibrate
- **cyclosporine**
- HIV protease inhibitors such as indinavir
- **morphine**
- oral steroids such as dexamethasone, **methylprednisolone**, prednisone, and prednisolone
- ospemifene
- **tamoxifen**
- **temazepam**
- theophylline
- thyroid medication such as **levothyroxine**
- **tizanidine**

Herbs and supplements

Ascorbic acid (vitamin C) may interact with contraceptive hormones.

St. John's wort may decrease the amount of hormones, which could result in pregnancy.

Resources

WEBSITES

"Ethinyl Estradiol and Norelgestromin." Health Library, University of Maryland Baltimore Washington Medical Center. <http://www.mybwmc.org/library/41/051845> (accessed February 25, 2015).

MedlinePlus. "Ethinyl Estradiol and Norelgestromin Transdermal Patch." U.S. National Library of Medicine, National

Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a602006.html> (accessed February 25, 2015).

Micromedex. "Ethinyl Estradiol And Norelgestromin (Transdermal Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/ethinyl-estradiol-and-norelgestromin-transdermal-route/description/drg-20062923> (accessed February 25, 2015).

Mylan Technologies. "Transdermal Technology." Mylan.com. <http://www.mylan.com/products/packaging-and-delivery-systems/transdermal-technology> (accessed February 25, 2015).

"Norelgestromin/Ethinylestradiol (Rx)—Ortho Evra, Xulane." Medscape.com. <http://reference.medscape.com/drug/ortho-evra-xulane-norelgestromin-ethinyl-estradiol-342765#91> (accessed February 25, 2015).

ORGANIZATIONS

U.S. Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30329, (800) CDC-INFO (232-4636), cdcinfo@cdc.gov, <http://www.cdc.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Norpramin see **Desipramine**

Nortriptyline

Definition

Nortriptyline is a tricyclic antidepressant.

Purpose

Nortriptyline is used to relieve symptoms of depression. The drug is more effective for endogenous depression than for other forms of depression. Endogenous depression is depression arising from metabolic changes within a person, such as chemical or hormonal imbalances. Nortriptyline is also used to treat premenstrual depression, panic disorder, chronic pain, and some skin conditions. In addition, nortriptyline is being investigated for the treatment of nicotine dependence.

Description

Tricyclic antidepressants act to change the balance of naturally occurring chemicals in the brain (called neurotransmitters) that regulate the transmission of nerve impulses between cells. The precise way in which



Nortriptyline, 50 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

nortriptyline elevates mood is not fully understood. The drug inhibits the activity of neurotransmitters such as acetylcholine, histamine, and 5-hydroxytryptamine. Studies have indicated that nortriptyline interferes with the release, transport, and storage of catecholamines, another group of chemicals involved in nerve impulse transmission.

U.S. brand names

Nortriptyline is sold in the United States under the brand name Pamelor, and it is also available under its generic name.

Recommended dosage

As with any antidepressant, the dose of nortriptyline must be carefully adjusted by the healthcare provider to produce the desired therapeutic effect. Nortriptyline is available in 10, 25, 50, and 75 milligram (mg) capsules, as well as in a solution of 10 mg per 5 milliliters (mL) of liquid. The usual dosage for nortriptyline is 25 mg given three or four times each day. The optimum total dose of the drug is 50–150 mg daily. Total dosage in excess of 150 mg is not recommended.

The therapeutic effects of nortriptyline, like other tricyclic antidepressants, appear slowly. Maximum benefit is often not evident for two to three weeks after starting the drug. People taking nortriptyline should be aware of this and continue taking the drug as directed even if they do not see immediate improvement.

Once symptoms of depression have been controlled, the lowest dosage that maintains the desired effect should be taken. People who take 100 mg or more of nortriptyline per day should have their blood tested periodically for nortriptyline concentrations. The results of these tests will show whether the dose is appropriate, too high, or too low.

Pediatric

The recommended dose for adolescents is 30–50 mg per day. Nortriptyline is not recommended for use by younger children.

Geriatric

The recommended dose for older adults (over age 60) is 30–50 mg per day.

Precautions

Children and adults up to age 24 taking antidepressant drugs, including nortriptyline, are at increased risk of developing suicidal thoughts and actions. Patients of any age taking nortriptyline should be monitored for signs of worsening depression or changes in behavior.

Nortriptyline may increase the possibility of having seizures. Patients should tell their physicians if they have a history of seizures, including seizures brought on by the abuse of drugs or alcohol. These people should use nortriptyline only with caution and be closely monitored by their physicians.

When used by people with schizophrenia, nortriptyline may worsen psychosis, increase hostility in some patients, or activate other symptoms that had not previously been expressed. When used by people with bipolar disorder, symptoms of mania may be magnified. Patients with a history of suicide attempts, thoughts of suicide, or drug overdose should be monitored carefully when using nortriptyline. Nortriptyline can either increase or decrease blood sugar levels, depending on the patients and their medical conditions. Nortriptyline should be used with great caution when patients are receiving electroconvulsive therapy.

Nortriptyline may increase heart rate and cause irregular heartbeat. It may also raise or lower blood pressure. It may be dangerous for people with cardiovascular disease, especially those who have recently had a heart attack, to take this drug or other antidepressants in the same pharmacological class. In rare cases in which patients with cardiovascular disease must receive nortriptyline, they should be monitored closely for cardiac rhythm disturbances and signs of cardiac stress or damage.

KEY TERMS

Acetylcholine—A naturally occurring chemical in the body that transmits nerve impulses from cell to cell. Generally, it has opposite effects from dopamine and norepinephrine; it causes blood vessels to dilate, lowers blood pressure, and slows the heartbeat. Central nervous system well-being is dependent on a balance among acetylcholine, dopamine, serotonin, and norepinephrine.

Antidepressant—Any of a group of medications given to relieve mood disorders, including anxiety disorders as well as major depression.

Catecholamine—A group of neurotransmitters synthesized from the amino acid tyrosine and released by the hypothalamic-pituitary-adrenal system in the brain in response to acute stress. The catecholamines include dopamine, serotonin, norepinephrine, and epinephrine.

Endogenous depression—Depression arising from causes within a person, such as chemical or hormonal imbalances.

Neurotransmitter—A chemical in the brain that transmits messages between neurons, or nerve cells.

A common problem with tricyclic antidepressants such as nortriptyline is sedation (drowsiness and lack of physical or mental alertness). This side effect is especially noticeable early in therapy. In most patients, sedation decreases or disappears entirely with time, but until then patients taking nortriptyline should not perform hazardous activities requiring mental alertness or coordination. The sedative effect is increased when nortriptyline is taken with other central nervous system depressants, such as alcoholic beverages, sleeping medications, other sedatives, or antihistamines. It may be dangerous to take nortriptyline in combination with these substances.

Pregnant or breastfeeding

Nortriptyline is classified as pregnancy category D, which means that it has been found to have adverse effects on the development of a fetus (referred to as teratogenic effects). It also passes into breast milk and is not recommended for use during pregnancy or by nursing mothers unless the benefits far outweigh the risks.

Other conditions and allergies

Like all tricyclic antidepressants, nortriptyline should be used cautiously and with close physician

supervision in people, especially the elderly, who have benign prostatic hypertrophy, urinary retention, and glaucoma, especially angle-closure glaucoma (the most severe form). Before starting treatment, people with these conditions should discuss the relative risks and benefits of treatment with their doctors to help determine if nortriptyline is the right antidepressant for them.

Side effects

Nortriptyline shares side effects common to all tricyclic antidepressants. The most frequent of these are dry mouth, constipation, urinary retention, increased heart rate, sedation, irritability, dizziness, and decreased coordination. As with most side effects associated with tricyclic antidepressants, the intensity is highest at the beginning of therapy and tends to decrease with continued use.

Dry mouth, if severe to the point of causing difficulty speaking or swallowing, may be managed by dosage reduction or temporary discontinuation of the drug. Patients may also chew sugarless gum or suck on sugarless candy in order to increase the flow of saliva. Some artificial saliva products may give temporary relief.

Men with prostate enlargement who take nortriptyline may be especially likely to have problems with urinary retention. Symptoms include having difficulty starting a urine flow and more difficulty than usual passing urine. In most cases, urinary retention is managed with dose reduction or by switching to another type of antidepressant.

Problems associated with the skin (loss of sensation, numbness and tingling, rashes, spots, itching, and puffiness), seizures, and ringing in the ears have also been reported. Nausea, vomiting, loss of appetite, diarrhea, and abdominal cramping are associated with nortriptyline usage. Skin rash, sensitivity to sunlight, and itching have been linked to nortriptyline use. People who think they may be experiencing any side effects from this or any other medication should talk to their physicians.

Interactions

Individuals should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs and supplements, before starting treatment with nortriptyline.

Drugs

Dangerously high blood pressure has resulted from the combination of tricyclic antidepressants, such as nortriptyline, and members of another class of antidepressants known as monoamine oxidase inhibitors (MAOIs).

Because of this, nortriptyline should never be taken in combination with monoamine oxidase inhibitors. Patients taking any MAOIs, such as phenelzine (Nardil) or tranylcypromine (Parnate), should stop taking the MAOI and wait at least 14 days before starting nortriptyline or any other tricyclic antidepressant. The same holds true when discontinuing nortriptyline and starting an MAOI.

Cimetidine (Tagamet) may slow the elimination of nortriptyline, thus increasing the amount of nortriptyline in the body. This can result in toxic levels or increased side effects. Quinidine also raises the circulating levels of the drug, requiring a decrease in the dosage of nortriptyline.

The sedative effects of nortriptyline are increased by other central nervous system depressants such as sedatives, sleeping medications, or medications used for other mental disorders such as schizophrenia. The symptoms of increased heart rate, blurred vision, and difficulty urinating are increased when nortriptyline is taken with other drugs such as **benztropine**, biperiden, trihexyphenidyl, and antihistamines.

Food and other substances

Alcohol enhances the sedative effects of nortriptyline and should be avoided.

Resources

BOOKS

Hall, Sharon M. "Tricyclic Antidepressants in the Treatment of Nicotine Dependence." In *Medication Treatments for Nicotine Dependence*, edited by Tony P. George. Boca Raton, FL: CRC Press, 2007.

Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger Publications, 2013.

PERIODICALS

Derry, S., et al. "Nortriptyline for Neuropathic Pain in Adults." *Cochrane Database of Systematic Reviews* 1, art. no. CD011209 (2015). <http://dx.doi.org/10.1002/14651858.CD011209.pub2> (accessed February 26, 2015).

Jaracz, J., et al. "Comparison of the Effects of Escitalopram and Nortriptyline on Painful Symptoms in Patients with Major Depression." *General Hospital Psychiatry* 37, no. 1 (2015): 36–39.

Kunte, H., J. Rentzsch, and G. Kronenberg. "A New Role for Nortriptyline in Depression Associated with Vascular Disease?" *American Journal of Psychiatry* 172, no. 2 (2015): 201.

OTHER

U.S. Food and Drug Administration. "Medication Guide—Pamelor™ (Nortriptyline HCl)." <http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088671.pdf> (accessed February 26, 2015).

WEBSITES

Micromedex. "Nortriptyline (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/nortriptyline-oral-route/description/drg-20071998> (accessed February 26, 2015).

National Alliance on Mental Illness. "Depression." <http://www.nami.org/Learn-More/Mental-Health-Conditions/Depression> (accessed February 26, 2015).

UK National Health Service (NHS). "Nortriptyline (Nortriptyline 10 mg Tablets)." <http://www.nhs.uk/Medicine-Guides/Pages/MedicineOverview.aspx?condition=Nocturnal%20enuresis&medicine=Nortriptyline> (accessed February 26, 2015).

ORGANIZATIONS

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.

National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.

National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

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Norvasc see **Amlodipine**

Novolog see **Insulin aspart**

NuvaRing see **Etonogestrel/ethinyl estradiol**

Nuvigil see **Armodafinil**

Nystatin

Definition

Nystatin is a topical and oral antifungal agent that is used to treat infections of the skin (cutaneous) and skin/mucous membranes (mucocutaneous) by susceptible species of the yeast-like fungus *Candida*. Nystatin is in drug classes known as mouth and throat products and polyenes.

Purpose

Nystatin is used to treat candida infections of the skin, mouth, esophagus, intestinal tract, and vagina and is sometimes prescribed for other uses. *Candida* species



Nystatin, 500,000 units. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

(spp.) are yeast-like fungi that occur normally on and in the body, especially the skin, mouth, intestinal tract, and genital area. Most candida infections are caused by *Candida albicans*. If the fungus overgrows, it can cause an infection referred to as candidiasis, which may become chronic. Candidiasis may develop on the skin, especially the skin folds of the neck, armpits, and groin, as well as mucous membranes of the mouth, throat, and vagina, and even the fingernails or eyes. Candidiasis of the mouth is called thrush, and it is common in infants and toddlers. Newborns can become infected with candida from their mothers before or during birth. If candida enters the bloodstream, it can spread to other parts of the body. This occurs especially in newborns, people with long-term intravenous catheters, and people with weakened (compromised) immune systems due to diseases such as HIV/AIDS or medications.

Topical nystatin can be used to treat skin infections and is the medication of choice for candida-related diaper rash. Oral nystatin is the drug of choice for treating oral thrush in infants and children. It is also used to treat candida infections of the airway, esophagus, and gastrointestinal tract. In some cases, nystatin is used to prevent candidiasis in susceptible people.

Description

Nystatin is a mixture of molecules called polyenes, which are chains of hydrocarbons with many double bonds. The drug is produced by the bacterium *Streptomyces noursei*. It is on the World Health Organization's

list of essential medicines for basic health facilities. Although many molds and yeasts are sensitive to nystatin, it is especially effective against *Candida* spp. However, the drug must come in direct contact with the yeast in order to kill it. Because nystatin is not absorbed through mucocutaneous membranes in the skin and gastrointestinal tract, it can be safely administered both topically and by mouth.

Nystatin is available in nonprescription and prescription strengths in a variety of forms for different purposes. Tablets, capsules, lozenges, powders, and liquid suspensions are taken by mouth. Oral thrush, as well as esophageal, gastrointestinal, and other internal and systemic infections, can be treated with a lozenge, called a pastille or troche, which is slowly dissolved in the mouth. Tablets or creams are inserted into the vagina to treat vaginal yeast infections. Powders, ointments, and creams are applied to the skin. Tablets and liquids should be stored at room temperature and away from excess heat and moisture (not in the bathroom). Powder, lozenges, and vaginal tablets and cream should be stored in the refrigerator.

U.S. brand names

There are various generic and brand-name formulations of nystatin. There are also combination products that include nystatin. U.S. brand names include:

- Bio-Statin
- Mycostatin
- Nilstat Suspension
- Nystatin Cream
- Nystatin Ointment
- Nystatin Powder
- Nystatin Suspension
- Nystatin Vaginal Tablets
- Nystop Powder

Canadian brand names

Canadian brand names for nystatin include:

- Mycostatin Suspension
- Nadostine
- Nadostine Sucrose-Free
- Nilstat Drops
- Nilstat Powder
- Nyaderm
- PMS-Nystatin

International brand names

Mycostatin is the most common of the large number of international brand names for nystatin.

KEY TERMS

Candida—Various species of yeast-like fungi, especially *C. albicans*, that are normal inhabitants of the human body but that can overgrow and cause infections.

Candidiasis—Yeast infection caused by *Candida* spp.

Pastille—Lozenge; troche; a solid, usually sweetened medication designed to dissolve in the mouth.

Polyenes—Organic compounds with many double bonds, especially within a long hydrocarbon chain.

Thrush—Infection with the fungus *Candida albicans* that causes white patches in the oral cavity.

Origins

Nystatin was discovered by the American microbiologists Rachel Fuller Brown and Elizabeth Lee Hazen in 1950 while they worked at the New York State Department of Health. Brown and Hazen analyzed hundreds of organisms cultured from soil samples for activity against *C. albicans*, as well as low toxicity toward animals and humans. The successful culture came from the garden of Hazen's friends, the Nourses, so the isolated soil bacterium was named for them. They named the fungicide produced by *S. noursei* "fungicidin." When this was discovered to be the name of another substance, they renamed it "nystatin" after New York State.

Recommended dosage

Dosages, the number of doses per day, the time between doses, and the duration of treatment depend on the nystatin formulation and the condition being treated. Oral doses are used several times a day until all of the lesions have completely disappeared. The usual adult dosage for oral thrush is one or two tablets or lozenges (200,000–400,000 units) taken three to five times per day or 500,000 units of oral suspension three to five times per day. The usual adult dosage for intestinal candidiasis is 500,000–1,000,000 units orally taken three times per day.

Additional instructions include:

- Lozenges are dissolved slowly and completely in the mouth over a period of 15 to 30 minutes, during which time the saliva is swallowed. Lozenges are never chewed or swallowed whole and should be used for at

least 48 hours after all symptoms of mouth infection are gone.

- For liquid suspensions, the bottle is shaken well before each use to mix the suspension evenly. If a dropper is supplied, it should be used to accurately measure the dose (4–6 milliliters [mL] or about 1 teaspoon). For mouth infections, half-doses are placed on each side of the mouth and held there or swished through the mouth for several minutes (as long as possible) before gargling and swallowing. For intestinal infections, the measured liquid is swallowed directly from the dropper. Dentures may need to be soaked every night in the oral suspension.
- For the dry powder, about 1/8 teaspoon (0.6 mL) is added to about 4 ounces (118 mL) of water, mixed, divided into several portions, and used immediately. Each portion is held in the mouth or swished around in the mouth for as long as possible, then gargled and swallowed. All of the liquid must be used.
- Treatment should be continued for up to 14 days or at least 48 hours after the disappearance of symptoms.
- Missed doses should be taken as soon as possible, unless it is almost time for the next dose, in which case the dose should be skipped and the regular schedule resumed.

For vaginal infections:

- The tablets or cream are inserted high into the vagina using the supplied applicator.
- The applicator is filled to the indicated level.
- Lying on one's back with knees up and apart, the applicator is gently inserted into the vagina, and the plunger is pushed down.
- The applicator is withdrawn and washed with soap and warm water.
- The hands are washed immediately to avoid spreading the infection.
- The tablets or cream are generally used once or twice a day.
- Vaginal tablets or cream are continued even if symptoms improve within a few days. They are generally used for two weeks by non-pregnant women. Pregnant women should use them for three to six weeks before giving birth.
- A sanitary pad can be used to protect clothing, but tampons should not be used, because they will absorb the medication.
- Women should not douche unless instructed to by their doctor.

For skin infections, the infected area is washed thoroughly. A small amount of the ointment or cream is

gently and thoroughly massaged into the skin. If used on the face, it must be kept away from the eyes. Nystatin ointment or cream is generally used several times per day. Nystatin powder is dusted on the feet and inside shoes and socks or stockings for foot infections.

Pediatric

The pediatric dosage for children five years and older is one or two lozenges or tablets three to five times daily for up to 14 days. Children under five should be given the oral suspension, because they may not be able to use lozenges or tablets safely. The usual doses for oral thrush are:

- 1 mL (100,000 units) of oral suspension four times per day for premature, low-birth-weight, and newborn infants
- 2 mL (200,000 units) of oral suspension four times per day for babies aged less than 1 month to less than 12 months
- 4–6 mL (about 500,000 units) of oral suspension four times per day, or one or two lozenges (200,000–400,000 units) four to five times daily for older children

Precautions

It is important to use nystatin for the full treatment duration to completely clear the infection, even if symptoms have subsided.

Pregnant or breastfeeding

Oral nystatin is in the U.S. Food and Drug Administration (FDA) pregnancy category C—it has not been associated with fetal harm if used during pregnancy, but its use is not recommended during pregnancy unless benefits outweigh potential risks. It is not known whether nystatin is excreted in human breast milk.

Vaginal nystatin suppositories are in the FDA pregnancy category A—they are considered safe during pregnancy and possibly necessary before delivery to prevent transmitting the infection to the newborn. Topical application of nystatin to the skin or mucous membranes is not absorbed by the body and so is considered safe during pregnancy and breastfeeding.

Other conditions and allergies

Patients should inform their doctor and pharmacist if they are allergic to nystatin or any other medications or to any foods, dyes, preservatives, or animals.

Side effects

Nystatin usually has few side effects. The doctor should be called immediately if any of the following side effects occur with oral tablets, lozenges, or liquids:

- diarrhea
- nausea
- stomach pain
- skin rash

The doctor should be called if severe or persistent itching, irritation, or burning occurs with nystatin vaginal tablets or cream or skin ointment or cream.

Interactions

The doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Herbs and supplements

The nutritional supplement brewer's yeast is the only known interaction with nystatin.

Resources

BOOKS

Gerald, Michael C. *The Drug Book: From Arsenic to Xanax, 250 Milestones in the History of Drugs*. New York: Sterling, 2013.

PERIODICALS

Feinberg, Arthur N., et al. "Pediatric Dermatologic Disorders." *Journal of Alternative Medicine Research* 6, no. 2 (2014): 95–137.

WEBSITES

American Academy of Pediatrics. "Thrush and Other Candida Infections." HealthyChildren.org. <http://www.healthychildren.org/English/health-issues/conditions/infections/pages/Thrush-and-Other-Candida-Infections.aspx> (accessed February 25, 2015).

Chemical Heritage Foundation. "Elizabeth Lee Hazen and Rachel Fuller Brown." <http://www.chemheritage.org/discover/online-resources/chemistry-in-history/themes/pharmaceuticals/preventing-and-treating-infectious-diseases/hazen-and-brown.aspx> (accessed February 25, 2015).

MedlinePlus. "Thrush—Children and Adults." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/ency/article/000626.htm> (accessed February 25, 2015).

Micromedex. "Nystatin (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/nystatin-oral->

route/description/drg-20065146 (accessed February 25, 2015).

ORGANIZATIONS

American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, IL 60007-1098, (847) 434-4000, (847) 434-8000, info@healthychildren.org, <http://www.healthychildren.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

World Health Organization, Avenue Appia 20, 1211 Geneva, Switzerland 27, +44 22 791 21 11, +41 22 791 31 11, info@who.int, <http://www.who.int/en>.

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REVIEWED BY JAMES E. WAUN, MD, RPH



Octreotide

Definition

Octreotide is an injected drug used to treat symptoms of certain conditions, including certain types of cancer. It is in the octapeptide drug class.

Purpose

Octreotide immediate-release injection is used to treat acromegaly—a condition characterized by the overproduction of growth hormone (GH)—in patients who cannot be treated with surgery, radiation, or another drug. Acromegaly causes joint pain and enlargement of the hands, feet, and facial features, among other symptoms. Treatment helps prevent the development of serious conditions such as diabetes and heart disease.

Octreotide has orphan drug status for treating symptoms of carcinoid tumors of the gastrointestinal tract and lung and certain other tumors, such as vasoactive intestinal peptide-secreting adenomas (VIPomas). Carcinoid tumors are rare, slow-growing, neuroendocrine cancers that overproduce hormones. VIPomas are hormone-releasing pancreatic tumors. Analogs of the hormone somatostatin, such as octreotide and lanreotide, are standard treatments for advanced carcinoid disease symptoms caused by hormone overproduction. Octreotide immediate-release injection can control severe watery diarrhea and flushing (sudden reddening of the face and neck) from VIPomas and certain other tumors and from carcinoid syndrome. Carcinoid syndrome develops in about 50% of patients with carcinoid tumors. About half of patients with carcinoid syndrome develop carcinoid heart disease (CHD). Octreotide does not prevent or decrease the risk of CHD or improve CHD heart abnormalities, nor does it usually shrink tumors. However, in about half of octreotide-treated patients, tumor growth is stabilized for periods of 8 to 16 months, and decreasing watery diarrhea helps reduce loss of body

fluids and minerals. Long-acting octreotide reduces injection frequency in patients with acromegaly, carcinoid tumors, and VIPomas who have responded to octreotide immediate-release injection. Octreotide is not a cure for acromegaly or carcinomas and is typically used in combination with other treatments, such as surgery, radiation, or other drugs.

Octreotide scans, also called octreoscans or somatostatin receptor scintigraphy (SRS), are used in cancer diagnosis. Octreotide bound to radioactive indium-111 is injected into a vein, travels through the blood, and attaches to carcinoid tumors. A special camera detects the radioactivity, revealing tumor sites. SRS can also help determine whether treatment with drugs such as octreotide or lanreotide might be useful.



Octreotide acetate. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Acromegaly—Overproduction of growth hormone by the pituitary gland; inhibited by octreotide.

Carcinoid—A benign or cancerous tumor usually arising from the mucosa of the gastrointestinal tract.

Carcinoid heart disease (CHD)—Heart abnormalities arising from carcinoid syndrome.

Carcinoid syndrome—Symptoms caused by hormones and other substances produced by carcinoid tumors that may be treated with octreotide.

Graft-versus-host disease (GVHD)—Life-threatening illness resulting from transplantation of foreign tissue.

Growth hormone (GH)—A polypeptide hormone that regulates growth and is secreted by the anterior lobe of the pituitary gland.

Hormones—Substances, such as somatostatin, that are produced in one area of the body and travel through the bloodstream to another part of the body, where they exert their effects.

Insulin-like growth factor-1 (IGF-1)—A growth factor that normally declines after puberty but that may be increased in certain cancers and other conditions.

Intramuscular (IM)—Injected into a muscle, such as the gluteal muscle of the buttock.

Intravenous (IV)—Injected into a vein.

Octapeptide—A peptide chain of eight amino acids, such as octreotide.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Orphan drug—A drug used to treat a rare disease or condition for which other medications are not available.

Receptor—A molecule, usually a protein, inside or on the surface of a cell, that binds to a specific substance, such as somatostatin or octreotide, to control specific processes in the body.

Somatostatin—A 14-amino-acid peptide hormone that inhibits the release of other hormones, such as growth hormone, insulin, and gastrin.

Somatostatin receptor scintigraphy (SRS)—A diagnostic technique using radioactive octreotide for locating certain carcinoid tumors.

Subcutaneous (SC)—Injected under the skin.

Vasoactive intestinal peptide (VIP)—A 28-amino-acid protein hormone with many physiological activities, including stimulating secretion by the small intestine and pancreas and dilating (relaxing) blood vessels.

Vasoactive intestinal peptide-secreting adenomas (VIPomas)—Pancreatic tumors that secrete vasoactive intestinal peptide and may be treated with octreotide.

Off-label uses

Octreotide is sometimes used to treat diarrhea caused by chemotherapy, radiation treatment, AIDS, and other conditions that cannot be cured and for which other diarrhea treatments are ineffective. Octreotide may be used for various other purposes, such as treating graft-versus-host disease.

Description

Octreotide is an eight-amino-acid peptide related to (an analog of) somatostatin, a hormone with numerous functions, including slowing the growth of neuroendocrine cells. Octreotide acts on somatostatin receptors, including those on tumors, to reduce abnormal production and secretion of GH and the secretion of VIP (vasoactive hormones that relax blood

vessels), glucagon (a hormone that raises blood sugar), secretin (a hormone that increases secretion by the pancreas and liver), and insulin-like growth factor-1 (IGF-1). Octreotide also blocks the release of serotonin (a neurotransmitter), gastrin (a hormone that induces the secretion of gastric juice), and pancreatic enzymes and suppresses the response of luteinizing hormone to gonadotropin-releasing hormone. As a result of these activities, octreotide, among other effects, decreases gastrointestinal blood flow and slows the passage of stool through the intestines. This decreases diarrhea by enabling more water to be absorbed from the stool.

Octreotide is supplied as solutions of 50, 100, 200, 500, and 1,000 micrograms per milliliter (mcg/mL). A long-acting version is supplied in kits of 10, 20, and 30 milligram (mg) suspensions.

Immediate-release or short-acting octreotide is usually injected under the skin (subcutaneously) one to four times per day at about the same times each day. It is stored in its original carton in the refrigerator and removed up to one hour before injecting, but it can be kept at room temperature for up to 14 days, protected from light. Multidose vials are discarded 14 days after the first use. Octreotide can also be injected as an intravenous (IV) solution, commonly prepared as 50–100 mcg per 50 mL of normal saline (NS), or continuously infused over 24 hours as a 1,200 mcg per 250 mL NS solution.

Long-acting octreotide is injected into buttock muscles (intramuscularly) by a doctor or nurse, usually once every four weeks. It is administered immediately after reconstitution of the suspension.

U.S. brand names

The U.S. brand names of octreotide acetate are Sandostatin for the immediate-release form and Sandostatin LAR for the long-acting form. Generic octreotide acetate is also available.

Canadian brand names

The Canadian brand names of octreotide acetate are Sandostatin for the immediate-release form and Sandostatin LAR for the long-acting form. Generic octreotide acetate is also available.

International brand names

Sandostatin and Sandostatin LAR are the most common of the many international octreotide brand names. Other common brand names include Octreotide Hospira, Octride, Proclosse, and Sandostatine.

Origins

Octreotide acetate was first approved by the U.S. Food and Drug Administration (FDA) in 1988.

Recommended dosage

Initially, octreotide is usually injected every day until the correct dosage is determined; patients are then switched to long-acting monthly injections.

- For acromegaly, the initial subcutaneous (SC) dose is 50 mcg every 8 hours, which can be increased up to 500 mcg every 8 hours if required. After two weeks of successful treatment, the dosage can be switched to 20 mg of suspension injected intramuscularly (IM) every four weeks for three months. Depending on symptom control, the dose may be adjusted up or down to 10–30 mg every four weeks, not to exceed 40 mg.

For patients being treated with radiation, subcutaneous injections are withdrawn for four weeks every year and intramuscular injections are withdrawn for eight weeks to allow for assessment.

- For carcinoid tumors, the usual initial dose is 100–600 mcg (SC) per day divided into doses every 6 to 12 hours, which may be increased up to 1,500 mcg per day. After two weeks of well-tolerated, successful treatment, patients may be switched to 20 mg IM injections every four weeks.
- For VIPomas, the usual initial dose is 200–300 mcg (SC) per day, divided into doses every 6 to 12 hours. After two weeks of successful treatment, 20 mg IM suspensions are injected every four weeks for two months, while continuing the SC solution injections for the first two weeks. The suspension dosage is adjusted up or down to 10–30 mg (IM) every four weeks.
- Carcinoid tumor and VIPoma symptoms may occasionally worsen during treatment, and patients can be switched back to immediate-release injections for a few days until symptoms are controlled.

Immediate-release SC injections may be performed at home by the patient or a friend or relative. The solution is first checked for cloudiness or particles. A different SC or IM injection site is used each time to avoid skin problems and is cleansed with rubbing alcohol. Syringes and needles are discarded in a special container. A missed dose of immediate-release solution should be injected as soon as possible, unless it is almost time for the next dose, in which case the dose should be skipped and the regular schedule resumed.

Pediatric

Octreotide is primarily used in children for off-label uses.

Geriatric

The recommended dosages for carcinoid tumors, VIPomas, and esophageal variceal bleeding in geriatric patients are the same as in adult patients. Acromegaly doses may require adjustment.

Other conditions and allergies

For patients with liver cirrhosis or on kidney dialysis, the initial dosage is 10 mg IM every four weeks, adjusted according to response. Other dose adjustments for kidney impairment are unnecessary.

Precautions

Diarrhea can cause dehydration and mineral depletion. Patients with diarrhea should:

- try to drink two to three quarts of fluids daily until diarrhea is controlled
- notify their healthcare provider if they experience dizziness; light-headedness; low urine output; dry mouth; unusual thirst; or dry, loose skin
- eat small, frequent, warm or room-temperature meals
- mix fruit juice with water to add calories and fluids
- eat high-sodium and high-potassium foods (soups, sports drinks, bananas) and foods high in soluble fiber (bananas and rice)
- avoid foods high in insoluble fiber (cereal and nuts)
- avoid gas-inducing foods (such as beans or broccoli), fatty foods (such as cheese or bacon), citrus fruits and juices, and high-lactose foods (milk products)
- notify the healthcare provider if diarrhea is not relieved after one or two octreotide doses or if symptoms do not improve or worsen
- not stop octreotide without consulting their healthcare provider because symptoms may return
- inform all doctors, nurses, pharmacists, and dentists of octreotide use
- call their healthcare provider if they experience increased thirst and urination, shakiness, sweating, chills, or weakness, because octreotide can affect blood glucose (sugar) levels
- call their healthcare provider if they have stomach pain, a swollen or bloated belly, vomiting, or constipation

Laboratory tests may be ordered to check responses to octreotide. Octreotide can cause vitamin B₁₂ and thyroid hormone levels to drop over time. Depression; a husky or hoarse voice; swelling of the front of the neck; fatigue; weakness; thinning hair; coarse, dry skin; or weight gain may be symptoms of thyroid problems.

Symptoms of octreotide overdose can include:

- slowed or irregular heartbeat
- dizziness
- fainting
- flushing
- diarrhea
- weakness
- weight loss

Pediatric

Octreotide's safety and effectiveness have not been established in pediatric patients, especially long-acting

octreotide in children under age six. Serious events and death have been reported, primarily in children under two, although it is not clear whether these were associated with octreotide use.

Pregnant or breastfeeding

Octreotide is in the FDA pregnancy category B, meaning that studies have not been performed in pregnant women, but animal tests have shown no drug-related birth defects. Women should tell their doctor if they become pregnant while using octreotide. Women with acromegaly who were unable to become pregnant may be able to conceive during treatment with octreotide. It is not known whether octreotide crosses into breast milk, but breastfeeding women should not use octreotide.

Other conditions and allergies

Patients should tell their doctor and pharmacist if they are allergic to octreotide or any ingredients in the octreotide injection, as well as any other medications, dyes, additives, foods, latex, or other substances. Patients should tell their doctor if they are receiving total parenteral nutrition (IV nutrients) and if they have or have ever had:

- diabetes
- heart or kidney disease
- liver disease, including hepatitis
- gallstones or gallbladder problems, since octreotide increases the risk of gallstones
- ulcerative colitis, fever, blood or mucus in the stool, or black-tar stools

Patients who take insulin for diabetes may be at higher risk for low blood glucose and may need less insulin. Oral diabetes medications may be less effective and may require higher doses. Blood glucose levels should be closely monitored.

Side effects

Common octreotide side effects are:

- gallbladder problems
- abnormal blood glucose levels (especially in people with diabetes)
- hypothyroidism (low thyroid function)
- slow heart rate (bradycardia)

Less common side effects include:

- electrocardiography (ECG) changes
- heart arrhythmia
- pancreatitis
- upper respiratory tract infection

- fatigue
- headaches
- malaise
- rash
- diarrhea
- nausea
- vomiting
- stomach cramps or abdominal pain
- pain or burning at injection site
- joint pain
- blurred vision
- decreased intestinal absorption of fats

Rare side effects are:

- anxiety
- muscle aches
- dizziness
- light-headedness
- feet swelling
- facial flushing
- goiter (non-cancerous thyroid tumor)
- blocked bile ducts

Other conditions and allergies

Serious allergic reactions are rare. Emergency medical help is required for symptoms including trouble breathing or swallowing; hives; itching; rash; severe dizziness; or swelling of the face, tongue, or throat.

Interactions

The doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used or planning to be used by patients. Patients should bring a list of all medications and supplements to medical appointments and carry the list with them in case of emergency.

Drugs

Octreotide should never be used in combination with:

- astemizole
- cisapride
- disopyramide
- ibutilide
- indapamide
- pentamidine
- pimozone

- procainamide
- quinidine
- **sotalol**
- terfenadine

An additional 53 drugs have serious interactions with octreotide, so alternatives should be used. Another 45 drugs are known to have significant interactions and require close monitoring. Common drugs that may require changing dosages or monitoring for side effects include:

- bromocriptine
- **cyclosporine**
- insulin and oral diabetes drugs
- some medications for high blood pressure and congestive heart failure, including beta blockers such as **atenolol**, labetalol, metoprolol, nadolol, and **propranolol**; bromocriptine; calcium channel blockers such as **amlodipine**, **diltiazem**, felodipine, **nifedipine**, nisoldipine, and verapamil; and diuretics

Resources

PERIODICALS

Patel, Chirdeep. "Carcinoid Heart Disease: Current Understanding and Future Directions." *American Heart Journal* 167, no. 6 (2014): 789–95.

OTHER

American Cancer Society. "Lung Carcinoid Tumor." <http://www.cancer.org/acs/groups/cid/documents/webcontent/003117-pdf.pdf> (accessed February 25, 2015).

WEBSITES

American Cancer Society. "Octreotide." <http://www.cancer.org/treatment/treatmentsandsideeffects/guidetocancerdrugs/octreotide> (accessed February 25, 2015).

MedlinePlus. "Octreotide Injection." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a693049.html> (accessed February 25, 2015).

"Octreotide (Rx)—Sandostatin, Sandostatin LAR." Medscape Reference. <http://reference.medscape.com/drug/sandostatin-lar-octreotide-342836#0> (accessed February 25, 2015).

ORGANIZATIONS

American Cancer Society, 250 Williams Street NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org/>.

National Cancer Institute, 9609 Medical Center Drive, BG 9609 MSC 9760, Bethesda, MD 20892-9760, (800) 4-CANCER (422-6237), <http://www.cancer.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Olanzapine

Definition

Olanzapine is classified as an atypical antipsychotic drug.

Purpose

Olanzapine is used to treat schizophrenia and to control manic episodes of bipolar disorder.

Off-label use

Olanzapine may be prescribed off label to treat symptoms of dementia related to Alzheimer's disease, but it is not approved by the U.S. Food and Drug Administration (FDA) for this purpose.

Description

Olanzapine is thought to modify the actions of several chemicals in the brain. Olanzapine is chemically related to another atypical antipsychotic agent, **clozapine**, but differs both chemically and pharmacologically from the earlier phenothiazine antipsychotics.

Olanzapine is available as 2.5, 5, 7.5, 10, 15, and 20 milligram (mg) tablets that can be swallowed and 5, 10, 15, and 20 mg tablets that disintegrate when placed under the tongue. Olanzapine is broken down by the liver.

A long-acting injection form of olanzapine is also available to treat schizophrenia, which obviates some of the issues of medication adherence that often complicate treatment. This form maintains therapeutic levels for two to four weeks.

U.S. brand names

Olanzapine is available in the United States under the brand names Zyprexa (oral tablets) and Zyprexa Zydis (disintegrating tablets).

Recommended dosage

The dosage of olanzapine varies depending upon the reason for its use. When used to treat schizophrenia, 5–10 mg is the typical starting dosage. If dosage adjustments are needed, increases are made in 5 mg increments once a week. When treating schizophrenia, a total daily dosage of 10–15 mg is usually effective. When olanzapine is used to treat acute manic episodes, initial doses of olanzapine are often 10–15 mg, and 20 mg per day may be needed for maximum effect. The safety of doses greater than 20 mg per day has not been determined.

Olanzapine is eliminated from the body more quickly in young people than in older (over age 60)

individuals, in men more quickly than in women, and in smokers more quickly than in nonsmokers. Dosage adjustments may be needed based upon individual patient characteristics.

Precautions

Like other antipsychotic medications, olanzapine carries a warning regarding use in elderly people with dementia, who suffer from an increased risk of death during treatment with these agents. The reason for the increase was unclear in studies, but most deaths were found to be related to either cardiovascular complications or complications associated with infection. Olanzapine is not approved by the FDA for the treatment of behavior problems in older adults with dementia.

Olanzapine has also been associated with the risk of developing a blood disorder.

Pregnant or breastfeeding

Women who are pregnant or breastfeeding should not take olanzapine. Babies born to mothers who took olanzapine during pregnancy may develop extrapyramidal symptoms (EPS) and withdrawal symptoms, including agitation, trouble breathing, and difficulty feeding.



Zyprexa (olanzapine), 2.5 mg. (© Cengage Learning®.)

KEY TERMS

Bipolar disorder—A mood disorder marked by alternating episodes of extremely low mood (depression) and exuberant highs (mania); formerly known as manic-depressive disorder.

Extrapyramidal symptoms—A group of side effects associated with antipsychotic medications and characterized by involuntary muscle movements, including contraction and tremor.

Off-label use—Drugs in the United States are approved by the Food and Drug Administration (FDA) for specific uses based on the results of clinical trials. However, it is legal for physicians to administer these drugs for other “off-label” uses. It is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Schizophrenia—A severe mental illness in which a person has difficulty distinguishing what is real from what is not real. It is often characterized by hallucinations, delusions, language and communication disturbances, and withdrawal from people and social activities.

Tardive dyskinesia—A disorder characterized by involuntary and repetitive body movements that sometimes develops after long-term use of antipsychotic medications.

Other conditions and allergies

Caution should be used in patients with heart disease, because the drug may cause blood pressure to fall too low, resulting in dizziness, rapid heartbeat, or fainting. Olanzapine should be used carefully in people with known seizure disorders since it may alter properties of the brain, making seizures occur more easily. People with liver disease should have their liver function monitored regularly while taking olanzapine. People with phenylketonuria, a disorder in which the body is unable to metabolize a protein called phenylalanine, should avoid olanzapine disintegrating tablets, because this form of the drug contains phenylalanine. Patients with diabetes mellitus should monitor their blood glucose levels if taking olanzapine or any other atypical antipsychotic, as drugs in this class may cause increases in glucose levels.

Side effects

Side effects that occur in more than 5% of patients taking olanzapine include involuntary movements,

weakness, dizziness, extreme drowsiness, nonviolent objectionable behavior, constipation, weight gain, dry mouth, low blood pressure, stomach upset, increased appetite, cold-like symptoms, or fever.

Other side effects that are possible include rash, body aches and pains, elevated liver enzymes, vision abnormalities, chest pain, or rapid heartbeats.

Olanzapine has the potential to produce a serious side effect called tardive dyskinesia. This syndrome consists of involuntary, uncoordinated movements that may appear late in therapy and that may not disappear even after the drug is stopped. Tardive dyskinesia involves involuntary movements of the tongue, jaw, mouth, face, or other groups of skeletal muscles. The incidence of tardive dyskinesia increases with increasing age and with increasing dosage of olanzapine. Women are at greater risk than men for developing tardive dyskinesia. There is no known effective treatment for tardive dyskinesia, although gradual (but rarely complete) improvement may occur over a long period.

An occasionally reported side effect of olanzapine is neuroleptic malignant syndrome. This is a complicated and potentially fatal condition characterized by muscle rigidity, high fever, alterations in mental status, and cardiac symptoms such as irregular pulse or blood pressure, sweating, tachycardia (fast heartbeat), and arrhythmias (irregular heartbeat).

Interactions

Individuals should alert their healthcare provider to all drugs they are currently taking, including over-the-counter drugs and supplements.

Drugs

Any drug that causes drowsiness may lead to decreased mental alertness and impaired motor skills when taken with olanzapine. Some examples include antidepressants such as **imipramine** (Tofranil) or paroxetine (Paxil), antipsychotics such as thioridazine (Mellaril), and some antihistamines. Because olanzapine may lower blood pressure, it may reduce blood pressure to dangerously low levels if taken with drugs that are used to treat high blood pressure. **Carbamazepine** (Tegretol), a drug commonly used to treat seizures, may decrease the effectiveness of olanzapine.

Food and other substances

Alcohol should be avoided while taking olanzapine due to its sedative effects.

Resources

BOOKS

Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger Publications, 2013.

PERIODICALS

Aydin, Burc, et al. "Olanzapine and Quetiapine Use During Breastfeeding: Excretion Into Breast Milk and Safe Breastfeeding Strategy." *Journal of Clinical Psychopharmacology* (February 14, 2015): e-pub ahead of print. <http://dx.doi.org/10.1097/JCP.0000000000000291> (accessed February 25, 2015).

Meltzer, Herbert Y., and William V. Bobo. "Interpreting the Efficacy Findings in the CATIE [Clinical Antipsychotic Trials of Intervention Effectiveness] Study: What Clinicians Should Know." *CNS Spectrums* 11, suppl. 7 (July 2006): 14–24.

Perera, V., A. Forrest, and J. Xu. "High-Dose Olanzapine for Bipolar Depression: Proceed with Caution." *Primary Care Companion for CNS Disorders* 16, no. 5 (2014). <http://dx.doi.org/10.4088/PCC.13l01620> (accessed February 25, 2015).

Schneider, Lon S., et al. "Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease." *New England Journal of Medicine* 355, no. 15 (October 2006): 1525–38.

Takeuchi, H., et al. "Effectiveness of Different Dosing Regimens of Risperidone and Olanzapine in Schizophrenia." *European Neuropsychopharmacology* (January 9, 2015): e-pub ahead of print. <http://dx.doi.org/10.1016/j.euro-neuro.2014.12.008> (accessed February 25, 2015).

WEBSITES

AHFS Consumer Medication Information. "Olanzapine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601213.html> (accessed February 25, 2015).

Micromedex. "Olanzapine (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/olanzapine-oral-route/description/drg-20071350> (accessed February 25, 2015).

National Alliance on Mental Illness. "Zyprexa® (Olanzapine)." [http://www2.nami.org/Content/ContentGroups/Helpline1/Zyprexa_\(olanzapine\).htm](http://www2.nami.org/Content/ContentGroups/Helpline1/Zyprexa_(olanzapine).htm) (accessed February 25, 2015).

ORGANIZATIONS

National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.

National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

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Oleptro see **Trazodone**

Olmesartan

Definition

Olmesartan medoxomil is an oral drug for treating hypertension (high blood pressure). It is in the drug class of angiotensin II-receptor blockers (ARBs).

Purpose

Olmesartan is used to help control high blood pressure, often in combination with other antihypertensive drugs. Lowering high blood pressure helps prevent heart attacks, strokes, and kidney problems. Olmesartan is a commonly prescribed ARB that can lower blood pressure more effectively than older ARBs such as **losartan**, and, like other ARBs, it is generally well tolerated. Lifestyle modifications, including diet, exercise, and stress reduction, may increase the effectiveness of olmesartan.

Off-label uses

Olmesartan medoxomil is used off label, or without specific approval by the U.S. Food and Drug Administration (FDA), for treating heart failure. Although



Benicar HCT (olmesartan/hydrochlorothiazide, 20 mg/12.5 mg). (© Cengage Learning®.)

KEY TERMS

Aldosterone—A steroid hormone produced by the adrenal cortex that regulates salt and water balance in the body.

Angioedema—Severe, painful, allergic swelling of the skin and sometimes other organs, including the mouth and throat.

Angiotensin II—A peptide hormone that narrows blood vessels (vasoconstriction), especially in the kidneys, and raises blood pressure.

Angiotensin II-receptor blocker (ARB)—Angiotensin II-receptor antagonist; a blood pressure-lowering drug, such as olmesartan, that blocks angiotensin II from binding to its receptor.

Angiotensin type 1 (AT1) and type 2 (AT2) receptors—Receptors located throughout the body that bind angiotensin II to mediate its vasoconstricting effects; blocked by olmesartan.

Angiotensin-converting enzyme (ACE) inhibitor—A blood pressure-lowering drug that inhibits the enzyme that converts angiotensin I to active angiotensin II.

Antagonist—A drug, such as olmesartan, that blocks the action of a substance by interacting with its receptor.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Congestive heart failure—A condition in which the heart is unable to maintain adequate circulation or pump out the venous blood.

Diuretic—“Water pill”; a medication that increases urine excretion and removes water and salt from the body, which helps lower blood pressure.

Hyperkalemia—Excess potassium in the blood.

Hypertension—High blood pressure.

Hypotension—Low blood pressure.

Pregnancy category—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk but no human studies exist, or adverse effects have been seen in animals but not in well-controlled human studies. Category C: No adequate human or animal studies exist, or adverse fetal effects have occurred in animal studies but there is no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk, and risks outweigh any benefits.

Receptor—A molecule, usually a protein inside or on the surface of a cell, that binds a specific substance to initiate a series of events.

Renin-angiotensin-aldosterone system (RAAS)—A signaling pathway that regulates blood pressure and is disrupted by olmesartan.

angiotensin II-converting enzyme (ACE) inhibitors remain the drug of choice for congestive heart failure, ARBs may be used in patients who cannot tolerate ACE inhibitors. Furthermore, unlike ACE inhibitors, ARBs do not increase levels of the inflammatory peptide bradykinin and are less likely to cause side effects such as cough and possibly angioedema (a serious allergic reaction).

Description

Olmesartan medoxomil is rapidly and completely metabolized in the gastrointestinal tract to release active olmesartan. Olmesartan is a selective, competitive angiotensin II-receptor antagonist (blocker). Angiotensin II is a peptide hormone that is a powerful vasoconstrictor for narrowing blood vessels throughout the body and especially in the kidneys, raising blood pressure.

Angiotensin II also stimulates the secretion of aldosterone by the adrenal gland, which causes the kidneys to retain more water and sodium and to excrete more potassium, increasing total blood volume and blood pressure.

Like other ARBs, olmesartan interferes with the renin-angiotensin-aldosterone system (RAAS)—a signaling pathway that controls blood pressure—to relax blood vessels and enable the blood to flow more readily. Olmesartan is not a peptide (a small protein), but it interacts reversibly with angiotensin type 1 and type 2 (AT1 and AT2) receptors that normally bind angiotensin II in many tissues. Olmesartan interaction with AT1 and AT2 receptors interferes with angiotensin II binding, thereby inhibiting its vasoconstricting and aldosterone-secreting effects and lowering blood

pressure. Olmesartan has 12,500 times greater affinity for the AT1 receptor than for the AT2 receptor, and its receptor interaction is long lasting.

ARBs such as olmesartan may inhibit the RAAS more completely than ACE inhibitors. Olmesartan also increases urinary flow rate and secretion of sodium, potassium, chloride, magnesium, uric acid, calcium, and phosphate.

Olmesartan activity peaks within 1 to 2 hours of ingestion and lasts 24 hours. Blood pressure-lowering effects are apparent within two weeks of initiating the drug, with maximum response within four to six weeks.

Olmesartan medoxomil is sold as film-coated tablets debossed with “Sankyo” and is available in the following strengths:

- 5 milligram (mg) round tablets debossed with “C12”
- 20 mg round tablets debossed with “C14”
- 40 mg oval tablets debossed with “C15”

The tablets should be stored at room temperature away from light and moisture (not in the bathroom). If a pharmacist-prepared suspension is used, it should be stored in the refrigerator and discarded after four weeks.

A 2014 study reported that the olmesartan/amlodipine/hydrochlorothiazide combination (Tribenzor) reduced blood pressure more effectively than single, dual, or other triple-combination drug therapies. Olmesartan is also available in dual-combination medications with the diuretic **hydrochlorothiazide** (Benicar HCT) and the calcium-channel blocker **amlodipine** besylate (Azor).

U.S. brand names

The U.S. brand name for olmesartan medoxomil is Benicar, produced by Daiichi Sankyo. As of January 2015, generic versions had received tentative approval from the FDA but were not yet on the market.

Canadian brand names

The Canadian brand name for olmesartan medoxomil is Olmetec.

International brand names

International brand names for olmesartan medoxomil include Benetor, Olmetec, Omesar, and Votum.

Origins

Benicar was originally approved by the FDA in 2002.

Recommended dosage

The usual initial dose of olmesartan medoxomil for hypertension is 20 mg once a day, which can be increased to 40 mg after two weeks if the response is inadequate. A diuretic or other antihypertensive agent may be added if olmesartan alone does not adequately control blood pressure.

Olmesartan is taken with or without food at the same time each day. If using a liquid form, the bottle should be shaken well and carefully measured with a specially supplied device (a household spoon will not deliver the correct dose). A missed dose should be taken as soon as possible, unless it is almost time for the next dose, in which case it should be skipped and the regular dosing schedule resumed.

Pediatric

The initial dosage is 10 mg per day for children aged 6 to 16 weighing 44–77 lb. (20–35 kg). This may be increased up to a maximum of 20 mg if the response is inadequate after two weeks. For pediatric patients weighing more than 77 lb. (35 kg), the initial dosage is 20 mg once daily, which may be increased up to 40 mg if the response is inadequate after two weeks.

Other conditions and allergies

Lower dosages should be considered in patients with possible low blood volume (intravascular volume depletion), such as those taking diuretics, or in patients with angioedema or severe congestive heart failure or who are undergoing surgery or anesthesia.

No adjustment is necessary for patients with kidney impairment and creatinine clearance below 40 milliliters (mL) per minute. Creatinine is a waste material that is filtered out of the body by the kidneys. Measuring the amount of creatinine in a patient's urine helps determine kidney function. A lower initial dosage should be considered, and maximum dosage should not exceed 20 mg per day in patients with creatinine clearance below 20 mL/min.

Precautions

To obtain the most benefit, olmesartan should be used exactly as prescribed. It should not be discontinued or the dosage altered without consulting the prescribing physician. Additionally:

- Patients should monitor their blood pressure regularly and notify their doctor if blood pressure readings or other conditions do not improve or worsen.
- ARBs have been known to cause high potassium levels (hyperkalemia) and kidney dysfunction. Tests, such as kidney function and serum potassium levels, should be

performed periodically to monitor responses and side effects.

- Olmesartan may cause headache or dizziness; patients should use caution when driving or engaging in other activities that require alertness until they know how the drug affects them. Patients should rise slowly from sitting or lying positions to reduce the risk of dizziness or light-headedness.
- Doctors and dentists should be informed of olmesartan use (and all prescription and nonprescription drugs and herbal products) before having any type of surgery.
- Olmesartan may cause high blood sugar levels (hyperglycemia) and high blood triglycerides.
- Kidney impairment and intestinal problems with severe chronic diarrhea and substantial weight loss have been reported with olmesartan use.

Symptoms of olmesartan medoxomil overdose can include:

- severe dizziness
- fainting
- slow or rapid heart rate
- low blood pressure (hypotension)

Pediatric

The safety and effectiveness of olmesartan have not been established in children under age six or under 44 lb. (20 kg). Olmesartan must not be used to treat hypertension in children younger than one year, because drugs such as olmesartan that act directly on the RAAS can adversely affect the development of immature kidneys.

Pregnant or breastfeeding

Olmesartan medoxomil carries a boxed warning to discontinue use as soon as possible if pregnancy occurs. Drugs that affect the RAAS can result in fetal and newborn injury or death. Olmesartan medoxomil is in the FDA pregnancy category C for the first trimester and D for the second and third trimesters. It is not known whether olmesartan is excreted in breast milk, but women are advised against breastfeeding while taking the drug.

Other conditions and allergies

Patients should inform their doctor and pharmacist of any and all allergies and provide their doctor with a complete medical history, especially a history of kidney or liver disease or dehydration (severe loss of water and minerals). Olmesartan should not be used by patients with:

- allergies or hypersensitivity reactions to olmesartan, any inactive ingredients in olmesartan, or any other ARBs

- diabetes or kidney impairment who are taking aliskiren
- bilateral renal artery stenosis (constriction)

Low blood volume (volume depletion) should be corrected before administering olmesartan; patients with volume or salt depletion due to salt restriction or prolonged diuretic use are at risk for hypotension from olmesartan.

Olmesartan should be used with caution in patients with unilateral renal artery stenosis and kidney insufficiency or significant aortic or mitral stenosis or who previously experienced angioedema with an ACE inhibitor.

Patients with diabetes should carefully monitor their blood glucose levels.

Side effects

Side effects occurring in 1%–10% of patients taking olmesartan include:

- dizziness
- headache
- fatigue
- diarrhea
- high blood sugar
- high triglycerides
- back pain
- bronchitis
- flulike symptoms
- nasal, sinus, or pharynx inflammation
- upper respiratory tract infection
- increased creatine phosphokinase
- blood or blood cells in the urine

Side effects occurring in less than 1% of patients include:

- abdominal pain
- joint pain
- arthritis
- increased bilirubin
- chest pain
- indigestion
- facial swelling (edema)
- gastroenteritis
- high blood cholesterol
- excess uric acid in the blood
- insomnia
- increased liver enzymes
- muscle pain
- nausea

- peripheral swelling
- bone pain
- rapid heartbeat
- urinary tract infection
- vertigo

Other possible side effects include angioedema and muscle tissue degeneration. Patients should consult their doctor if side effects are severe or persistent and should call their doctor immediately if they experience:

- fainting
- symptoms of hyperkalemia, such as muscle weakness or slow or irregular heartbeat
- unusual decrease in the amount of urine
- severe or persistent diarrhea

Other conditions and allergies

Very serious allergic reactions to olmesartan medoxomil are rare. Patients should seek emergency help if they experience symptoms of allergic or anaphylactic reactions, including:

- rash
- itching or swelling, especially of the face, tongue, or throat
- severe dizziness
- difficulty breathing

Interactions

The doctor and pharmacist should be informed of all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Drugs

More than 100 drugs have significant interactions with olmesartan and require using alternatives or close monitoring. Drugs of particular concern include:

- Other RAAS-blocking drugs, such as another ARB, ACE inhibitors (e.g., **benazepril**, **captopril**, **enalapril**, **fosinopril**, **lisinopril**, moexipril, perindopril, **quinapril**, **ramipril**, trandolapril), or aliskiren increase the risk of hypotension, hyperkalemia, and kidney impairment, including acute renal failure.
- Olmesartan should not be coadministered with intravenous potassium phosphates.
- In patients taking lithium, olmesartan may increase the risk of lithium toxicity.

- mTOR inhibitors such as temsirolimus may increase the risk of angioedema.
- Bile-acid-binding resins for reducing cholesterol, such as cholestyramine, **colesevelam**, and colestipol, should be taken at least four hours after olmesartan.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), such as **ibuprofen** or naproxen, may decrease the effectiveness of ARBs. Patients should check labels on all NSAIDs, cough and cold products, and diet aids, because they can contain ingredients that increase blood pressure or worsen heart failure.
- Potassium, potassium-sparing diuretics (such as amiloride, **spironolactone**, and triamterene), high-dose trimethoprim, or **oral contraceptives** containing drospirenone may increase the risk of hyperkalemia.
- Psychotropics, such as atypical antipsychotics and **mirtazapine**, may increase olmesartan's effects.
- Selective serotonin reuptake inhibitors (SSRIs), lithium, and valproate may increase diarrhea.

Herbs and supplements

Potassium supplements may increase the risk of hyperkalemia. Patients should avoid ephedra, yohimbe, and ginseng, which can worsen hypertension, and garlic, which can further lower blood pressure.

Food and other substances

Olmesartan does not eliminate the need for recommended diet and exercise regimens to help control hypertension. Olmesartan is not affected by foods, but patients should consult their doctor before using salt supplements. Alcohol should be limited.

Resources

BOOKS

Yanagisawa, Hiroaki, Hiroyuki Koike, and Shini-chiro Miura. "Olmesartan Medoxomil, an Angiotensin II Receptor Blocker." In *Case Studies in Modern Drug Discovery and Development*, edited by Xianhai Huang and Robert G. Aslanian. Hoboken, NJ: John Wiley & Sons, 2012.

PERIODICALS

- Omboni, Stefano, et al. "Olmesartan vs. Ramipril in Elderly Hypertensive Patients: Review of Data from Two Published Randomized, Double-Blind Studies." *High Blood Pressure & Cardiovascular Prevention* 21, no. 1 (2014): 1–19.
- Punzi, Henry A. "Efficacy and Safety of Olmesartan/Amlodipine/Hydrochlorothiazide in Patients with Hypertension Not at Goal with Mono, Dual or Triple Drug Therapy: Results of the Champion Study." *Therapeutic Advances in Cardiovascular Disease* 8, no. 1 (2014): 12–21.

WEBSITES

Humphries, Andrea, et al. "Choosing Medicines for High Blood Pressure: A Review of the Research on ACEIs, ARBs, and DRIs." Effective Health Care Program, Agency for Healthcare Research and Quality. <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=758> (accessed February 28, 2015).

"Olmesartan." University of Maryland Baltimore Washington Medical Center Health Library. <http://www.mybwmc.org/library/41/094048> (accessed February 28, 2015).

"Olmesartan (Rx)—Benicar." Medscape.com. <http://reference.medscape.com/drug/benicar-olmesartan-342326#91> (accessed February 28, 2015).

O'Riordan, Michael. "No CV Risk with Olmesartan in Diabetics, Says FDA Review." Medscape.com. <http://www.medscape.com/viewarticle/827288> (accessed February 28, 2015).

ORGANIZATIONS

Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, (301) 427-1364, <http://www.ahrq.gov/>.

National Heart, Lung, and Blood Institute (NHLBI), PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbiinfo@nhlbi.org, <http://www.nhlbi.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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that itch, release tears or fluids, and may hurt. The symptoms are similar to those of conjunctivitis caused by an infection, which is commonly referred to as pink eye. However, allergic conjunctivitis is not contagious.

Olopatadine helps relieve the symptoms, especially itching, by covering the eyes with the antihistamine and helping to ease the release of histamines and resulting symptoms.

Description

Olopatadine is an eyedrop available only by prescription. It comes in a small bottle that allows users to apply a drop into each eye to relieve itching and allergy symptoms. It is intended for regular, daily use for best effect until seasonal allergy symptoms pass or the doctor recommends stopping use.

U.S. brand names

In the United States, olopatadine is sold under the brand names Pataday and Patanol, both made by Alcon Laboratories. Pataday is a slightly stronger (0.2%) solution than Patanol (0.1%).

Canadian brand names

In Canada, olopatadine is sold under the brand names Pataday and Patanol.

Olopatadine

Definition

Olopatadine is a solution used as a drop for the eyes to relieve itching, swelling, and redness in the eyes caused by allergic reactions. Olopatadine is in a class of drugs called antihistamines.

Purpose

When a person who has allergies comes in contact with an allergic trigger, also called an allergen, it can cause the release of chemicals called histamines and lead to itching and other symptoms. Antihistamines such as olopatadine have substances in them that either reduce or block histamines.

When allergens come in contact with the eyes, the irritation can result in a condition called allergic conjunctivitis, which is a condition of red, swollen eyes



Olopatadine (Patanol), 0.1%. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Antihistamines—Medicines that block the action of histamines, chemicals in the body that trigger allergic reactions.

Conjunctivitis—Swelling and irritation of the conjunctiva, the clear lining of the eyelids and the whites of the eyes. Allergic conjunctivitis is caused by exposure to allergens.

International brand names

Internationally, olopatadine is sold under the following brand names:

- Alacot
- Alchek
- Alcon Patanol S
- Alerchek
- Alercon
- Allelock
- Contova
- Lopadine
- O-Din
- Oflocet
- Oftadina
- Oloblu
- Olodin
- Olopak
- Olopat
- Olpadin
- Olpadin-DS
- Opat
- Opatanol
- Opopan
- Pataday
- Patadine
- Patalon
- Patanase
- Patanol
- Patanol S
- Winolap

Recommended dosage

The recommended dosage for adults and children ages two and older of the olopatadine 0.1% solution is to place one drop in each affected eye two times per day,

applying drops six to eight hours apart. Doctors recommend applying the drops at the same time each day to aid in remembering to use them. If using the stronger 0.2% solution, the recommended dosage is one drop in each affected eye one time a day.

If a dose is missed, it is important to use the drops as soon as possible once remembered. However, if it is nearly time for the next dose, it is best to skip the missed dose and simply go on to the next scheduled use of olopatadine.

Precautions

Olopatadine is not intended for use in relieving itching or irritation caused by contact lenses. Some people may be allergic to olopatadine or an ingredient in the drug's solution. People prescribed olopatadine should carefully follow the doctor's or package's instructions on how to properly use the eyedrops to make sure the medicine works as it should and to prevent infection of the eye.

It is important to keep the olopatadine solution stored in its original container, with the top on the bottle. The applicator should not be rinsed after use, because this can add water into the medicine.

Pediatric

Olopatadine has not been established as safe or effective in children younger than age two.

Pregnant or breastfeeding

Olopatadine is in the FDA pregnancy category C, meaning that it has been tested only in animals, not in humans. Women who are pregnant should only use the drug if the potential benefits outweigh potential risks. Women who are nursing should use caution if breastfeeding and using olopatadine.

Other conditions and allergies

It is not recommended to wear contact lenses when eyes are red. Further, an ingredient in olopatadine called benzalkonium chloride can be absorbed by soft contact lenses. Olopatadine should not be used while wearing contact lenses.

Side effects

Olopatadine can cause side effects, including:

- burning, stinging, or dryness in the eyes
- headache
- blurred vision
- changes in taste
- sore throat

Interactions

Sometimes, the use of other drugs, supplements, or herbal remedies can interact with the use of an antihistamine. Anyone prescribed olopatadine should inform the doctor of any other drugs they are taking and any other eyedrops or eye solutions being used.

Drugs

Because olopatadine is used only in the eyes, it does not have a lengthy list of drug interactions. Still, it is best to talk with a doctor about other drugs being taken. For example, other antihistamines or decongestants could add to the side effects of olopatadine, such as dryness in the eyes.

Herbs and supplements

There have been some reports of interaction between olopatadine and cannabis use.

Resources

PERIODICALS

Bonney, Asha G., and Ran D. Goldman. "Antihistamines for Children with Otitis Media." *Canadian Family Physician* 60, no. 1 (2014): 43–46.

Fitzsimons, Roisin, et al. "Antihistamine Use in Children." *Archives of Disease in Childhood Education and Practice Edition* (August 21, 2014): e-pub ahead of print. <http://dx.doi.org/10.1136/archdischild-2013-304446> (accessed February 25, 2015).

OTHER

Alcon Laboratories. "Pataday Prescribing Information." Alcon.com. http://ecatalog.alcon.com/pi/Pataday_us_en.pdf (accessed February 25, 2015).

Alcon Laboratories. "Patanol." Alcon.com. http://ecatalog.alcon.com/PI/Patanol_us_en.pdf (accessed February 25, 2015).

WEBSITES

MedlinePlus. "Olopatadine Ophthalmic." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a602025.html> (accessed February 25, 2015).

"Olopatadine Drops." Drugs.com. <http://www.drugs.com/cdi/olopatadine-drops.html> (accessed February 25, 2015).

"Patanol." RxList.com. <http://www.rxlist.com/patanol-drug.htm> (accessed February 25, 2015).

ORGANIZATIONS

American Academy of Allergy, Asthma & Immunology, 555 E. Wells Street, Suite 1100, Milwaukee, WI 53202-3823, (414) 272-6071, <http://www.aaaai.org/>.

American Academy of Ophthalmology, 655 Beach Street, San Francisco, CA 94109, (415) 561-8500, (415) 561-8533, aaof@aao.org, <http://www.aao.org/>.

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Omeprazole

Definition

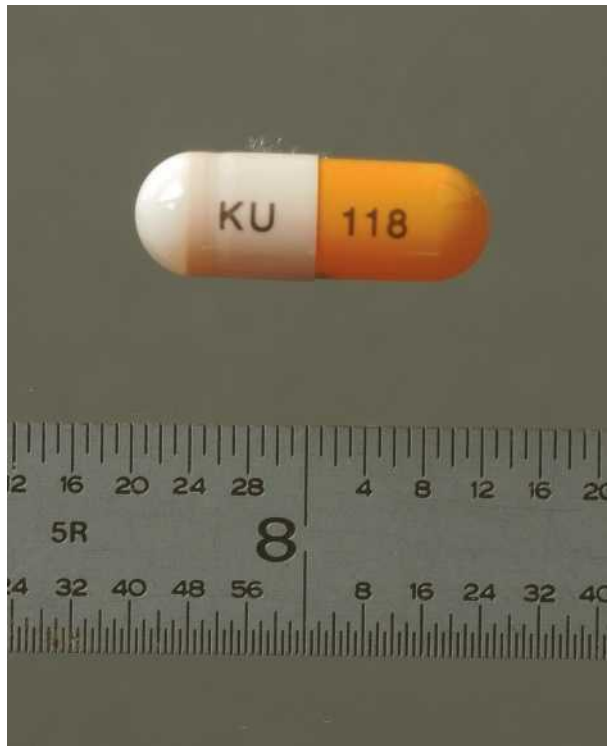
Omeprazole is a medicine available without a prescription to help treat frequent heartburn. The medicine is also available by prescription to treat heartburn and other symptoms of gastroesophageal reflux disease (GERD) and ulcers in the stomach or intestine. It is in a class of drugs called proton pump inhibitors.

Purpose

People who have GERD have symptoms such as pain near the breast bone that burns, especially when they lie down or bend over. The pain is called by the backing up, or reflux, of acids made naturally in the stomach through the opening in the esophagus that normally carries food down into the stomach. Although GERD may seem harmless, the constant reflux of acids can damage the thin lining of the esophagus, leading to ulcers. Proton pump inhibitors block much of the acid production.

Description

The prescription form of omeprazole comes in a delayed-release capsule. This allows the medicine to be



Omeprazole (delayed release), 20 mg. (© Cengage Learning®.)

KEY TERMS

Gastroesophageal reflux disease (GERD)—A condition characterized by the passage of stomach acid back into the esophagus through the small muscle that normally allows food to travel down from the esophagus into the stomach. GERD can cause heartburn and lead to ulcers in the esophagus.

Osteoporosis—A disease of the bones that becomes progressively worse, usually with age. The bones weaken and become brittle, breaking easily.

Proton pump inhibitor—A type of drug that reduces how much acid is made by glands that are located in the stomach's lining. When less acid is made, less makes its way back into the esophagus, and the symptoms of gastroesophageal reflux disease are eased.

Ulcer—A sore or break in the skin or lining of an organ.

released in the intestine to avoid being broken down by stomach acids. Over-the-counter formulas come as delayed-release tablets. Omeprazole was the first proton pump inhibitor to become available without a prescription.

U.S. brand names

In the United States, omeprazole is sold as the brand names Prilosec and Prilosec OTC. A product that combines omeprazole with sodium bicarbonate, the active ingredient in antacids, is sold as Zegerid and Zegerid OTC.

Recommended dosage

For heartburn or prevention of heartburn, adults should take one delayed-release tablet/capsule with 20 milligrams (mg) of omeprazole once a day before eating for up to 14 days. Adults who take omeprazole for GERD symptoms usually take 20 mg a day for up to four weeks. For an ulcer in the duodenum, the first part of the small intestine, a 20 mg tablet/capsule once a day before a meal should lead to healing in four to eight weeks. Adults with a gastric, or stomach, ulcer usually take 40 mg of omeprazole by mouth once a day before eating for four to eight weeks.

Pediatric

Dosage for children is based on their weight. For children ages 1 to 16, the recommended dose for treating GERD is 5 mg once a day for children who weigh between 5 and 10 kilograms (kg, or 11–22 lb.), and

10 mg once a day for children weighing between 10 and 20 kg (22–44 lb.). Once a child reaches 20 kg of weight, the adult dose of 20 mg a day is recommended. Infants generally take 0.7 mg of omeprazole per kg (2.2 lb.) of body weight. A liquid version of the drug can be given to children, or parents can empty the contents of an omeprazole capsule containing the appropriate dose into a cool glass of water or into a serving of applesauce.

Precautions

Improvement of symptoms after using omeprazole does not rule out the possibility of stomach cancer as the cause of symptoms. The doctor should perform typical a diagnostic examination based on signs and symptoms. Use of omeprazole and other proton pump inhibitors may increase risk of diarrhea caused by stomach bacteria. Long-term use of the drug at higher doses or multiple times per day has been shown to increase risk of fractures from osteoporosis.

Pediatric

It has not been established whether omeprazole is safe or effective in infants less than 12 months old.

Pregnant or breastfeeding

Omeprazole is a category B drug and has not been tested adequately in pregnant women. Animal studies have shown some harmful effects, and a pregnant woman should discuss the drug's use with her doctor. In general, a pregnant woman should only use omeprazole if the possible benefits from the medication outweigh risks to her unborn child. Omeprazole has been found in breast milk of women using the drug, and women who are breastfeeding should use caution when taking the medication.

Other conditions and allergies

People who have liver disease or problems with liver function should have reduced dosages of omeprazole.

Side effects

Omeprazole can cause side effects in people who take the medication, including:

- gas and constipation
- nausea and vomiting
- headache

Some side effects of omeprazole use can be severe and should be reported to a doctor immediately. These include:

- itching, rash, or hives
- problems breathing or swallowing
- swelling of the tongue, lips, throat, face, hands, or lower limbs

PATIENT PROFILE

A 65-year-old man complaining of upper abdominal discomfort consisting of pressure and heartburn pain, especially after going to bed in the evening, was diagnosed with gastroesophageal reflux disease (GERD). He was not actually experiencing reflux, or regurgitation of stomach contents, but he did have a cough and slight hoarseness, indicative of acid rising up into the esophagus from the stomach. His doctor recommended several lifestyle modifications such as raising the head of the bed, making sure to avoid lying down for at least two hours after eating, reducing alcohol consumption, and avoiding spicy or gas-producing foods. His doctor also prescribed once-a-day delayed-release omeprazole to help reduce excess acid. The patient was advised to take omeprazole at the same time each day, preferably in the morning before eating. Because omeprazole takes a few days to begin relieving stomach symptoms, he was also told that he could take antacids such as Maalox, Mylanta, or Tums before meals in addition to the omeprazole. These nonprescription remedies offer temporary relief of chronic acid reflux, although they do not prevent erosion of the esophageal walls from contact with stomach acid or help the esophagus to heal.

The patient's initial dose of omeprazole was a 20 mg delayed-release capsule to be taken once a day. The doctor explained that taking it for four weeks may be sufficient to relieve his symptoms, but that dosage could be increased to 40 mg per day for another four weeks if symptoms persisted. This eight-week treatment with omeprazole sometimes stops gastroesophageal reflux completely, and additional treatment is not always necessary. However, after four days of taking

omeprazole, the patient began to experience diarrhea every morning after eating breakfast, and then again several times during the day, usually after eating. Since omeprazole was the only recent change the patient had made, he notified his doctor in case the medication was the underlying cause of diarrhea. The doctor confirmed that diarrhea was a possible side effect of omeprazole, but that it usually subsided after the body adjusted to the medication. The patient was advised to continue taking omeprazole for three more days, completing a full week of treatment, and then they would reevaluate. After enduring three more days of diarrhea, the patient was unwilling to continue.

The patient scheduled another visit with his doctor to discuss his continuing symptoms and to seek a solution that would alleviate his stomach discomfort without digestive side effects exacerbating his discomfort. After discussing the issue with his physician, he was advised to continue with the lifestyle measures and to add a specific type of antacid called a histamine receptor antagonist (H2RA) to his daily regimen. These antacids include cimetidine (Tagamet HB), famotidine (Pepcid AC), and ranitidine (Zantac). They control gastroesophageal reflux differently than omeprazole, acting to block the production of histamine by stomach cells that normally stimulates gastric acid secretion. In this way, less acid is produced, which results in less reflux of acid into the esophagus. Less exposure of the esophageal walls to stomach acid then allows the esophagus to heal from previous reflux. For this patient, switching to this type of treatment relieved GERD symptoms and was well tolerated without notable side effects.

- headaches or dizziness
- extreme fatigue
- watery stools and diarrhea

Interactions

Drugs can interact with one another, reducing the effects of one drug or increasing side effects. It is important to tell the doctor about any medications, herbal remedies, or vitamin supplements being taken before starting omeprazole therapy.

Drugs

Omeprazole interacts with some antiretroviral drugs used to treat AIDS, including atazanavir (Reyataz) and nelfinavir (Viracept), making the antiretrovirals work less

effectively. Omeprazole can increase toxicity of other antiretroviral drugs, so anyone receiving treatment for AIDS should avoid omeprazole and other proton pump inhibitors until discussing their use thoroughly with a doctor.

Use of a drug called **rifampin** (Rifadin, Rifater), which is used to treat tuberculosis, can decrease the effectiveness of omeprazole in people who take both medications. Omeprazole also interacts with blood thinners such as **warfarin** (Coumadin) and with **clopidogrel** (Plavix), which is used to help prevent severe problems in people with heart and blood vessel disease.

Herbs and supplements

Use of St. John's wort while taking omeprazole can reduce the proton pump inhibitor's effectiveness. It is important to inform the doctor about use of iron

supplements while taking omeprazole. In addition, studies have shown that use of proton pump inhibitors such as omeprazole may affect how well the body absorbs and uses vitamins, especially calcium, magnesium, and vitamins B₁₂ and C.

Resources

PERIODICALS

Humphrey, Melissa L., Nooshin Barkhordari, and Yaman Kaakeh. "Effects of Omeprazole on Vitamin and Mineral Absorption and Metabolism." *The Journal of Pharmacy Technology* 28, no. 6 (2012): 243–48.

Regenbogen, Elliot, et al. "Esophageal Reflux Disease Proton Pump Inhibitor Therapy Impact on Sleep Disturbance: A Systematic Review." *Otolaryngology - Head and Neck Surgery* 146, no. 4 (2012): 524–32.

WEBSITES

MedlinePlus. "Omeprazole." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a693050.html> (accessed February 7, 2015).

"Omeprazole." Drugs.com. <http://www.drugs.com/omeprazole.html> (accessed February 7, 2015).

"Prilosec." RxList.com. <http://www.rxlist.com/prilosec-drug.htm> (accessed February 7, 2015).

Procter & Gamble. "Prilosec OTC." <http://www.prilosecotc.com/> (accessed February 7, 2015).

ORGANIZATIONS

American Gastroenterological Association, 4930 Del Ray Avenue, Bethesda, MD 20814, (301) 654-2055, (301) 654-5920, <http://www.gastro.org/>.

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, 1501 Bethlehem Pike, Flourtown, PA 19031, (215) 233-0808, naspghan@naspghan.org, <http://www.naspghan.org/>.

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REVIEWED BY GREGORY A. PRATT, RPh

Omnicef see **Cefdinir**

Ondansetron

Definition

Ondansetron is an antiemetic medication classified as a 5-HT₃ receptor antagonist. This classification means that the drug works by binding to a specific type of serotonin receptor (5-HT₃) in the brain. When 5-HT₃ receptors are stimulated, a person typically feels nauseated, but ondansetron and other members of this class of drugs stop the urge to vomit by preventing



Ondansetron, 4 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

serotonin, a neurotransmitter, from attaching to the 5-HT₃ receptors.

Purpose

Ondansetron is used for the following conditions in adults:

- prophylaxis (prevention) of nausea and vomiting induced by cancer chemotherapy
- prophylaxis of postoperative nausea and vomiting (PONV)
- prophylaxis of nausea and vomiting induced by radiation therapy

Ondansetron cannot be used to prevent or treat motion sickness.

In children, ondansetron is used for prophylaxis of chemotherapy-induced nausea and vomiting (CINV) and prophylaxis of PONV.

Off-label use

Ondansetron is used off label to treat the following conditions:

- cholestatic pruritus, a condition in which patients with advanced liver disease develop itching skin due to the accumulation of bile acids deposited in the skin
- hyperemesis gravidarum, persistent vomiting and nausea that occurs during pregnancy and results in dehydration

- alcohol abuse
- rosacea, a skin disorder
- spinal opioid-induced pruritus, itching caused by epidural or intrathecal administration of opioid pain relievers

Description

Ondansetron is available in five different formulations: tablets, oral disintegrating tablets (ODT), oral liquid, oral film strips, and an injectable liquid. Ondansetron and ondansetron ODT tablets as well as the oral film are available in two dosages: 4 and 8 milligrams (mg). The oral liquid contains 4 mg of the drug per 5 milliliters (mL) and is strawberry flavored. The injectable form of the drug delivers 2 mg of ondansetron per 1 mL of solution.

Ondansetron and ondansetron ODT tablets are most commonly either round or oval, depending on the manufacturer, and are usually white for the 4 mg tablets and yellow or yellow-orange for the 8 mg tablets. Patients prescribed the ondansetron ODT tablets should open the drug package with dry hands and place the tablet in the mouth, allowing it to dissolve there without chewing. The tablet should not be swallowed whole.

The oral film formulation of ondansetron is packaged as individual peppermint-flavored strips in either 4 mg or 8 mg doses. The strips dissolve in the mouth in about 10 seconds; they should not be chewed or swallowed whole. Patients who use the oral film strips should be careful to wash their hands after swallowing the strip.

The injectable form of ondansetron is administered intramuscularly (into a muscle) or intravenously (into a vein) only by a physician or nurse in a hospital; patients are prescribed an oral form of ondansetron for use at home.

Ondansetron may be taken with or without food. Patients who are prescribed the standard oral tablets should take them with a full glass of water at the times directed by the healthcare provider. All forms of ondansetron should be stored at room temperature away from heat, direct light, and moisture (not in the bathroom).

U.S. brand names

Ondansetron is sold in the United States under the brand names Zofran (for the injectable solution, oral solution, and standard tablets), Zofran ODT (for the oral disintegrating tablets), and Zuplenz (for the oral film).

The standard oral tablets, ODT tablets, oral solution, and injectable solution are also available in the United States as generic ondansetron, manufactured by Teva Pharmaceuticals, Baxter Healthcare, and several other

KEY TERMS

Antiemetic—Any medication given to prevent or treat nausea and vomiting.

Emetogenic—Referring to a substance or procedure intended or likely to cause vomiting.

Hyperemesis gravidarum—A complication of pregnancy marked by intractable nausea, vomiting, and dehydration.

Long QT syndrome—An inherited heart condition in which delayed repolarization of the heart muscle following a heartbeat increases the risk of ventricular arrhythmias, which may lead in turn to dizziness, fainting, and sudden death due to ventricular fibrillation.

Phenylketonuria (PKU)—An inherited disorder in which the body lacks an enzyme needed to digest the amino acid phenylalanine. Untreated PKU results in intellectual disabilities and seizures; treatment requires lifelong adherence to a diet low in phenylalanine.

Prophylaxis—Referring to the use of a medication or other treatment to prevent sickness or disease.

Serotonin—A neurotransmitter derived from the amino acid tryptophan. About 90% of serotonin is produced in the specialized enterochromaffin cells in the gastrointestinal tract, with the remaining 10% produced in the central nervous system.

Serotonin syndrome—A potentially life-threatening condition resulting from excessively high levels of serotonin in the body, usually resulting from drug interactions, drug overdoses, or the recreational use of certain drugs. Symptoms include racing or pounding heartbeat, tremor, shivering, sweating, dilated pupils, and hyperresponsive reflexes.

firms. The oral film is available only under the brand name Zuplenz and is distributed by Galena Biopharma.

Canadian brand names

Canadian brand names for ondansetron include Zofran ODT, Apo-Ondansetron, Gen-Ondansetron, Ondansetron Sandoz, and PMS-Ondansetron.

International brand names

Ondansetron is sold under a number of brand names worldwide, including Anset, Cetron, Emetron, Noventron, Ofran, Ondanz, Setron, Vometron, and Zordil.

Origins

Ondansetron was developed by GlaxoSmithKline in the early 1990s and was first approved by the U.S. Food and Drug Administration (FDA) as an injectable solution in January 1991. Its formulation as an oral tablet was approved in December 1992. The oral liquid formulation of ondansetron was approved by the FDA in January 1997. The drug went off patent in 2006. In December 2006, the FDA approved the oral disintegrating tablet (ODT) formulation of ondansetron; it approved the oral film formulation of the drug in July 2010.

Recommended dosage

Adult dosages include:

- Chemotherapy-induced nausea and vomiting (CINV), prophylaxis, by mouth: For moderately emetogenic chemotherapy, 8 mg is started 30 minutes before chemotherapy, then given again every 12 hours for one to two days after chemotherapy. For severely emetogenic chemotherapy, 24 mg is given by mouth starting 40 minutes before chemotherapy.
- Chemotherapy-induced nausea and vomiting (CINV), prophylaxis, by injection: 0.15 mg per kilogram (kg, or 2.2 lb.) of body weight is given intravenously over a period of 15 minutes, 30 minutes before chemotherapy. Additional doses may be administered 4 and 8 hours after the first dose, not to exceed 16 mg per dose.
- Postoperative nausea and vomiting (PONV), prophylaxis: Administer 4 mg by injection either intravenously or intramuscularly immediately before anesthesia or after the procedure, or give 16 mg by mouth 1 hour before anesthesia. Patients weighing more than 80 kg (176 lb.) may need an additional 4 mg by intravenous injection.
- Radiation-induced nausea and vomiting, prophylaxis, total-body radiation: 8 mg is taken by mouth 1 to 2 hours before radiation therapy; this dose should be administered each day of treatment. For single high-dose fraction therapy to the abdomen, 8 mg is taken by mouth 1 to 2 hours before radiation therapy, followed by subsequent doses every 8 hours after the first dose for one or two days after completion of therapy. For daily fractionated doses to the abdomen, 8 mg is taken by mouth 1 to 2 hours before radiotherapy, followed by subsequent doses every 8 hours after the first dose on each day that radiotherapy is given.

Pediatric

Dosing schedules in children and adolescents include:

- CINV, prophylaxis, by mouth: For children 4–12 years old, give 4 mg by mouth starting 30 minutes before

chemotherapy; give another dose 4 and 8 hours after the first dose, and then dose every 8 hours for one or two days after chemotherapy. For children and adolescents over 12 years of age, give 8 mg by mouth starting 30 minutes before chemotherapy, followed by additional doses every 12 hours for one or two days after chemotherapy, or give a single dose of 24 mg. The safety of ondansetron is not established in children younger than 4.

- CINV, prophylaxis, by injection: For children over six months of age: give 0.15 mg/kg intravenously over a period of 15 minutes, 30 minutes before chemotherapy, and repeat the dose 4 and 8 hours after the first dose. The total amount given should not exceed 16 mg per dose. The safety of injectable ondansetron is not established in infants younger than six months.
- PONV, prophylaxis: For children between the ages of one month and 12 years weighing less than 40 kg (88 lb.), give 0.1 mg/kg by intravenous injection. For children weighing more than 40 kg, give 4 mg intravenously. For children and adolescents over 12 years of age, give 4 mg by intravenous or intramuscular injection either immediately before anesthesia or after the procedure, or give 16 mg by mouth one hour before anesthesia. Patients weighing more than 80 kg (176 lb.) may need an additional 4 mg of ondansetron given intravenously.

Precautions

Patients using ondansetron should take extra care when driving or operating hazardous machinery, as drowsiness is a common side effect of the drug.

Pediatric

Ondansetron should not be given to children younger than age four.

Children with phenylketonuria (PKU) should not be given ondansetron ODT tablets, as they contain phenylalanine.

Pregnant or breastfeeding

Ondansetron is classified as a pregnancy category B drug, which means it is not expected to harm an unborn baby. It is not known whether the drug passes into breast milk, so the manufacturer recommends cautious use in nursing mothers. Women taking ondansetron should still tell their healthcare provider if they are pregnant or planning to become pregnant.

Other conditions and allergies

Dosages of ondansetron should be reduced in patients with severe liver impairment. In addition,

patients with any of the following conditions should not use ondansetron:

- congenital long QT syndrome
- use of either apomorphine or dronedarone
- known hypersensitivity to ondansetron or other drugs in the same class (dolasetron, palonosetron, tropisetron, granisetron, etc.)
- severe liver disease, including cirrhosis
- severe electrolyte imbalance

Side effects

The most common side effects of ondansetron include:

- headache
- constipation or diarrhea
- fatigue
- drowsiness
- pain at injection site
- mild anxiety

Less common side effects include:

- dry mouth
- urinary retention
- feeling cold
- elevated liver function test results
- hiccups
- joint pain

Patients who experience any of the following side effects should contact their healthcare provider at once:

- sudden swelling of the face, arms, legs, eyes, lips, or tongue, or problems with swallowing or breathing (symptoms of angioedema, a severe allergic reaction to the drug)
- yellow discoloration of the skin or the whites of the eyes (symptoms of jaundice)
- blurred vision or temporary vision loss (lasting a few hours)
- slowed heart rate, heart palpitations, dizziness, or fainting
- signs of serotonin syndrome (overly high levels of serotonin in the body), such as hallucinations, agitation, fever, fast heart rate, overactive reflexes, nausea, vomiting, diarrhea, loss of coordination, or fainting
- severe pain, nausea and vomiting, or swelling in the stomach or abdominal area

Interactions

Individuals should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs and supplements.

Drugs

Patients taking either apomorphine or dronedarone should not use ondansetron. Apomorphine (a drug used to treat Parkinson's disease) interacts with ondansetron to induce a sudden drop in blood pressure and loss of consciousness. Dronedarone, a drug used to treat cardiac arrhythmias, interacts with ondansetron to increase the effects of ondansetron and increase the patient's risk of a prolonged QT interval. Other drugs that increase the risk of prolonged QT interval include:

- antipsychotic drugs (**haloperidol**, **clozapine**, **olanzapine**, perphenazine, chlorpromazine, etc.)
- fluoroquinolone antibiotics (**ciprofloxacin**, ofloxacin, norfloxacin, **levofloxacin**, etc.)
- drugs given to treat heart arrhythmias (quinidine, sotalol, flecainide, dofetilide, propafenone, amiodarone, disopyramide)
- tyrosine-kinase inhibitors used to treat cancer (lapatinib, nilotinib, dasatinib, crizotinib, sunitinib, etc.)
- tricyclic antidepressants (clomipramine, **nortriptyline**, desipramine, **doxepin**, **amitriptyline**, **imipramine**, etc.)
- **methadone**

Carbamazepine and **phenytoin** decrease the effectiveness of ondansetron. Other drugs known to interact with ondansetron include octreotide, antifungal medications (e.g., posaconazole, itraconazole, voriconazole), and triptans (e.g., naratriptan, **sumatriptan**, frovatriptan, **zolmitriptan**).

Herbs and supplements

Patients taking ondansetron should avoid herbal preparations containing St. John's wort because it decreases the effectiveness of ondansetron.

Food and other substances

Grapefruit increases the effectiveness of ondansetron.

Cigarette smoking reduces the effectiveness of ondansetron.

Resources

BOOKS

- Antonsen, Erik, et al, eds. *Emergency Medicine: An Evidence-Based Review*. Philadelphia: Wolters Kluwer Health, 2015.
- Irwin, Margaret, and Lee Ann Johnson, eds. *Putting Evidence into Practice: A Pocket Guide to Cancer Symptom*

Management. Pittsburgh: Oncology Nursing Society, 2014.

Wolfe, M. Michael, and Robert C. Lowe, eds. *Pocket Guide to Gastrointestinal Drugs*. Chichester: John Wiley and Sons, 2014.

PERIODICALS

Doggrell, S. J., and J. C. Hancox. "Cardiac Safety Concerns for Ondansetron, an Antiemetic Commonly Used for Nausea Linked to Cancer Treatment and following Anaesthesia." *Expert Opinion on Drug Safety* 12, no. 3 (2013): 421–31.

Johnson, B. A., et al. "Determination of Genotype Combinations That Can Predict the Outcome of the Treatment of Alcohol Dependence Using the 5-HT(3) Antagonist Ondansetron." *American Journal of Psychiatry* 170, no. 9 (2013): 1020–31.

Morrow, G. R., R. M. Navari, and H. S. Rugo. "Clinical Roundtable Monograph: New Data in Emerging Treatment Options for Chemotherapy-Induced Nausea and Vomiting." *Clinical Advances in Hematology and Oncology* 12, no. 3 suppl. 9 (2014): 1–14.

Niebyl, J. R., and G. G. Briggs. "The Pharmacologic Management of Nausea and Vomiting of Pregnancy." *Journal of Family Practice* 63, no. 2 suppl. (2014): S31–S37.

Rehill, R. H. "Prevention of Postoperative Nausea and Vomiting: A Thought on Ondansetron." *Anesthesia and Analgesia* 119, no. 4 (2014): 1003–4.

WEBSITES

AHFS Consumer Medication Information. "Ondansetron." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601209.html> (accessed March 6, 2015).

Micromedex. "Ondansetron (Injection Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/ondansetron-injection-route/description/drg-20065221> (accessed February 18, 2015).

Micromedex. "Ondansetron (Oral Route, Oral Mucosal Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/ondansetron-oral-route-oral-mucosal-route/description/drg-20074421> (accessed February 18, 2014).

Physicians' Desk Reference. "Zofran." PDR Health. <http://www.pdrhealth.com/drugs/zofran> (accessed March 6, 2015).

U.S. Food and Drug Administration. "Ondansetron (Marketed as Zofran) Information." <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm271924.htm> (accessed February 18, 2015).

ORGANIZATIONS

American Cancer Society, 250 Williams Street NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org/>.

American College of Gastroenterology (ACG), 6400 Goldsboro Road, Suite 200, Bethesda, MD 20817, (301) 263-9000, info@acg.gi.org, <http://gi.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Oral contraceptives

Definition

Oral contraceptives are drugs taken by mouth to help prevent pregnancy. They are also referred to as "the pill," OCs, or birth control pills.

Purpose

Oral contraceptives contain synthetic forms of two hormones that are usually produced naturally in the body. These hormones, estrogen and progestin, regulate a woman's menstrual cycle. When taken in the proper amounts and following a specific schedule, oral contraceptives are very effective in preventing pregnancy. Studies show that fewer than 1 in every 100 women who use oral contraceptives correctly becomes pregnant during the first year of use.

Taking oral contraceptives may also have several benefits outside of their ability to prevent pregnancy. Research indicates that with 10–12 years of oral contraceptive use, a woman's risk of ovarian cancer is reduced by up to 80%. There may also be an approximate 50% decrease in the rate of endometrial cancers in women who take birth control pills. Another well-known, noncontraceptive benefit of taking oral contraceptives is improvement in acne. The combination oral contraceptive ethinyl estradiol/norgestimate is approved by the U.S. Food and Drug Administration (FDA) for the



Jolessa oral contraceptive. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

treatment of acne. Another positive effect of oral contraceptive use is improvement in abnormal uterine bleeding. Older women may benefit from using oral contraceptives because the pills can increase bone mass as women enter their menopausal years, when osteoporosis is a growing concern.

Description

For pregnancy to occur, an egg must mature inside a woman's ovary, be released, and travel to the fallopian tube. This occurs on average once every 28 days. A male sperm must also reach the fallopian tube and fertilize the egg. Then fertilized egg travels to the woman's uterus (womb), where it lodges in the uterine lining and develops into a fetus. The main way that oral contraceptives prevent pregnancy is by keeping an egg from fully maturing. Eggs that are not fully mature cannot be fertilized. In addition, birth control pills thicken mucus in a woman's cervix, through which the sperm has to swim. This makes it more difficult for sperm to reach the egg. Oral contraceptives also thin the uterine lining so that a fertilized egg cannot lodge there and develop.

Birth control pills cause both positive and negative side effects. For example, a woman's menstrual periods are regular and usually lighter when she is taking oral contraceptives, and the pills may reduce the risk of ovarian cysts, breast lumps, pelvic inflammatory disease, and other medical problems. However, taking birth control pills can increase the risk of heart attack, stroke, and blood clots in women with a family history of heart disease. Serious side effects such as these are more likely in women over 35 years of age who smoke cigarettes and in those with specific health problems such as high blood pressure, diabetes, or a history of breast or uterine cancer. A woman who wants to use oral contraceptives should ask her physician for the latest information on the risks and benefits of all types of birth control and should consider her age, health, and medical history when deciding what to use.

Oral contraceptives come in a wide range of estrogen-progestin combinations. The birth control pills in use today contain much lower doses of estrogen than those available in the past; these changes have reduced the likelihood of negative side effects. Some pills contain only progestin. These are prescribed mainly for women who need to avoid estrogens. They may not be as effective in preventing pregnancy as the estrogen-progestin combinations.

Birth control pills come in tablet form, in containers designed to help women keep track of which tablet to take each day. The tablets are different colors, indicating the amounts of hormones they contain. Some may contain no hormones at all. These are included simply to

KEY TERMS

Cyst—An abnormal sac or enclosed cavity in the body, filled with liquid or partially solid material.

Endometriosis—A condition in which tissue, like that normally found in the lining of the uterus, is present outside the uterus. The condition often causes pain and bleeding.

Estrogen—A female hormone produced by the ovaries that stimulates the growth of the lining of the uterus.

Fallopian tube—One of a pair of slender tubes that extend from each ovary to the uterus. Eggs pass through the fallopian tubes to reach the uterus.

Fetus—A developing baby inside the womb.

Fibroid tumor—A noncancerous tumor formed of fibrous tissue.

Hormone—A substance that is produced in one part of the body, then travels through the bloodstream to another part of the body where it has its effect.

Jaundice—Yellowing of the eyes and skin due to the buildup of a bile pigment (bilirubin) in the blood.

Migraine—A throbbing headache that usually affects only one side of the head. Nausea, vomiting, increased sensitivity to light, and other symptoms often accompany migraine.

Mucus—Thick fluid produced by the moist membranes that line many body cavities and structures.

Ovary—A reproductive organ in females that produces eggs and hormones.

Pelvic inflammatory disease (PID)—Inflammation of the female reproductive tract, caused by any of several microorganisms. Symptoms include severe abdominal pain, high fever, and vaginal discharge. Severe cases can result in sterility.

Progestin—A synthetic or natural drug that acts on the uterine lining.

Uterus—A hollow organ in a female in which a fetus develops until birth.

help women stay in the habit of taking a pill every day, as the hormone combination needs to be taken only on certain days of the menstrual cycle. Keeping the tablets in their original container and taking them exactly on schedule is very important. They will not be as effective if taken in the wrong order or if doses are missed.

U.S. brand names

There are many types of oral contraceptives available; some commonly used brands are Demulen, Desogen, Loestrin, Lo/Ovral, Nordette, Ortho-Novum, Ortho-Tri-Cyclen, Estrostep, Ortho-cept, Alesse, Levlite, and Ovcon.

Recommended dosage

The dose schedule depends on the type of oral contraceptive. The two basic schedules are a 21-day schedule and a 28-day schedule. On the 21-day schedule, one tablet is taken each day for 21 days, no tablets are taken for 7 days, and then the cycle is repeated. On the 28-day schedule, one tablet is taken each day for 28 days, and then the cycle is repeated. Carefully follow the instructions provided with the drug. For additional information or explanation, check with the physician who prescribed the medicine or the pharmacist who filled the prescription.

Pills should be taken at the same time every day. Taking doses more than 24 hours apart may increase the chance of side effects or pregnancy. Missing a dose increases the risk of pregnancy. If a dose is missed, follow the package directions or check with the physician who prescribed the medicine for instructions. It may be necessary to use another form of birth control for some time after missing a dose.

Taking an oral contraceptive with food or at bedtime will help prevent nausea, a side effect that sometimes occurs during the first few weeks of use. Nausea usually goes away as the body adjusts to the medicine.

Precautions

Precautions associated with oral contraceptives include:

- No form of birth control is 100% effective in preventing pregnancy in sexually active women. However, oral contraceptives are highly effective when used properly. Individuals should discuss their options with a healthcare professional.
- Oral contraceptives do not protect against acquired immune deficiency syndrome (AIDS) or other sexually transmitted diseases. For protection against such diseases, use a latex condom unless either partner is allergic to latex.
- Oral contraceptives are not effective immediately after a woman begins taking them. Physicians recommend using other forms of birth control for one to three weeks after starting the pill.
- Smoking cigarettes while taking oral contraceptives greatly increases the risk of serious side effects. Women

who take oral contraceptives should not smoke cigarettes.

- Seeing a physician regularly while taking oral contraceptives is very important. The physician will note any unwanted side effects and may switch the patient to a different contraceptive.
- Anyone taking oral contraceptives should tell the healthcare professional in charge before having any surgical or dental procedures, laboratory tests, or emergency treatment.
- These drugs increase sensitivity to sunlight. Women using oral contraceptives should avoid too much sun exposure and should not use tanning beds, tanning booths, or sunlamps until they know how the medicine affects them. Some women taking oral contraceptives may get brown splotches on exposed areas of their skin. These usually go away over time after the women stop taking birth control pills.
- When possible, birth control pills should be stopped for one month before, and not started again until two weeks after, major surgery involving prolonged immobility and/or an increased risk of blood clots.
- Oral contraceptives may cause the gums to become tender and swollen or to bleed. Careful brushing and flossing, gum massage, and regular cleaning may help prevent this problem. Check with a physician or dentist if gum problems develop.
- Before taking these drugs, individuals should let the physician know if she has any medical problems, or if she is taking any medications, including over-the-counter and herbal medications.
- Oral contraceptives may continue to affect the menstrual cycle for some time after a woman stops taking them. Women who miss periods for several months after stopping this medicine should check with their physicians.

Pregnant or breastfeeding

Women who become pregnant or who think they may be pregnant while taking birth control pills should stop taking them immediately and check with their physicians. Women who want to start taking oral contraceptives again after pregnancy should not refill their old prescriptions without checking with their physicians. The physician may need to change the prescription.

Women who are breastfeeding should check with their physicians before using oral contraceptives. The hormones in the pills may reduce the amount of breast milk produced and may be present in the milk. They may also cause jaundice and enlarged breasts in nursing babies whose mothers take the drug.

Other conditions and allergies

Oral contraceptives may improve or worsen some medical conditions. The possibility that they may make a condition worse does not necessarily mean they cannot be used. In some cases, women may just need to be tested or followed more closely for medical problems while using oral contraceptives. Before using oral contraceptives, women with any of these medical problems should make sure their physicians are aware of their conditions:

- Female conditions such as menstrual problems, endometriosis, or fibroid tumors of the uterus. Birth control pills usually make these problems better, but may sometimes make them worse or more difficult to diagnose.
- Heart or circulation problems, including recent or past blood clots or stroke. Women who already have these problems may be at greater risk of developing blood clots or circulation problems if they use oral contraceptives, especially if they smoke.
- Breast cysts, lumps, or other noncancerous breast problems. Oral contraceptives generally protect against these conditions, but physicians may recommend more frequent breast exams for women taking the pills.
- Breast cancer or other cancer (now or in the past, or family history). Oral contraceptives may make some existing cancers worse. Women with a family history of breast cancer may need more frequent screening for the disease if they decide to use birth control pills.
- Migraine headaches. This condition may improve but sometimes worsens with the use of birth control pills.
- Diabetes. Blood glucose (sugar) levels may increase slightly when oral contraceptives are used. Usually this increase is not enough to affect the amount of diabetes medicine needed. However, blood glucose needs to be monitored closely while taking oral contraceptives.
- Depression. This condition may worsen in women who already have it or may (rarely) occur again in women who were depressed in the past.
- Gallbladder disease, gallstones, high blood cholesterol, or chorea gravidarum (a nervous disorder). Oral contraceptives may make these conditions worse.
- Epilepsy, high blood pressure, heart or circulation problems. Oral contraceptives may make these conditions worse by increasing fluid buildup.

Anyone who has had unusual reactions to estrogens or progestins in the past should let her physician know before taking oral contraceptives. The physician should also be told about any allergies to foods, dyes, preservatives, or other substances.

Side effects

Serious side effects are rare in healthy women who do not smoke cigarettes. In women with certain health problems, however, oral contraceptives may cause problems such as liver cancer, noncancerous liver tumors, blood clots, or stroke. Healthcare professionals can help women weigh the benefits of being protected against unwanted pregnancy and offer information on alternate forms of birth control.

The most common minor side effects include emotional liability (mood swings), nausea, vomiting, abdominal cramping or bloating, breast pain, tenderness or swelling, swollen ankles or feet, weight gain, and fatigue. These usually go away as the body adjusts to the drug and do not need medical attention unless they persist or interfere with normal activities.

Other side effects should be brought to the attention of the physician who prescribed the medicine. Check with the physician as soon as possible if any of the following side effects occur:

- missed periods, longer periods, or bleeding or spotting between periods
- headaches
- vaginal infection, itching, or irritation
- increased blood pressure

Women who have any of the following symptoms should get emergency help right away. These symptoms may be signs of blood clots:

- sudden changes in vision, speech, breathing, or coordination
- severe or sudden headache
- coughing up blood
- sudden, severe, or continuing pain in the abdomen or stomach
- pain in the chest, groin, or leg (especially in the calf)
- weakness, numbness, or pain in an arm or leg

Other rare side effects may occur. Anyone who has unusual symptoms while taking oral contraceptives should get in touch with her physician.

Interactions

Oral contraceptives interact with a number of other medicines. When this happens, the effects of one or both of the drugs may change or the risk of side effects may be greater. Before beginning oral contraceptives, a woman should let her physician know all other prescription and nonprescription drugs, herbal remedies, and dietary supplements she is taking and should ask whether the possible interactions can interfere with drug therapy.

Drugs

These drugs may make oral contraceptives less effective in preventing pregnancy. Anyone who takes these drugs should use an additional birth control method for the entire cycle in which these drugs are used:

- ampicillin
- barbiturates
- **carbamazepine** (Tegretol)
- corticosteroids
- **griseofulvin** (Gris-PEG, Fulvicin)
- **modafinil** (Provigil)
- **oxcarbazepine** (Trileptal)
- penicillin V
- **phenytoin** (Dilantin)
- primidone (Mysoline)
- **rifampin** (Rifadin)
- ritonavir (Norvir)
- tetracyclines

In addition, taking the following drugs while using oral contraceptives may increase the risk of side effects or interfere with the drug's effects:

- theophylline—effects of this medicine may increase, along with the chance of unwanted side effects and possible toxicity
- cyclosporine—effects of this medicine may increase, along with the chance of unwanted side effects

The lists above do not include every drug that may interact with oral contraceptives. Be sure to check with a physician or pharmacist before combining oral contraceptives with any other prescription or nonprescription (over-the-counter) medicine. As with any medication, the benefits and risks should be discussed before use.

Herbs and supplements

The herb St. John's wort may reduce the effectiveness of oral contraceptives.

Resources

BOOKS

Eig, Jonathan. *The Birth Control Pill: How Four Crusaders Reinvented Sex and Launched a Revolution*. New York: Norton & Company, 2014.

Manon, Parry. *Broadcasting Birth Control: Mass Media and Family Planning*. New Brunswick: Rutgers University Press, 2013.

PERIODICALS

Goldstein, R. L., U. D. Upadhyay, and T. R. Raine. "With Pills, Patches, Rings, and Shots: Who Still Uses Condoms? A

Longitudinal Cohort Study." *Journal of Adolescent Health* 52, no. 1 (2013): 77–82.

Grossman, Daniel, et al. "Interest in Over-the-Counter Access to Oral Contraceptives among Women in the United States." *Contraception* 88, no. 4 (2013): 544–52.

Yu, Jingbo, and Henry Hu. "Inappropriate Use of Combined Hormonal Contraceptives for Birth Control among Women of Reproductive Age in the United States." *Journal of Women's Health* 22, no. 7 (2013): 595–603.

WEBSITES

Mayo Clinic staff. "Birth-Control Pills." MayoClinic.org. <http://www.mayoclinic.org/healthy-living/birth-control/basics/birth-control-pills/hlv-20049454> (accessed February 18, 2015).

MedlinePlus. "Birth Control." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/birthcontrol.html> (accessed February 18, 2015).

Planned Parenthood Federation of America Inc. "Birth Control." <http://www.plannedparenthood.org/health-info/birth-control> (accessed February 18, 2015).

ORGANIZATIONS

American Congress of Obstetricians and Gynecologists, 409 12th Street SW, Washington, DC 20024, (202) 638-5577, (800) 673-8444, resources@acog.org, <http://www.acog.org/>.

International Federation of Gynecology and Obstetrics, FIGO House, Suite 3—Waterloo Court, 10 Theed Street, London SE1 8ST, United Kingdom, +44 20 7928 1166, figo@figo.org, <http://www.figo.org/>.

Planned Parenthood Federation of America, 434 West 33rd Street, New York, NY 10001, (800) 230-PLAN (7526), (212) 245-1845, <http://www.plannedparenthood.org/>.

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REVIEWED BY JAMES E. WAUN, MD, RPH

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Ortho Evra see **Norelgestromin/ethinyl estradiol**

Orudis see **Ketoprofen**

Oseltamivir

Definition

Oseltamivir phosphate is an oral antiviral drug for treating acute symptoms of influenza ("flu") within the first 48 hours of onset. It is also used to prevent the flu. Oseltamivir is in a class of medications called neuraminidase inhibitors.



Tamiflu (oseltamivir phosphate), 75 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Influenzas are common respiratory infections caused by several different viruses. Oseltamivir is approved by the U.S. Food and Drug Administration (FDA) for treating some types of uncomplicated flu in adults and children aged two weeks and older. It is also approved for the prevention of some types of flu in adults and children aged one year and older who have been exposed to the virus or during influenza outbreaks. Oseltamivir can shorten the duration and reduce the severity of flu symptoms—including stuffy or runny nose, sore throat, cough, muscle or joint pain, fatigue, headache, fever, and chills—and improve survival. It does not prevent bacterial infections that can occur as influenza complications.

Most otherwise healthy people are not treated with oseltamivir or another antiviral, but oseltamivir may be used to treat patients who are very ill or hospitalized with the flu or are at risk for serious complications. These include adults aged 65 and older, children under age 5 and especially under age 2, children under age 19 on long-term aspirin therapy, pregnant women, American Indians, Alaska Natives, and people with:

- asthma
- neurological and neurodevelopmental conditions
- blood disorders, such as sickle-cell disease
- chronic lung disease
- endocrine disorders such as diabetes

- heart disease
- kidney or liver disorders
- metabolic disorders
- morbid obesity
- weakened immune systems due to disease or medication

Description

Oseltamivir, as well as zanamivir (Relenza), are neuraminidase inhibitors that are believed to trap flu viruses within cells, preventing them from bursting out and infecting additional cells. This lowers the “viral load” in the body, shortening the illness and reducing the risk of complications such as pneumonia. Although oseltamivir does not prevent transmission of the virus to others, it may reduce the risk of contagion.

Oseltamivir can treat both influenza types A and B, but is most often used against influenza A, the most common type in the United States and the cause of global pandemics. Flu viruses are categorized according to the subtypes of their two outer-coat proteins: hemagglutinin (HA or H), which enables the virus to bind to host cells and initiate infection, and neuraminidase (NA or N), which enables newly formed viruses to burst the host cell and spread to other cells. Because flu viruses recombine to express different HA and NA proteins, each flu season, the U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) test circulating viruses for their susceptibility to the four FDA-approved flu drugs. Although oseltamivir is most effective if initiated within 48 hours of symptom onset, the WHO recommends that because of the high mortality associated with influenza A H5N1 and H7N9 and evidence that these viruses continue to replicate (reproduce) for a longer period, oseltamivir use should be considered later in the course of the illness.

U.S. brand names

Oseltamivir is marketed under the brand name Tamiflu in the United States, Canada, and most countries worldwide.

Origins

Oseltamivir phosphate was first approved by the FDA in 1999 as 30, 45, and 75 milligram (mg) oral capsules and a 6 mg per milliliter (mL) oral liquid suspension. In 2012, the FDA expanded approval to use in children as young as two weeks, making it the only flu medication approved for treating children under one year. Tamiflu is covered by U.S. patents until 2016. Although

KEY TERMS

Hemagglutinin (HA, H)—A protein in the outer coat of viruses that enable them to bind to cells and initiate infection.

Influenza A—A common, moderate-to-severe respiratory disease that affects humans and animals such as swine and birds and has caused global pandemics.

Influenza B—A relatively genetically stable virus that only infects humans, especially children, and usually causes milder illness than influenza A and epidemics rather than pandemics.

Neuraminidase (NA, N)—An enzyme on the surfaces of flu viruses that is involved in the release of viral particles from infected cells and that is inhibited by oseltamivir.

Prophylactic—Protective measures to prevent disease.

Tamiflu—The brand name of oseltamivir phosphate.

Zanamivir—Relenza; an antiviral neuraminidase inhibitor similar to oseltamivir.

generic oseltamivir is sold online, the FDA has warned against potentially fraudulent online products.

Recommended dosage

The usual adult dosage for treating acute influenza is 75 mg twice a day for five days—possibly longer for patients hospitalized with the flu. The usual adult prophylactic dosage following close contact with an infected person is 75 mg once a day for 10 days. Treatment should begin within 48 hours of exposure. The prophylactic dosage for community flu outbreaks is 75 mg once a day for up to 6 weeks and up to 12 weeks in patients with compromised immune systems. Patients who have difficulty swallowing capsules can carefully open the capsules over a small bowl, add a small amount of sweetened liquid, stir, and swallow the entire mixture immediately. A missed dose should be taken as soon as possible, but if it is two hours or less to the next scheduled dose, the missed dose should be skipped and the regular dosing schedule resumed. The doctor should be consulted if several doses are missed.

The oral suspension should be measured using the device provided by the manufacturer or by the pharmacy for pharmacist-prepared suspensions. A household

teaspoon should never be used to measure the oral suspension. Additional dosing instructions include:

- The suspension is well shaken for about five seconds to mix it evenly.
- The bottle is opened by simultaneously pushing on and turning the cap.
- The measuring-device plunger is pushed down completely to the tip, and the tip is inserted into the bottle.
- The bottle with device attached is turned upside down.
- The plunger is slowly pulled back until the prescribed amount reaches the appropriate marking. Large doses may need to be measured twice.
- The bottle is turned upright, and the measuring device is removed slowly.
- The suspension is administered directly into the mouth.
- The bottle cap is replaced and tightly closed.
- The plunger is removed from the measuring device, and both parts are rinsed under running tap water and air-dried before reassembly.
- The doctor or pharmacist should explain how to measure the dose if a measuring device is not available.

Capsules should be stored at room temperature away from excess heat and moisture (not in the bathroom). Commercial suspensions can be stored at room temperature for up to 10 days and in the refrigerator for up to 17 days. Pharmacist-prepared suspensions can be stored at room temperature for up to 5 days and in the refrigerator for up to 35 days. The suspension must not be frozen.

Pediatric

Acute influenza in children is treated for five days at the following doses:

- 3 mg per kilogram (kg, or 2.2 lb.) of body weight twice daily for babies ages two weeks to one year
- 30 mg twice daily for children weighing 15 kg (33 lb.) or less
- 45 mg twice daily for children weighing 15.1–23 kg (33–51 lb.)
- 60 mg twice daily for children weighing 23.1–40 kg (51–88 lb.)
- 75 mg twice daily for children ages 13 and older

The above doses are administered once daily for prophylaxis within 48 hours of exposure, except that the prophylactic dosage for children aged 12 and younger weighing at least 40.1 kg (88 lb.) is 75 mg. The FDA has not approved prophylactic treatment for children under one year, but the American Academy of Pediatrics recommends 3 mg/kg for babies ages three months to one year and, if critically necessary, for infants under

three months. Prophylactic therapy is continued for ten days after exposure and for up to six weeks during community outbreaks.

For children older than one year, oral suspensions are measured and administered as described above. For children under one year, the pharmacist will provide the proper measuring device, since the manufacturer-supplied device cannot accurately measure smaller doses.

Other conditions and allergies

For adults with severe kidney impairment, the treatment dosage is 75 mg once a day for five days, and the prophylactic dosage is 75 mg every other day or 30 mg once a day.

Precautions

The entire prescribed oseltamivir course should be completed, even if symptoms disappear. Stopping the drug early or skipping doses may not completely clear the infection or protect against the flu. The doctor should be called if symptoms do not begin to improve or continue after the course is completed. Symptoms of oseltamivir overdose can include nausea and vomiting.

Pediatric

Children and teenagers appear to be particularly susceptible to psychiatric effects of the flu, with or without oseltamivir treatment. Symptoms may include:

- abnormal behavior
- confusion
- agitation
- anxiety
- hallucinations
- seizures
- self-harm or suicide

Pregnant or breastfeeding

Oseltamivir is in the FDA pregnancy category C. There are no well-controlled data from human pregnancies, but animal studies show that the drug crosses the placenta and may affect the fetus. Surveillance and other data from human pregnancies have not shown an increased risk for adverse outcomes, but oseltamivir should be taken during pregnancy only if potential benefits outweigh potential risks to the fetus.

Oseltamivir and its active metabolites are excreted in human milk, and effects on nursing infants are unknown. Oseltamivir should be used during breastfeeding only if potential benefits to the mother outweigh potential risks to the baby.

Other conditions and allergies

The doctor and pharmacist should be informed of allergies to oseltamivir, any of its ingredients, or any other medications. The doctor should be informed if the patient has:

- previously used oseltamivir to treat or prevent flu
- fructose intolerance, since oseltamivir suspension is sweetened with sorbitol
- any condition that affects the immune system, such as HIV/AIDS, since oseltamivir effectiveness for flu prevention has not been established in immunocompromised patients
- heart, lung, or kidney disease, since oseltamivir effectiveness for influenza treatment has not been established in people with chronic cardiac and/or respiratory diseases

Side effects

Serious side effects from oseltamivir are rare. The doctor should be informed if any of the following side effects are severe or persistent:

- nausea
- vomiting
- stomach pain
- diarrhea
- headache

The doctor should be called immediately if any of the following serious side effects occur:

- psychiatric symptoms, which can affect adults as well as children and teens
- rash, hives, or blisters on the skin
- mouth sores
- itching
- swelling of the face or tongue
- difficulty breathing or swallowing
- hoarseness
- confusion
- speech problems
- shaky movements

Pediatric

The risks of very rare serious side effects from oseltamivir must be weighed against the risk of serious illness or death from flu. Serious psychiatric events have occurred in children and teens treated with oseltamivir.

Interactions

It is very important that the doctor and pharmacist be informed of any and all prescription and nonprescription

medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of all medications and supplements to every medical appointment and carry the list with them in case of emergency.

Drugs

Drugs that may require altering dosages or monitoring for side effects include:

- medications that affect the immune system, such as azathioprine
- cancer chemotherapy medications
- **cyclosporine**
- **methotrexate**
- sirolimus
- oral steroids such as dexamethasone, **methylprednisolone**, or **prednisone**
- **tacrolimus**

Oseltamivir may make intranasal flu vaccines less effective if taken up to 48 hours before or up to two weeks after the vaccine is administered. Oseltamivir does not replace the need for an annual flu vaccine.

Food and other substances

Oseltamivir can be taken with or without food, but it is less likely to cause stomach upset if taken with food or milk.

Resources

PERIODICALS

- Franklin, Jessica M., et al. "Equity in the Receipt of Oseltamivir in the United States During the H1N1 Pandemic." *American Journal of Public Health* 104, no. 6 (2014): 1052–58.
- Freemantle, Nick, et al. "Oseltamivir: The Real World Data." *British Medical Journal* 348, no. 7953 (2014): 22.
- Jefferson, Tom, et al. "Oseltamivir for Influenza in Adults and Children: Systematic Review of Clinical Study Reports and Summary of Regulatory Comments." *British Medical Journal* 348, no. 7953 (2014): 11.
- Mortada, Maya, Patricia Neuenschwander, and S. Sheiraz. "Influenza and Oseltamivir Phosphate (Tamiflu) in Infants: What You Need to Know." *Pediatric Nursing* 40, no. 1 (2014): 16–20.
- Nguyen-Van-Tam, Jonathan S., Peter J. M. Openshaw, and Karl G. Nicholson. "Antivirals for Influenza: Where Now for Clinical Practice and Pandemic Preparedness?" *Lancet* 384, no. 9941 (2014): 386–87.
- Uyeki, Timothy M. "Preventing and Controlling Influenza with Available Interventions." *New England Journal of Medicine* 370, no. 9 (2014): 789–91.

WEBSITES

- Centers for Disease Control and Prevention. "What You Should Know about Flu Antiviral Drugs." <http://www.cdc.gov/flu/antivirals/whatyoushould.htm> (accessed February 18, 2015).
- MedlinePlus. "Avian Influenza." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/ency/article/007263.htm> (accessed February 18, 2015).
- MedlinePlus. "Oseltamivir." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699040.html> (accessed February 18, 2015).
- "Oseltamivir Dosage." Drugs.com. <http://www.drugs.com/dosage/oseltamivir.html> (accessed February 18, 2015).
- U.S. Department of Health and Human Services. "Treatment." FLU.gov. <http://www.flu.gov/symptoms-treatment/treatment/index.html#antiviral-medications> (accessed February 18, 2015).
- U.S. Food and Drug Administration. "Tamiflu (Oseltamivir Phosphate) Information." <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107838.htm> (accessed February 18, 2015).
- Wolford, Ben. "Big Pharma Plays Hide-the-Ball with Data." *Newsweek*, November 13, 2014. <http://www.newsweek.com/2014/11/21/medical-science-has-data-problem-284066.html> (accessed February 18, 2015).
- World Health Organization. "Avian Influenza." http://www.who.int/mediacentre/factsheets/avian_influenza/en (accessed February 18, 2015).

ORGANIZATIONS

- American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, IL 60007-1098, (847) 434-4000, (847) 434-8000, info@healthychildren.org, <http://www.healthychildren.org/>.
- National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, MSC 9806, Bethesda, MD 20892-9806, (301) 496-5717, Fax: (301) 402-3573, (866) 284-4107, <http://www.niaid.nih.gov/>.
- U.S. Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30329, (800) CDC-INFO (232-4636), cdcinfo@cdc.gov, <http://www.cdc.gov/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.
- World Health Organization, Avenue Appia 20, Geneva 27, Switzerland 1211, +41 22 791 21 11, +41 22 791 31 11, info@who.int, <http://www.who.int/en>.

Margaret Alic, PhD

REVIEWED BY KEVIN GLAZA, RPh

Otrexup see **Methotrexate**

Oxcarbazepine

Definition

Oxcarbazepine belongs to the class of drugs known as anticonvulsants, which are used to treat seizure disorders. Oxcarbazepine, like other anticonvulsants, works to decrease abnormal neuronal electrical signaling in the brain.

Purpose

Oxcarbazepine is used to treat partial seizures, which arise from discrete portions of the brain and may cause involuntary movements of a discrete body part such as the fingers. When consciousness is maintained, the seizure is known as a simple partial seizure. When consciousness is lost, the seizure is a complex partial seizure. Oxcarbazepine is used to treat these types of partial seizures in both children and adults. It may be used as monotherapy or in combination with other antiseizure medications.

Description

Oxcarbazepine is an anticonvulsant medication that works by stabilizing abnormal electrical activity in the brain. Brain cells called neurons use electrical signals to communicate with each other as a part of normal functioning. The electrical signals are created through

the use of charged molecules called ions, such as sodium and chloride. The surfaces of neurons contain openings that conduct these ions called ion channels. Neurons propagate electrical signals by opening and closing ion channels on their respective surfaces as the signal travels from one neuron to the next. Seizure disorders are not fully understood, but they are known to involve abnormal electrical signaling among neurons. Anticonvulsants help control seizures by stabilizing both the rate and the amount of signaling that occurs. Oxcarbazepine helps by decreasing the amount of sodium signaling and propagation.

U.S. brand names

Oxcarbazepine is sold under the brand name Trileptal.

Recommended dosage

Oxcarbazepine is taken as an oral medication. The dosage used varies depending on the medical condition being treated, individual patient response to the medication regarding its effectiveness, and individual patient response to the medication regarding side effects. Some people naturally require a higher dose of oxcarbazepine in order to achieve the desired effect. Other patients require a lower dose either for effect or because they quickly develop side effects that are not tolerable.

Oxcarbazepine used for partial seizures as an adjunct treatment in combination with other anticonvulsants is usually dosed at 600 milligrams (mg) taken twice a day. Patients may start at 300 mg twice daily for the first week of treatment and gradually work their way up to the dose needed for effect. Oxcarbazepine used as monotherapy is started at the same low doses and gradually brought up to 1,200 mg twice a day over a time period of several weeks. Any previous adjunct medications are gradually decreased simultaneously. The maximum dose of oxcarbazepine used is 2,400 mg per day. Patients are dosed at the lowest possible effective dose to avoid the development of adverse side effects. Slowly increasing the dose helps with minimizing side effects, and some side effects lessen with continued use. Patients are periodically reassessed to determine whether there is need for continued treatment with oxcarbazepine. All anticonvulsants including oxcarbazepine need to be slowly tapered off if discontinued, to avoid a rebound seizure syndrome.

Pediatric

Children are given lower doses based on their weight, with the same regimen of gradually increasing dosages.



Oxcarbazepine, 600 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Ion—Charged molecule such as sodium or chloride used in neuronal signaling in the brain.

Ion channel—Physical opening on the surface of neurons that allows the passage of charged ions propagating neuronal signaling in the brain.

Monoamine oxidase inhibitors (MAOIs)—Type of antidepressant medication that affects various kinds of neurotransmitters.

Neuron—Nerve cells in the brain that produce nerve impulses.

Neuronal signaling—The pathway by which neurons communicate; can be electrical or chemical.

Seizure—A sudden attack, spasm, or convulsion.

Serotonin syndrome—A potentially life-threatening drug reaction involving an excess of the neurotransmitter serotonin, usually occurring when too many medications that increase serotonin are taken together.

Geriatric

Oxcarbazepine should be administered cautiously in elderly patients, who may require dosage adjustments due to coexisting health conditions.

Precautions

Kidney and liver function, as well as blood electrolytes and behavioral changes, may be monitored while taking oxcarbazepine. Oxcarbazepine may reduce the amount of sodium in the blood to dangerous levels. When a patient discontinues the use of oxcarbazepine, the dose needs to be tapered down slowly. If oxcarbazepine is abruptly discontinued without tapering, there may be an increase in the incidence of seizures.

Pregnant or breastfeeding

Oxcarbazepine is classified as category C for pregnancy, which means that either there are no adequate human or animal studies or that adverse fetal effects were found in animal studies but there is no available human data. The decision to use category C drugs in pregnancy is generally based on weighing the critical needs of the mother against the risk to the fetus. Other lower category agents are used whenever possible. Oxcarbazepine is also excreted into breast milk; the safety of use when breastfeeding is unknown and thus not recommended.

Other conditions and allergies

Oxcarbazepine may not be appropriate for use or may require caution in patients with dementia, depression, past suicide attempts, kidney dysfunction, dehydration, diarrhea, or electrolyte abnormalities.

Side effects

Sensitivity to oxcarbazepine varies among patients, and some patients may find that even lower doses are more than their body system can tolerate. Common side effects of oxcarbazepine include nausea; vomiting; abdominal pain; headache; dizziness; fatigue; drowsiness; confusion; nervousness; impaired concentration, speech, and coordination; vision and gait changes; tremor; electrolyte abnormalities; changes in liver enzymes; skin rash and acne; hair loss; and sensitivity to sunlight. Rare but serious potential side effects include severe and possibly dangerous electrolyte abnormalities; changes in various types of blood cells, including decrease in immune function and severe anemia; toxic and life-threatening skin reactions; severe allergic reactions; inflammation of the pancreas; and risk of suicide.

Interactions

Patients should make their doctor aware of all medications and supplements they are taking before using oxcarbazepine.

Drugs

Drugs that affect the liver may alter the metabolism of oxcarbazepine, resulting in too much or too little of the drug in the body. This could lead to increased side effects or even toxic doses. Likewise, oxcarbazepine may affect the metabolism of other drugs, leading to greater or lower doses of those drugs than therapeutically desired. For example, oxcarbazepine may lower levels of antiviral medications such as rilpivirine; other drugs on which oxcarbazepine has this effect are cholesterol medications such as **atorvastatin**, antibiotics such as **clarithromycin**, chemotherapeutics such as temsirolimus, and oral contraceptives. Individuals taking birth control pills should use a second form of protection when taking oxcarbazepine.

Oxcarbazepine should not be used at the same time as monoamine oxidase inhibitors (MAOIs), which are a class of antidepressant drugs. Use of these medications during the same period may cause a medical condition called serotonin syndrome, which can be severe and life-threatening. Symptoms may include high blood pressure, high fever, nausea, diarrhea, headache, sweating, increased heart rate, tremor, muscle twitching, delirium, shock, coma, and death. Switching between drug

treatment with an MAOI to oxcarbazepine may require a waiting period of up to several weeks between drugs. Other drugs that cannot be combined with oxcarbazepine due to risk of serotonin syndrome include the antibiotic **linezolid**.

Herbs and supplements

Oxcarbazepine should not be used with large doses of the herbal supplements ginkgo biloba or St. John's wort, as the combination may decrease the efficacy of oxcarbazepine and induce seizures. The herbal supplements evening primrose, valerian, and kava kava should also be avoided and may induce seizures.

Food and other substances

Using alcohol while taking oxcarbazepine may create toxic reactions in the body and should be avoided.

Resources

BOOKS

Brunton, Laurence, et al. *Goodman and Gilman's the Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill Medical, 2011.

PERIODICALS

- Kellinghaus, C., S. Berning, and F. Stögbauer. "Use of Oxcarbazepine for Treatment of Refractory Status Epilepticus." *Seizure* 23, no. 2 (2014): 151–54.
- Kim, D., et al. "Cognitive and Psychosocial Effects of Oxcarbazepine Monotherapy in Newly Diagnosed Partial Epilepsy." *Clinical Neuropharmacology* 37, no. 4 (2014): 100–107.
- Kim, S. M., et al. "Effect of Oxcarbazepine on Background EEG Activity and Cognition in Epilepsy." *Journal of Epilepsy Research* 3, no. 1 (2013): 7–15.

OTHER

Johns Hopkins. "Oxcarbazepine (Trileptal)." http://www.hopkinsmedicine.org/neurology_neurosurgery/centers_clinics/peripheral_nerve/patient_info/OXCARBAZEPINE_2007.pdf (accessed February 26, 2015).

WEBSITES

- Epilepsy Foundation. "Oxcarbazepine." <http://www.epilepsy.com/medications/oxcarbazepine> (accessed February 26, 2015).
- Micromedex. "Oxcarbazepine (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/oxcarbazepine-oral-route/description/drg-20067615> (accessed February 26, 2015).
- National Alliance on Mental Illness. "Oxcarbazepine (Trileptal)." [http://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Oxcarbazepine-\(Trileptal\)](http://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Oxcarbazepine-(Trileptal)) (accessed February 26, 2015).
- U.S. Food and Drug Administration. "Safety: Trileptal (Oxcarbazepine) Tablets and Oral Suspension." <http://www.fda.gov/safety/medwatch/safetyinformation/ucm342622.htm> (accessed February 26, 2015).

ORGANIZATIONS

- Epilepsy Foundation, 8301 Professional Place East, Suite 200, Landover, MD 20785-2353, (800) 332-1000, Contact Us@efa.org, <http://www.epilepsy.com/>.
- National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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REVIEWED BY KEVIN GLAZA, RPh

Oxybutynin

Definition

Oxybutynin chloride is a medication used to treat problems related to the bladder and frequent or uncontrolled urination. The drug, which is only available with a prescription, is in a class of medicines called antispasmodics or anticholinergics.



Oxybutynin chloride, 5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

A person with an overactive bladder may experience the need to urinate more urgently and more often than normal, and sometimes the bladder may leak urine. Drugs such as oxybutynin chloride can control bladder muscles and relieve some of these symptoms in people who have an overactive bladder. It may also help individuals who have problems controlling their bladder because of damage to nerves or disorders that affect the nerves that normally control bladder function.

Description

Oxybutynin chloride is often taken by mouth, as either a liquid syrup or a tablet. Some tablets come in extended-release, or long-acting, forms that only need to be taken once per day. A topical form of the drug is available as a gel that can be spread on the skin over the bladder area. The topical form also comes in a transdermal patch.

U.S. brand names

In the United States, oxybutynin chloride is sold under the brand name Ditropan. It also is sold as Ditropan XL for the extended-release form. The topical gels are sold as Gelnique and Gelnique 3%.

Recommended dosage

Adults who take oxybutynin chloride for urinary frequency or incontinence usually begin with a dose of 5 milligrams (mg) of syrup or tablets two to three times a day by mouth. For the extended-release tablets, one 5 mg or 10 mg tablet may be taken each day. Doses can be increased if not effective but should not exceed 30 mg per day. Three pumps of the gel is applied for a total of 84 mg of oxybutynin chloride once per day; it may be applied to the skin of the stomach, upper arms, and shoulders or thighs.

Pediatric

Children between ages one and five can take 0.2 mg per kilogram (kg, or 2.2. lb.) of their body weight of oral oxybutynin chloride, usually in liquid syrup form, two to four times per day. Children older than age five take 5 mg twice or three times each day. Children older than age six may take the 5 mg extended-release tablet once per day.

Precautions

Some people react to oxybutynin chloride with a swelling called angioedema that occurs under the skin's surface. Use of oxybutynin chloride can cause some people to retain too much urine, which can lead to

KEY TERMS

Anticholinergic—A class of drugs that affect nerve impulses of a type of parasympathetic nerves, which are involuntary nerves that control the function of organs such as the bladder.

Antispasmodic—Drugs that prevent or stop spasms, or the involuntary tightening and movement of muscles.

Topical—Refers to drugs that act or work by being applied to the surface of the body, such as being spread on the skin.

Urinary incontinence—The loss of bladder control, usually with symptoms that vary from minor leaking to wetting that cannot be controlled.

infection. Some people who use oxybutynin chloride experience sleepiness and should use caution driving or operating heavy machinery until they know how the medicine affects them. It can be difficult to cool the body when using oxybutynin gel, and extreme heat should be avoided.

Pediatric

The topical, or gel, form of oxybutynin chloride has not been tested in children and should not be used to help children who have bladder control problems. Only children who can swallow the extended-release tablet whole should take it.

Pregnant or breastfeeding

Oxybutynin chloride is a pregnancy category B drug. No adequate studies have been done in women, and those who are pregnant should only take the drug if the potential benefit outweighs possible risk to the unborn child. It is not known whether oxybutynin chloride is passed from a nursing mother to her infant, so women who are breastfeeding should use the medicine with caution. Some of the effects on the gastrointestinal, or digestive, system can be a particular problem in people who have conditions such as gastroesophageal reflux disease.

Side effects

Oxybutynin chloride can cause side effects, including:

- dryness of the mouth, eyes, nose, or skin
- constipation and stomach pain

- diarrhea and nausea
- blurry vision
- dizziness and confusion
- gas and heartburn
- headache
- sleepiness
- nervousness
- back and joint pain
- swelling of hands, arms, or lower legs and feet

Some side effects can be severe and should be reported to a doctor immediately. These include:

- rash and hives
- swelling in the face and mouth area
- problems with breathing or swallowing
- rapid or irregular heartbeat
- frequent and painful urination

In addition to these side effects, use of topical oxybutynin chloride can cause a rash or redness and swelling on the skin where applied.

Interactions

Some drugs and other substances can cause interactions with oxybutynin chloride that either decrease the drug's effectiveness or increase unwanted side effects. It is important to tell the doctor about all drugs, herbal remedies, and supplements being taken before using oxybutynin chloride.

Drugs

Use of oxybutynin chloride along with other anticholinergic drugs can increase side effects of both drugs. Oxybutynin may also adversely interact with certain drugs used to treat Alzheimer's disease.

Food and other substances

Drinking alcohol can intensify side effects such as drowsiness.

Resources

PERIODICALS

Marinkovich, Serge P., et al. "The Management of Overactive Bladder Syndrome." *British Medical Journal* 344 (2012): 1–7.

Wood, Lauren N., and Jennifer T. Anger. "Urinary Incontinence in Women." *British Medical Journal* 349 (2014): g4531.

OTHER

Janssen Pharmaceuticals Inc. "Prescribing Information: Ditropan XL." <http://www.janssenpharmaceuticalsinc.com/assets/ditropanxl.pdf> (accessed February 19, 2015).

WEBSITES

Actavis. "Gelnique 3%." Gelnique.com. <http://www.gelnique.com/> (accessed February 19, 2015).

"Ditropan XL." Rxlist.com. <http://www.rxlist.com/ditropan-xl-drug.htm> (accessed February 19, 2015).

MedlinePlus. "Oxybutynin." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682141.html> (accessed February 19, 2015).

MedlinePlus. "Oxybutynin Topical." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a613027.html> (accessed February 19, 2015).

"Oxybutynin." Drugs.com. <http://www.drugs.com/oxybutynin.html> (accessed February 19, 2015).

ORGANIZATIONS

American Geriatrics Society, 40 Fulton Street, 18th Floor, New York, NY 10038, (212) 308-1414, Fax: (212) 832-8646, info.amger@americangeriatrics.org, <http://www.americangeriatrics.org/>.

Urology Care Foundation, 1000 Corporate Boulevard, Linthicum, MD 21090, 410-689-3700/410-689-3998/800-828-7866, info@urologycafoundation.org, <http://www.urologyhealth.org/>.

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Oxycodone

Definition

Oxycodone is a semisynthetic narcotic analgesic. It is marketed alone and in combination with non-narcotic analgesics such as **aspirin** and acetaminophen. The drug is intended for control of acute and chronic moderate to severe pain where use of an opioid is indicated. The drug is available in short-acting and sustained-action dosage forms.

Purpose

Oxycodone is used in control of acute and chronic moderate to severe pain. Although it is most often discussed in terms of cancer pain, the drug has also been effective in treating pain from other causes including post-operative pain and dental pain.

Oxycodone is commonly used in combination with non-narcotic analgesics. One study showed that the combination of oxycodone with acetaminophen was as



Oxycontin, 60 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

effective as a higher dose of oxycodone alone. Another study reported that combination oxycodone with **ibuprofen** extended the duration of action of pain relief beyond that of oxycodone alone. At the same time, it is important to consider the toxicity of the non-narcotic components of these combinations.

Off-label use

Although oxycodone and other narcotic analgesics have been widely used for control of other pain syndromes, the Cochrane Collaboration performed a meta-analysis of published studies in which oxycodone was used for neuropathic pain. They concluded that “no convincing, unbiased evidence suggests that oxycodone (as oxycodone CR) is of value in treating people with painful diabetic neuropathy or postherpetic neuralgia. There is no evidence at all for other neuropathic pain conditions, or for fibromyalgia. Adverse events typical of opioids appear to be common.”

Description

Generic oxycodone is available as a 5-milligram (mg) capsule, a solution containing 5 mg per 5 milliliters (mL), and a concentrate containing 100 mg/5 mL. The concentrate has a very high potency and must be measured with extreme care; it should only be used in patients with existing opioid tolerance.

Oxycodone is classified as a Schedule II drug by the U.S. Drug Enforcement Administration (DEA). Schedule II

drugs carry some approved medical uses but have a very high potential for abuse and dependence. Use of oxycodone extended-release products must meet certain requirements outlined by the U.S. Food and Drug Administration’s (FDA) Risk Evaluation and Mitigation Strategy (REMS). This helps manage known or potential serious risks associated with a drug product and ensures that the benefits of a drug outweigh its risks. Healthcare providers who prescribe oxycodone and similar drugs should take an approved continuing education course for their specialty.

U.S. brand names

Because of oxycodone’s high abuse potential, it is sold as a sustained-release abuse-deterrent tablet in 10 mg, 15 mg, 20 mg, 40 mg, 60 mg, and 80 mg strengths. The estimated duration of action is 12 hours. The abuse-deterrent formulation utilizes an outer coating that is difficult to crack, cut, or break. It resists attempts to dissolve the tablet, forming a thick, sticky gel that cannot be injected. A second form of oxycodone using abuse-deterrent technology will be sold under the brand name Aversion by Acura Pharmaceuticals. This product was formerly sold as Oxecta by Pfizer.

Oxycodone combined with acetaminophen is sold under various brand names including Endocet, Magnacet, Percocet, and Roxicet, as well as a generic formulation. The available formulations contain 325 mg of acetaminophen and 2.5 mg, 5 mg, 7.5 mg, or 10 mg of oxycodone.

Oxycodone with aspirin is available as Endodan, Percodan, and as a generic formulation. All products contain 325 mg of aspirin and 4.835 mg of oxycodone.

Oxycodone with ibuprofen is sold under the brand name Combunox. Each tablet contains 400 mg of ibuprofen and 5 mg of oxycodone.

Recommended dosage

Dosing of oxycodone is subject to a number of considerations. For treatment of patients who are not already on opioid therapy, 5–15 mg may be administered every four to six hours as needed for pain. For control of chronic pain, dosing may start at the lowest level needed to achieve acceptable results on a regularly scheduled basis (every four to six hours) to prevent the reoccurrence of pain.

Dosing varies for patients already receiving narcotic analgesics. Dosage must be adjusted to avoid the risk of dependence and to reduce the number of adverse effects.

Pediatric

There is no approved pediatric indication for oxycodone, though physicians experienced with the drug may choose to use it off label.

KEY TERMS

Analgesic—A drug that relieves pain.

Dependence—A state in which a person requires a steady concentration of a particular substance to avoid experiencing withdrawal symptoms.

Drug schedule—A method of classifying drugs, including narcotics, sedatives, hallucinogens, and other drugs that are restricted under federal and state laws in the United States. Schedule I substances have no approved medical use, while Schedules II, III, and IV have approved uses. The higher the schedule, the lower the degree of restriction.

Hypoventilation—Reduced ventilation in the air sacs in the lungs, resulting in above-normal carbon dioxide pressure.

Ibuprofen—A nonsteroidal anti-inflammatory drug that may be used to relieve mild to moderate pain and reduce fever. Common brand names are Advil and Motrin.

Narcotic—A drug that reduces pain and induces sleep. The term is usually applied to opium derivatives, but in modern use has been expanded to include other controlled substances such as cocaine and marijuana.

Off label—Use of a drug in a dose, or for a purpose that has not been specifically approved by the U.S. Food and Drug Administration (FDA). The off-label use of drugs may be necessary when insufficient information has been submitted for formal FDA approval, but there is strong evidence in the medical literature and/or in professional practice that the drug is safe and effective for the purpose intended.

Opioid—A narcotic derived from the naturally occurring substances found in opium, including but not limited to morphine and codeine. Also refers to the compounds that have been developed based on the chemical structures of naturally occurring narcotics.

Palpitations—Having an unpleasant awareness of your own heartbeat. The heartbeat may be completely normal or may be abnormal.

Respiratory—Breathing. Respiratory depression is weak, shallow breathing. Respiratory arrest is stopping breathing.

Semisynthetic—A drug that is derived from a natural substance but is chemically modified to alter certain properties, such as to make the drug more effective or safer.

Other conditions and allergies

For patients with impaired liver function, dosing should be administered at one-third to one-half of the normal dose to avoid toxicity. The lowest possible dose needed to obtain results should be used.

Precautions

Oxycodone carries a boxed warning, which is the most severe warning required by the FDA. Individuals most at risk for opioid abuse include those with a history of substance abuse (including family history) or mental disorders (including depression). All patients should be monitored during treatment for signs of misuse or abuse.

Hypoventilation (respiratory depression) can occur with oxycodone use, and the drug should only be administered by experienced healthcare providers. The risk is highest at the start of treatment or after a dose increase.

If tablets are used, they should be swallowed whole and never crushed, dissolved, or chewed. This can cause too much of the drug to be released at once, resulting in a potentially fatal overdose.

Geriatric

Elderly patients are at increased risk of experiencing respiratory depression when using oxycodone.

Pregnant or nursing

Oxycodone is in pregnancy category B, which means that animal studies have failed to demonstrate a risk to the fetus but no well-controlled studies in pregnant women are available. As a precaution, oxycodone should only be used when benefits outweigh the potential risks.

Oxycodone is excreted in human breast milk, and withdrawal symptoms have been noted in nursing infants of mothers who abruptly stopped using opioid analgesics. Infants of mothers taking oxycodone should not be breastfed, and nursing mothers should not be prescribed oxycodone.

Other conditions and allergies

Individuals with breathing problems, such as asthma or chronic obstructive pulmonary disorder (COPD), are at increased risk of experiencing respiratory depression.

Side effects

The following side effects apply only to oxycodone. In fixed-combination formulas, additional adverse effects may be caused by the additional ingredients. Side effects may include:

- agitation
- cardiac arrest
- chest pain
- coma
- dizziness
- dry mouth
- dysphoria (feelings of depression or anxiety)
- euphoria (an exaggerated sense of elation)
- fainting or faintness
- heartbeat abnormalities
- heart attack
- itching
- mental clouding/depression
- nausea
- nervousness
- respiratory/circulatory depression
- respiratory arrest
- restlessness
- sedation
- seizures
- shock
- sweating, flushing, or warmth of face/neck/chest
- urine retention
- vision disturbances
- vomiting
- weakness

Interactions

Oxycodone interacts with many drugs that produce similar effects or have similar side effects. If these drugs are used with oxycodone, the effects are multiplied.

Drugs

SEDATION. All narcotic analgesics make people feel sleepy. When they are used at the same time as other drugs with a similar effect, the combined effect may cause extreme impairment. Drugs that have this effect are tranquilizers, antidepressants, antianxiety drugs, and older antihistamines.

Patients using over-the-counter cold remedies should avoid products that contain doxylamine (Ny-Quil), **diphenhydramine** (Benadryl), and chlorpheniramine.

Individuals should consult with their doctor or pharmacist on appropriate alternative treatments.

RESPIRATORY DEPRESSION. Oxycodone and other narcotic analgesics impair breathing. This is seen most often in elderly individuals but also in people with breathing problems such as asthma and chronic pulmonary obstructive disease (COPD). Benzodiazepine drugs such as **diazepam** (Valium), **alprazolam** (Xanax), and others also inhibit breathing, and the use of any of these drugs with oxycodone can cause severe problems. Drugs in this class carry a wide range of uses, including to treat anxiety or convulsions. They are also used as muscle relaxants and as sedatives before some surgical procedures.

METABOLISM. Oxycodone is eliminated from the body after being metabolized in the liver. An enzyme called CYP3A4 assists in this metabolism, and many other drugs can either increase or decrease the levels of this enzyme. Drugs that are CYP3A4 inducers speed the elimination of oxycodone from the body, reducing its effectiveness. CYP3A4 inhibitors stop the elimination of oxycodone, which can lead to a toxic build-up of the narcotic in the body.

- **Carbamazepine** and phenytoin—used to control seizures—are CYP3A4 inducers. These drugs will reduce the effects of oxycodone. In patients who have become dependent on the narcotic, use of these drugs may cause withdrawal syndrome.
- **Ketoconazole** is an antifungal and CYP3A4 inhibitor. In one study, patients treated with ketoconazole and oxycodone showed three times the normal blood levels of oxycodone. Other antifungal drugs have similar effects.
- Drugs used to treat human immunodeficiency virus (HIV) and other antiretroviral drugs may be either inhibitors or inducers of CYP3A4. This applies even to drugs with similar therapeutic actions.
- **Erythromycin** and other related antibiotics may inhibit CYP3A4 and increase the duration of narcotic effects.

There are many other drugs that affect the levels of CYP3A4, as well as some natural products. Patients should inform their healthcare providers of all medications they are currently taking, including over-the-counter drugs and herbal or dietary supplements.

Food and other substances

Alcohol should be avoided while taking oxycodone.

Resources

PERIODICALS

Chaparro, L. E., et al. "Opioids Compared with Placebo or Other Treatments for Chronic Low Back Pain: An Update of the Cochrane Review." *Spine* 39, no. 7 (2014): 556–63.

- Derry, S., C. J. Derry, and R. A. Moore. "Single Dose Oral Ibuprofen plus Oxycodone for Acute Postoperative Pain in Adults." *Cochrane Database of Systematic Reviews* 6, art. no. CD010289 (June 26, 2013). <http://dx.doi.org/10.1002/14651858.CD010289.pub2> (accessed February 11, 2015).
- Duh, M. S., et al. "Risk of Hepatotoxicity-Related Hospitalizations Among Patients Treated with Opioid/Acetaminophen Combination Prescription Pain Medications." *Pain Medicine* 11, no. 11 (2010): 1718–25.
- Fanelli, G., P. Cherubino, and C. Compagnone. "Opioid Use for Chronic Pain Management in Italy: Results from the Orthopedic Instant Pain Survey Project." *Orthopedic Reviews* 6, no. 2 (2014): 5309.
- Manchikanti, L., et al. "Opioid Epidemic in the United States." *Pain Physician* 15, suppl. 3 (2012): ES9–38.
- Gaskell, H., et al. "Oxycodone for Neuropathic Pain and Fibromyalgia in Adults." *Cochrane Database of Systematic Reviews* 6, art. no. CD010692 (June 23, 2014). <http://dx.doi.org/10.1002/14651858.CD010692.pub2> (accessed February 11, 2015).
- Gatti, A., et al. "Oxycodone/Paracetamol: A Low-Dose Synergic Combination Useful in Different Types of Pain." *Clinical Drug Investigation* 30, suppl. 2 (2010): 3–14.
- Kummer, O., et al. "Effect of the Inhibition of CYP3A4 or CYP2D6 on the Pharmacokinetics and Pharmacodynamics of Oxycodone." *European Journal of Clinical Pharmacology* 67, no. 1 (2011): 63–71.

WEBSITES

- Faragon, John, and Francine Cournos. "Opioid Pain and Addiction Management Medications–Drug Interactions with HIV Antiretrovirals." New York and New Jersey AIDS Education and Training Center. http://www.nynjaetc.org/documents/PainMgmt2013_000.pdf (accessed February 11, 2015).

WEBSITES

- Mayo Clinic staff. "Oxycodone (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/oxycodone-oral-route/description/drg-20074193> (accessed February 7, 2015).
- MedlinePlus. "Oxycodone." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682132.html> (accessed February 7, 2015).
- U.S. Drug Enforcement Administration. "Drug Scheduling." <http://www.dea.gov/druginfo/ds.shtml> (accessed February 11, 2015).
- U.S. Food and Drug Administration. "FDA Approves Abuse-Deterrent Labeling for Reformulated OxyContin," April 16, 2013. <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm348252.htm> (accessed February 11, 2015).
- U.S. Food and Drug Administration. "FDA Approves New Extended-Release Oxycodone with Abuse-Deterrent Properties," July 23, 2014. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm406407.htm> (accessed February 11, 2015).

- U.S. Food and Drug Administration. "List of Extended-Release and Long-Acting Opioid Products Required to Have an Opioid REMS." <http://www.fda.gov/drugs/drugsafety/Informationbydrugclass/ucm251735.htm> (accessed February 7, 2015).

- U.S. Food and Drug Administration. "Oxycodone (Marketed as OxyContin) Information." <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm207173.htm> (accessed February 11, 2015).

- U.S. Food and Drug Administration. "Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release and Long-Acting Opioids." <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm> (accessed February 11, 2015).

ORGANIZATIONS

- American Academy of Pain Management, 975 Morning Star Drive, Suite A, Sonoma, CA 95370, (209) 533-9744, info@aapainmanage.org, <http://www.aapainmanage.org/>.
- Canadian Pain Society, 250 Consumers Road, Suite 301, Toronto, Ontario M2J 4V6, (416) 642-6379, Fax: (416) 495-8723, office@canadianpainsociety.ca, <http://www.canadianpain.society.ca/>.

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Oxycodone/acetaminophen

Definition

Oxycodone/acetaminophen is a prescription-only medication that combines acetaminophen, a nonprescription painkiller (analgesic), and **oxycodone**, an opioid analgesic.

Purpose

Oxycodone/acetaminophen is used to treat moderate to moderately severe pain. The extended-release formulation is intended for the treatment of acute pain for which other types of pain medications are inadequate.

Description

Oxycodone/acetaminophen is available as oval or round tablets in blue, white, orange, yellow, and beige, scored or non-scored; and as red or red-and-white capsules. The imprints on tablets or printing on capsules varies depending on the manufacturer.

Tablets are available in a variety of combinations, including:

- 2.5 milligrams (mg) of oxycodone combined with 325 mg of acetaminophen



Endocet (oxycodone/acetaminophen, 10 mg /325 mg).

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- 5 mg of oxycodone combined with 325 mg of acetaminophen
- 7.5 mg of oxycodone combined with 325 mg of acetaminophen
- 7.5 mg of oxycodone combined with 500 mg of acetaminophen
- 10 mg of oxycodone combined with 325 mg of acetaminophen
- 10 mg of oxycodone combined with 650 mg of acetaminophen

Capsules supply 5 mg of oxycodone hydrochloride combined with 500 mg of acetaminophen.

Liquid formulations provide 5 mg of oxycodone and 325 mg of acetaminophen for every 5 milliliters (mL) of medication.

Due to the presence of oxycodone, oxycodone/acetaminophen combinations are all classified by the U.S. Drug Enforcement Administration (DEA) as Schedule II drugs. This means that these medications:

- are medically accepted as therapeutic agents
- carry a high potential for abuse (although less so than Schedule I drugs)
- carry a high potential of initiating severe psychological or physical dependence
- possess a side effect profile that is potentially dangerous

U.S. brand names

Oxycodone/acetaminophen is sold in the United States under the brand names Endocet, Percocet, Primlev, Roxicet, Xartemis XR, and Xolox [DSC].

Canadian brand names

Oxycodone/acetaminophen is sold in Canada under the brand names Apo-Oxycodone/Acet, Endocet, Percocet, Percocet-Demi, PMS-Oxycodone-Acetaminophen, Ratio-Oxycocet, Rivacocet, and Sandoz-Oxycodone/Acetaminophen.

International brand names

Oxycodone/acetaminophen is sold under a variety of brand names internationally, including Tailening (China), Targin (Australia, Austria, Switzerland, Germany, Italy, Denmark, Israel), and Targinact (Estonia, France, United Kingdom).

Recommended dosage

The recommended dosages for the treatment of adults with oxycodone/acetaminophen are as follows:

- For treating acute pain using the extended-release formulation, the recommended dosage is two tablets every 12 hours. The maximum dose must not be greater than 4 grams (g) acetaminophen per day.
- For pain management using the immediate-release formulation, the recommended dosage is 2.5–10 mg of oxycodone every 6 hours. The maximum dose must not be greater than 4 g acetaminophen per day.

Pediatric

Pediatric patients are dosed with oxycodone at 0.1–0.2 mg per kilogram (kg, or 2.2 lb.) of body weight every 4–6 hours. The maximum dose must not be greater than 90 mg/kg/day of acetaminophen in children under 99 lb. (45 kg). In children over 99 lb. (45 kg), the maximum dose of acetaminophen must not be greater than 4 g per day.

Geriatric

Elderly individuals can receive the same dose as other adults, although care should be taken to monitor closely for side effects, and dosages should be titrated downward accordingly.

Other conditions and allergies

For individuals with kidney or liver impairment, the dosage of the extended-release form should be decreased to one tablet every 12 hours.

KEY TERMS

Analgesic—A drug used to control pain.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Narcotics—A class of chemicals that contain opium or opium derivatives. These drugs decrease pain, often cause drowsiness, may induce a sense of euphoria or well-being, and have profound side effects that include respiratory depression in overdoses and addictive potential.

Opioid—A substance that resembles opium and binds to the same types of receptors in the body, producing similar effects in pain relief, pleasure, and addictiveness. These substances do not actually contain opium, but are synthetically produced to mimic its therapeutic benefits.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

Precautions

Several boxed warnings are included with this product.

- A boxed warning is included with this product regarding the risk of using acetaminophen, which has the potential to damage the liver, usually due to overdose of the product. Overdose has sometimes occurred unintentionally, when more than one acetaminophen-containing product has been taken concurrently. Acute liver failure may result in the need for a liver transplant, or death.
- A boxed warning is included with this product regarding oxycodone's potential for life-threatening respiratory depression. Particular care should be taken with patients who have demonstrated a previous intolerance to opioid pain medications. Additionally, using more than one type of medication that has the potential for respiratory depression can greatly increase the threat of respiratory failure. These effects are also increased in the elderly, debilitated patients, and individuals with pre-existing respiratory conditions.
- A boxed warning is included with this product regarding the serious consequences of accidental ingestion.

- A boxed warning is included with this product regarding the risk for misuse, abuse, addiction, and overdose.

Because of oxycodone/acetaminophen's addictive potential, sudden discontinuation after long-term use of the drug can lead to symptoms of withdrawal, including nausea, vomiting, diarrhea, teary eyes, runny nose, severe sweating, itchy skin, twitchy muscles, and uncontrollable yawning.

Additional precautions include:

- Oxycodone/acetaminophen should not be used in patients who are acutely intoxicated with ethanol, hypnotics, centrally acting analgesics, opioids, or psychotropic drugs.
- Oxycodone/acetaminophen can cause drowsiness and can impair physical abilities, as well as mental processing and alertness.
- Oxycodone/acetaminophen can cause severe constipation, which can be particularly problematic for individuals with unstable angina or who have recently had a heart attack.
- Oxycodone/acetaminophen has been associated with severe skin reactions, including pustules, blistering, and peeling. The presence of a rash should prompt discontinuation of the drug.
- Oxycodone/acetaminophen can cause low blood pressure, especially in individuals who are dehydrated or who have cardiovascular conditions.
- Postanesthesia patients with slowed bowel motility may be at particular risk for complications from the constipating effects of oxycodone/acetaminophen.

Geriatric

Elderly and debilitated patients are at particular risk of complications from oxycodone/acetaminophen use, especially effects on the central nervous system, respiratory system, and constipating effects. Oxycodone/acetaminophen should be used with extreme caution and close monitoring in this population.

Pregnant or breastfeeding

Oxycodone/acetaminophen is a pregnancy category C drug, meaning that risk to the fetus cannot be ruled out in pregnant individuals. If possible, use of this drug should be avoided. Babies who have been acutely exposed to oxycodone/acetaminophen before birth may be born with decreased respiratory drive and a weak suck. A boxed warning is included with this product regarding the risk of neonatal abstinence syndrome (withdrawal) occurring in babies who have been exposed to oxycodone in utero. Babies who have been exposed to

oxycodone/acetaminophen chronically before birth may experience withdrawal symptoms after birth when they are no longer receiving oxycodone/acetaminophen through the placenta. These babies may require treatment to avoid severe symptoms.

Oxycodone/acetaminophen is known to pass into breast milk. It should be avoided by breastfeeding women.

Other conditions and allergies

Oxycodone/acetaminophen should be avoided or carefully monitored in people with specific conditions, including:

- adrenal problems (may be exacerbated with oxycodone/acetaminophen use, leading to symptoms such as sexual problems, problems with fertility, mood issues, and weak bones)
- history of substance abuse or alcoholism (due to drug's addictive potential)
- gallbladder problems (may cause spasms in one of the gallbladder valves, resulting in severe pain)
- head injury (may complicate the assessment and course of traumatic brain injuries and other causes of brain swelling or affect respiratory function if used in the setting of head injury or coma)
- severe respiratory problems, including asthma (unless patient is mechanically ventilated)
- functional bowel obstruction
- alcohol use
- morbid obesity
- prostate disease
- psychoses
- seizure disorders
- narrowing in the gastrointestinal tract
- liver or kidney disease
- suicidality

Oxycodone/acetaminophen should not be given to individuals with a known sensitivity to oxycodone, acetaminophen, opiate or opioid drugs, or other ingredients within a specific delivery formulation. It should be used with caution in individuals who have had previous reactions to opiates or opioids.

Side effects

The most common side effects of oxycodone/acetaminophen treatment include:

- flushing
- headache, drowsiness, confusion, unclear thinking, depression

- sweating, itching
- dehydration
- constipation
- dry mouth
- urinary retention
- weak muscles
- shortness of breath, respiratory depression
- euphoria
- agitation, hallucinations
- upset stomach, nausea, vomiting
- laboratory evidence of liver damage

Rare but serious signs of a significant allergic reaction to oxycodone/acetaminophen should prompt the individual to seek immediate medical care. These include:

- difficulty breathing or swallowing
- hoarse voice
- wheezing, shortness of breath, cough
- fever
- pain in the abdomen
- blue skin or lips
- yellow cast to the skin or the whites of the eyes
- headache
- stiff neck
- confusion
- seizures
- swollen face, lips, tongue, or throat
- rash, hives, blisters, or peeling skin
- dizziness

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

The following may increase oxycodone/acetaminophen's side effects:

- alpha- and beta-agonists
- opioid analgesics
- amphetamines
- anticholinergic agents
- antiemetics

- **aripiprazole**
- antipsychotic agents
- cannabis
- crizotinib
- droperidol
- hydrocodone
- **hydroxyzine**
- magnesium sulfate
- methotrimeprazine
- mifepristone
- **zolpidem**

Drugs classified as CYP3A4 inhibitors have a profound effect on oxycodone/acetaminophen, and may greatly increase the risk of potentially fatal side effects. There are many drugs in this group, including:

- amiodarone
- anastrozole
- **azithromycin**
- cannabinoids
- cimetidine
- **clarithromycin**
- clotrimazole
- **cyclosporine**
- danazol
- delavirdine
- dexamethasone
- diethyldithiocarbamate
- **diltiazem**
- disulfiram
- entacapone
- **erythromycin**
- ethinyl estradiol
- **fluconazole**
- **fluoxetine**
- **fluvoxamine**
- gestodene
- indinavir
- isoniazid
- **ketoconazole**
- **metronidazole**
- mibefradil
- miconazole
- nefazodone
- nelfinavir
- nevirapine
- norfloxacin
- norfluoxetine
- **omeprazole**
- oxiconazole
- **paroxetine**
- propoxyphene
- quinidine
- quinine
- **ranitidine**
- ritonavir
- saquinavir
- sertindole
- **sertraline**
- troglitazone
- troleandomycin
- **valproic acid**

Oxycodone/acetaminophen may increase the side effects of the following:

- opioid analgesics
- antiemetics (antinausea drugs)
- antipsychotic agents
- beta-blockers
- buprenorphine
- calcium channel blockers
- desmopressin
- diuretics
- hydrocodone
- hydroxyzine
- monoamine oxidase inhibitors (MAOIs)
- methotrimeprazine
- **metoclopramide**

Herbs and supplements

Kava kava may increase the side effects of oxycodone/acetaminophen, and oxycodone/acetaminophen may increase the side effects of kava kava.

Food and other substances

Alcohol may increase the side effects of oxycodone/acetaminophen, and oxycodone/acetaminophen may increase the side effects of alcohol.

Resources

BOOKS

- Aronson, J. K. *Meyler's Side Effects of Analgesics and Anti-inflammatory Drugs*. Oxford: Elsevier, 2010.
- Benzon, Honorio T. *Essentials of Pain Medicine*. 3rd ed. Philadelphia: Saunders, 2011.

Smith, Howard S. *Current Therapy in Pain*. Philadelphia: Saunders, 2009.

Waldman, Steven D. *Pain Management*. 2nd ed. Philadelphia: Saunders, 2011.

WEBSITES

"Acetaminophen." Drugs.com. <http://www.drugs.com/acetaminophen.html> (accessed March 6, 2015).

MedlinePlus. "Acetaminophen." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a681004.html> (accessed March 3, 2015).

MedlinePlus. "Oxycodone." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682132.html> (accessed March 6, 2015).

"Oxycodone." Drugs.com. <http://www.drugs.com/mtm/oxycodone.html> (accessed March 6, 2015).

U.S. National Library of Medicine. "LactMed: Acetaminophen." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+330> (accessed March 6, 2015).

U.S. National Library of Medicine. "LactMed: Oxycodone." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?>

[dbs+lactmed:@term+@DOCNO+378](#) (accessed March 6, 2015).

ORGANIZATIONS

American Chronic Pain Association, PO Box 850, Rocklin, CA 95677, (800) 533-3231, APAC@theacpa.org, <http://www.theacpa.org/>.

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

National Pain Foundation, 14828 W 6 Avenue, Suite 16-B, Room 1, Golden, CO 80401-5000, (720) 541-6808, (720) 541-6809, <http://www.thenationalpainfoundation.org/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rosalyn S. Carson-DeWitt, MD

REVIEWED BY CHRISTY McDONALD LENAHA, DNP, MSN, APRN, FNP-BC

Oxycontin see **Oxycodone**

P

Paliperidone

Definition

Paliperidone is a medication used in the treatment of the psychiatric diseases schizophrenia and schizoaffective disorder. Paliperidone belongs to a class of drugs known as atypical antipsychotics, which specifically act on two natural body chemicals, serotonin and dopamine. These chemicals are types of neurotransmitters involved in normal brain function and can affect the psychosis and other symptoms of schizophrenia and schizoaffective disorder. Paliperidone acts as a neurotransmitter blocker, inhibiting the effects of serotonin and dopamine.

Purpose

Paliperidone is a type of drug known as an atypical antipsychotic; atypical antipsychotics are thought to have fewer adverse side effects than older antipsychotic drugs. The decision to use paliperidone alone or in combination with other drugs depends on the particular medical disorder, the response of the patient to the medication, and individual health parameters.

Description

Paliperidone works by inhibiting the absorption of the neurotransmitters serotonin and norepinephrine. Specifically, paliperidone blocks the signaling of these neurotransmitters in the brain by binding their corresponding neurotransmitter receptors. The pathology of schizophrenia is thought to involve the overactivity of neurotransmitter signaling in some areas of the brain and underactivity in others; antipsychotics such as paliperidone help address the deficits but do not completely treat the disorder. The symptoms of schizophrenia known as positive symptoms, such as psychosis, are best treated with paliperidone. The negative and cognitive symptoms such as withdrawal and difficulty reasoning are not as well addressed with paliperidone, but paliperidone has more impact on these types of symptoms than older

antipsychotics. Paliperidone is also effective in treating mania, which is a mixed state of mood elevation and depression.

U.S. brand names

Paliperidone is sold under the brand name Invega.

Recommended dosage

Paliperidone is taken as an oral medication. The available doses are 1.5, 3, 6, and 9 milligram (mg) pills. The 9 mg dose is an extended-release formulation. Patients being treated for schizophrenia are usually started at 6 mg, taken in the morning. The dose is gradually increased to the most effective dose that does not cause intolerable side effects. The daily dose may be



Invega ER (paliperidone extended release), 9 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Atypical antipsychotics—A group of medications for the treatment of psychotic symptoms that were introduced in the 1990s. They are sometimes called serotonin dopamine antagonists (SDAs).

Cognitive—Associated with thinking, learning, perception, awareness, and judgment.

Dopamine—A type of neurotransmitter involved in regulation of concentration, impulse control, judgment, mood, attention span, psychostimulation, and disease states such as addiction and depression.

Mania—Physiological state of hyperactivity experienced by patients with certain psychiatric illnesses involving inappropriate elevated mood, pressured speech, poor judgment, and sometimes psychotic episodes.

Negative symptoms—Symptoms of schizophrenia characterized by the absence or elimination of certain behaviors, such as initiative, speech, or affect.

Neuroleptic malignant syndrome—Dangerous reaction to antipsychotic medications that involves temperature instability, muscular rigidity, and altered mental status.

Neuronal signaling—The electrical or chemical pathway by which neurons communicate.

Neurotransmitter—One of a group of chemicals secreted by a nerve cell (neuron) to carry a chemical

message to another nerve cell, often as a way of transmitting a nerve impulse. Examples of neurotransmitters include acetylcholine, dopamine, serotonin, and norepinephrine.

Neurotransmitter receptor—A physical recipient for chemicals called neurotransmitters. Receptors sit on the surface of cells that make up body tissues, and once bound to the neurotransmitter, they initiate the chemical signaling pathway associated with neurotransmitters.

Positive symptoms—Symptoms that are characterized by the production or presence of abnormal or excessive behaviors, including hallucinations and thought-process disorder.

Prolactin—Hormone responsible for endocrine function, including lactation.

Psychosis—Loss of contact with reality that may involve false beliefs or hallucinations.

Schizoaffective disorder—Having symptoms of both schizophrenia and bipolar disorder.

Schizophrenia—Severe psychiatric illness involving the disintegration of thought processes and sometimes including hallucinations.

Serotonin—A type of neurotransmitter involved in regulation of the blood vessels, brain processes, and disease states such as depression.

increased by 3 mg roughly every five to seven days. The maximum dose is 12 mg per day. Dosing for schizoaffective disorder is similar. If side effects develop or if other drugs are to be used in combination with paliperidone, the dose may be decreased. Side effects impacting the immune system may require a lower dose or complete discontinuation of the drug. Patients are periodically reassessed for the need of treatment.

Other conditions and allergies

The dose is decreased if the patient has impairment of kidney function or severe liver disease.

Precautions

Paliperidone is an atypical antipsychotic medication, a class that was developed for the purpose of avoiding some of the side effects often seen with older, typical antipsychotic medications. As a class, these medications are less

likely to cause medication-induced movement disorders than the older medications but still have the potential to cause some significant movement-related effects. Patients taking paliperidone must be monitored for the development of movement disorders as well as stiffness, mental status changes, and increased temperature associated with a dangerous syndrome known as neuroleptic malignant syndrome. However, paliperidone is less likely to cause these disorders than many other types of antipsychotic medications. Patients taking paliperidone must have their immune system function monitored via periodic blood tests, as the drug can cause dangerous decreases in white blood cells. High blood glucose (sugar) levels may also develop, especially in patients at risk for diabetes. Blood glucose is measured before initiating paliperidone dosing and then monitored periodically. Paliperidone carries a risk of low blood pressure and possible temporary loss of consciousness, especially in older or dehydrated patients rising quickly from a lying-down position.

Geriatric

Paliperidone should not be used in elderly patients to treat symptoms of dementia; use of paliperidone for this purpose is not approved by the U.S. Food and Drug Administration (FDA), and elderly patients taking paliperidone for dementia-related symptoms are at increased risk of stroke or death.

Pregnant or breastfeeding

Paliperidone is classified as category C for pregnancy, which means either that there are no adequate human or animal studies or that adverse fetal effects were found in animal studies, but there is no available human data. The decision whether to use category C drugs during pregnancy is generally based on weighing the critical needs of the mother against the risk to the fetus. Other, lower category agents are used whenever possible. There are data that suggest paliperidone is considered unsafe for use during breastfeeding, so its use is not recommended.

Other conditions and allergies

Paliperidone may not be appropriate for use or may require caution in patients with heart abnormalities or disease, liver dysfunction, kidney dysfunction, history of stroke or seizure, diabetes, immune dysfunction, dehydration, diarrhea, or electrolyte abnormalities.

Side effects

Sensitivity to paliperidone varies among patients, and some patients may find that even lower doses are more than their body system can tolerate. Common side effects of paliperidone include headache, dizziness, dry mouth, cough, nausea, upset stomach, weight gain, fatigue, increased heart rate, excess salivation, anxiety, tremor, heart rhythm abnormalities, skin sensitivity to sunlight, and fever. Antipsychotics such as paliperidone that act to antagonize dopamine receptors may cause an increase in prolactin, the hormone that causes lactation in women and impotence in men. Low blood pressure or a drop in blood pressure upon standing may result in loss of consciousness.

Rare but serious potential side effects include severe movement disorders, high blood glucose or overt diabetes, stroke, severe difficulty swallowing, dangerous changes in heart rhythm, seizures, and changes in blood cells including anemia and decreased immune function. A rare but dangerous possible side effect is neuroleptic malignant syndrome, a reaction involving very high body temperature, altered mental status, and muscular rigidity.

Interactions

Patients should make their doctor aware of all medications and supplements they are taking before using paliperidone.

Drugs

Drugs that affect the liver may alter the metabolism of paliperidone, resulting in too little or too much of the drug in the body. This could lead to increased side effects or even toxic doses. Likewise, paliperidone may affect the metabolism of other drugs, leading to greater or lower doses than therapeutically desired.

Many drugs may cause toxicity and adversely affect heart rhythm when used in combination with paliperidone. These drugs include multiple types of heart medications, including dronedarone and amiodarone; the antimalaria drug mefloquine; the chemotherapeutic toremifene; the antifungal drug voriconazole; the antibiotics **azithromycin**, **clarithromycin**, and **ciprofloxacin**; and antipsychotics such as pimozide and **ziprasidone**, among many others. The drug bromocriptine used in various neurological and endocrine disorders may cause dangerously low blood pressure when used with paliperidone. Sedative drugs such as codeine may result in severe sedation.

Herbs and supplements

The herbal supplement Siberian ginseng causes antagonizing effects and decreases the effectiveness of paliperidone, as well as exacerbating many psychiatric conditions. Herbal supplements such as calendula, capsicum, kava, and lemon balm may cause additive effects of severe sedation in patients using paliperidone.

Food and other substances

Using alcohol while taking paliperidone may create toxic reactions in the body and should be avoided.

Resources

BOOKS

Brunton, Laurence L., et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill Medical, 2011.

Stargrove, Mitchell Bebel, et al. *Herb, Nutrient, and Drug Interactions: Clinical Implications and Therapeutic Strategies*. St. Louis: Mosby, 2007.

PERIODICALS

Savitz, A. J., et al. "Efficacy and Safety of Paliperidone Extended Release in Adolescents with Schizophrenia: A Randomized, Double-Blind Study." *Journal of the American Academy of Children and Adolescent Psychology* 54, no. 2 (2015): 126–37.

Üçok, A., et al. "Effects of Paliperidone Extended Release on Functioning Level and Symptoms of Patients with Recent Onset Schizophrenia: An Open-Label, Single-Arm, Flexible-Dose, 12-Months Follow-Up Study." *Nordic Journal of Psychiatry* (December 31, 2014): e-pub ahead of print. <http://dx.doi.org/10.3109/08039488.2014.996252> (accessed February 26, 2015).

OTHER

U.S. Food and Drug Administration. "Invega [prescribing information]." http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021999s0181bl.pdf (accessed February 26, 2015).

WEBSITES

AHFS Consumer Medication Information. "Paliperidone." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a607005.html> (accessed February 26, 2015).
Micromedex. "Paliperidone (Intramuscular Route)." Mayo Clinic.org. <http://www.mayoclinic.org/drugs-supplements/paliperidone-intramuscular-route/description/drg-20073158> (accessed February 26, 2015).

ORGANIZATIONS

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.
National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.
National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

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Pamelor see **Nortriptyline**

Pantoprazole

Definition

Pantoprazole is a medication used to treat gastroesophageal reflux disease (GERD), a condition that allows some acid from the stomach to return up to the esophagus. Pantoprazole is in a class of drugs called proton pump inhibitors (PPIs).

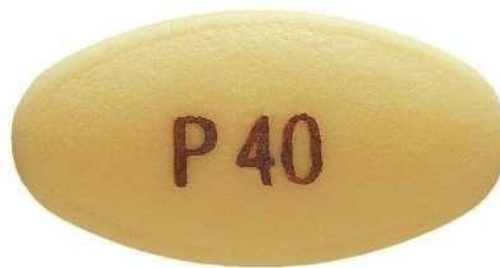
Purpose

Individuals with GERD experience a burning sort of pain near the breast bone, which is commonly referred to

as heartburn. Heartburn is a hallmark sign of GERD. Although the condition may seem harmless, the constant reflux of stomach acid can eventually harm the thin lining of the esophagus. Pantoprazole and similar proton pump inhibitors reduce the amount of acid made in the stomach, which helps control GERD symptoms. Reducing stomach acid also helps prevent and heal sores in the esophagus caused by the acid reflux, a condition called erosive esophagitis. Sometimes pantoprazole is used to treat a rare condition called Zollinger-Ellison syndrome, which occurs when tumors form in the pancreas or duodenum and cause the stomach to produce more acid than normal.

Description

Pantoprazole comes in a tablet with delayed-release action that is taken by mouth. This means the tablet waits to release the medicine in the intestine so that the acids in the stomach do not break down the medicine. The medicine also comes as granules in a capsule that can be sprinkled into water or soft food and dissolved. Some people may receive the injected form of the drug, which is given by a healthcare provider intravenously (through injection into a vein). Pantoprazole is usually used for short-term management of GERD or for control of damage to the esophagus; it is not a medicine that is taken to immediately relieve heartburn.



Pantoprazole, 40 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Duodenum—The first portion of the small intestine, which is the tube-like organ between the stomach and the large intestine that helps with food digestion.

Esophagus—The tube that carries food from the mouth to the stomach.

Gastroesophageal reflux disease (GERD)—A condition that involves the passage of stomach acid back into the esophagus through the small opening that normally allows food to travel down from the esophagus to the stomach. GERD can cause heartburn and lead to damage such as sores called ulcers in the esophagus.

Pancreas—A small organ in the upper abdomen that produces insulin and enzymes that aid in food digestion.

Proton pump inhibitor (PPI)—A type of medicine that reduces how much acid is made by glands that are located in the stomach's lining. When less acid is made, less can make its way back into the esophagus, easing heartburn and damage from GERD.

U.S. brand names

In the United States, pantoprazole is sold as the brand name Protonix.

Recommended dosage

Dosage of pantoprazole depends on the patient's age and the reason for taking the medication. The following are examples of some recommended doses:

- For adults who have erosive esophagitis from GERD, the usual dose is 40 mg of pantoprazole once a day for up to eight weeks. To heal and maintain healing of erosive esophagitis, adults may take 40 mg once a day for an additional eight weeks if the esophagitis has not healed after the first course of treatment.
- For treatment of Zollinger-Ellison syndrome and similar problems related to excess production of acid in the stomach, an adult may take 40 mg of pantoprazole twice a day. Doctors may adjust dosages depending on each individual patient. Some individuals may need more than the recommended dose and may need to take the medicine as long as necessary to control acid production.

Pediatric

To treat erosive esophagitis from GERD in children ages five and older, doctors recommend 20 mg of

pantoprazole once a day for up to eight weeks. Children who weigh more than 40 kilograms (kg), or about 88 pounds, can receive the adult dosage of 40 mg once per day.

Precautions

Some people may be allergic to pantoprazole or ingredients in the medication. Some individuals who take pantoprazole develop a complication called interstitial nephritis, which is an inflammation, or swelling, of spaces in the kidneys that can cause problems with how the kidneys work. Individuals can develop stomach problems such as inflammation and irritation of the stomach lining (gastritis) from taking pantoprazole for too long a period. Some people who take pantoprazole also experience an infection-related form of severe diarrhea.

Pediatric

Safety and effectiveness of pantoprazole have not been demonstrated in children under 12 months. There is no appropriate dosage of the drug available for children younger than five years old.

Pregnant or breastfeeding

Pantoprazole is a pregnancy category B drug. Animal studies have shown no harmful effects to fetuses, but no adequate studies have been conducted in pregnant women. Pantoprazole should only be used by a woman who is pregnant when clearly required. It is not clear whether pantoprazole is passed from a mother to infant while breastfeeding. Women who want to breastfeed should discuss the use of pantoprazole with their healthcare provider and consider whether to choose not to breastfeed or to stop using pantoprazole while nursing.

Side effects

Pantoprazole can cause side effects, including:

- nausea and vomiting
- headache
- gas and constipation
- dry mouth
- joint pain

Some side effects of pantoprazole can be severe and should be reported to the physician immediately. These include:

- rash, hives, and itching
- peeling or blistering skin
- problems swallowing or breathing
- rapid or irregular heartbeat

- swollen eyes, face, tongue, mouth, or throat
- dizziness or severe fatigue
- seizures or muscle spasms
- severe diarrhea

Interactions

Some drugs or substances can interact with one another, affecting how well a drug works or worsening side effects. Anyone taking pantoprazole should tell their healthcare provider about all medications, herbal remedies, and vitamins and supplements being taken.

Drugs

Pantoprazole may interfere with several drugs or affect how they are absorbed in the body. The following interactions are especially important:

- Pantoprazole can interfere with how well some antiretroviral drugs work. These drugs are taken to treat HIV/AIDS.
- Individuals who take anticoagulants (blood thinners) such as **warfarin** (Coumadin) should be sure to tell all of their healthcare providers that they are taking pantoprazole, because the proton pump inhibitor can affect clotting and cause severe bleeding and even death.

Resources

PERIODICALS

- Hussain, Nazia, and Narrah Nailah. "Peptic Ulcer Disease." *InnovAIT* 7, no. 7 (2014): 404–12.
- Klassen, Sheila, Joan C. Krepinsky, and Ally P. Prebtani. "Pantoprazole-Induced Acute Interstitial Nephritis." *Canadian Medical Association Journal* 185, no. 1 (2013): 56–9.

OTHER

- American College of Gastroenterology. "Do You Have GERD?" <http://s3.gi.org/patients/pdfs/UnderstandGERD.pdf> (accessed February 19, 2015).

WEBSITES

- MedlinePlus. "Pantoprazole." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601246.html> (accessed February 19, 2015).
- "Pantoprazole." Drugs.com. <http://www.drugs.com/pantoprazole.html> (accessed February 19, 2015).
- Pfizer Inc. "Protonix (Pantoprazole Sodium) Delayed Release Tablets." Protonix.com. <https://www.protonix.com/about-protonix> (accessed February 19, 2015).

ORGANIZATIONS

- American Gastroenterological Association, 4930 Del Ray Avenue, Bethesda, MD 20184, (301) 654-2055, (301) 654-5920, <http://www.gastro.org/>.

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, 1501 Bethlehem Pike, Flourtown, PA 19031, (215) 233-0808, naspgan@naspgan.org, <http://www.gikids.org/>.

Teresa G. Odle, BA, ELS

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Paroxetine

Definition

Paroxetine is an antidepressant drug. It is classified as a selective serotonin reuptake inhibitor (SSRI).

Purpose

Paroxetine is approved by the U.S. Food and Drug Administration (FDA) for treatment of depression and for the following anxiety disorders: obsessive-compulsive disorder (OCD), panic disorder, generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), social anxiety disorder, and premenstrual dysphoric disorder (PMDD).

Description

Paroxetine increases the amount of serotonin (also called 5-HT) available in the brain. Serotonin is a neurotransmitter, or a chemical in the brain that carries nerve impulses between neurons. The sending neuron releases serotonin into a little gap between neurons called the synapse. The receiving neuron picks up the serotonin



Paroxetine, 10 mg. (U.S. National Library of Medicine, Pillbox)

KEY TERMS

Anxiety—A psychological state characterized by strong feelings of worry, nervousness, apprehension, or agitation; may also be accompanied by physical symptoms, including sweating, tension, and increased pulse.

Depression—A mental state characterized by excessive sadness and loss of interest in life; other symptoms may include altered sleep or eating patterns, loss of concentration, agitation, lack of energy, and, in severe cases, attempts at self-harm or suicide.

Monoamine oxidase inhibitors (MAOIs)—A group of antidepressant drugs that decrease the activity of monoamine oxidase, a neurotransmitter found in the brain that affects mood.

Neurotransmitter—A naturally occurring chemical in the body that carries chemical messages to nerve cells, often by transmitting nerve impulses. Central nervous system well-being is dependent on a balance among the neurotransmitters acetylcholine, dopamine, serotonin, and norepinephrine.

Selective serotonin reuptake inhibitors (SSRIs)—A class of antidepressants that works by blocking the reabsorption of serotonin in brain cells, raising the level of the chemical in the brain.

Serotonin—5-Hydroxytryptamine; a substance that occurs throughout the body with numerous effects, including neurotransmission. Low serotonin levels are associated with mood disorders, particularly depression and obsessive-compulsive disorder.

from the synapse, allowing the nerve impulse to continue on its way.

Researchers think that depression and certain other disorders may be caused, in part, because there is not enough available serotonin in the brain. Normally, once a nerve impulse has crossed the synapse, serotonin is reabsorbed by the sending neuron that released it. Once reabsorbed, this serotonin is no longer available and cannot interact with a receiving neuron. Paroxetine blocks the reabsorption, or reuptake, of serotonin, leaving it available to stimulate receiving neurons. Therefore, paroxetine facilitates the transmission of nerve impulses by increasing the amount of serotonin that is available in the brain.

The benefits of paroxetine develop slowly over a period of up to four weeks. Patients should be aware of this and continue to take the drug as directed, even if they feel no immediate improvement.

U.S. brand names

Paroxetine is sold in the United States under the brand name Paxil.

Recommended dosage

The recommended dosage of paroxetine is 20–50 milligrams (mg) per day. The drug should be taken only once per day. An appropriate initial dosage is 20 mg. Dosage changes should not be made more frequently than once per week.

Geriatric

Older patients should start out taking 10 mg per day. The total dosage should not exceed 40 mg per day.

Other conditions and allergies

Individuals with liver or kidney disease may require a reduced dosage and should not take more than 40 mg per day.

Precautions

Like other SSRIs, paroxetine carries a warning regarding use in children and adults up to the age of 24, who appear to have an increased risk of developing suicidal thoughts or actions while using these agents. Patients of any age should be monitored for signs of worsening depression while taking paroxetine.

Hyponatremia (abnormally low concentration of sodium in the blood) has been associated with the use of paroxetine. In all cases, this condition resolved when the drug was discontinued. Most of these instances occurred among older individuals who were also taking diuretics (water pills).

Other conditions and allergies

Paroxetine may lower the threshold for a manic episode among people with bipolar disorder. For this reason, the drug should be used only with caution and under close supervision in these patients. It may also increase the chance of having a seizure in people with a history of seizure disorders.

Side effects

Common side effects associated with paroxetine include headache, weakness, chills, malaise, nausea, and sleepiness. Other complaints include dry mouth,

dizziness, tremors, constipation, diarrhea, and problems with ejaculation.

In general, the incidence of side effects increases as the dosage of paroxetine increases.

Interactions

Individuals taking paroxetine should consult with their healthcare provider regarding potential interactions between paroxetine and other drugs, including over-the-counter drugs and supplements.

Drugs

There is the potential for a fatal interaction with another class of antidepressant drugs called monoamine oxidase inhibitors (MAOIs). There have been reports of dangerously elevated body temperature, muscle rigidity, and rapid changes in vital signs, including heart rate and blood pressure. Mental changes ranging from extreme agitation to delirium and coma have also been reported. Because of this, paroxetine should never be taken in combination with MAOIs. Patient taking any MAOIs—for example, Nardil (phenelzine sulfate) or Parnate (tranylcypromine sulfate)—should stop the MAOI and then wait at least 14 days before starting paroxetine or any other antidepressant. The same holds true when discontinuing paroxetine and starting an MAOI.

The combination of paroxetine with the antipsychotic drug thioridazine has the potential to cause fatal cardiac arrhythmias (irregular heartbeat). The use of paroxetine in combination with tryptophan may result in unwanted reactions, including agitation, restlessness, and gastrointestinal distress. Paroxetine may also increase the chance of having a seizure in people with a history of seizure disorders. People taking anticonvulsants to control seizures should be closely monitored, and a physician may need to adjust the dosage of their seizure medication.

Phenobarbital at dosages greater than 100 mg per day decreases the effectiveness of paroxetine in some persons. Paroxetine has been reported to increase the effects of procyclidine.

Resources

BOOKS

- Adams, Michael, Norman Holland, and Jeanine Brice. *Core Concepts in Pharmacology*. Boston: Pearson, 2015.
- Von Boxtel, Chris J., Budiono Santoso, and I. Ralph Edwards. *Drug Benefits and Risks: International Textbook of Clinical Pharmacology*. 2nd ed. Amsterdam: IOS Press, 2008.

PERIODICALS

- Gorlyn, M., et al. "Treatment-Related Improvement in Neuropsychological Functioning in Suicidal Depressed Patients: Paroxetine vs. Bupropion." *Psychiatry Research* 225, no. 3 (2015): 407–12.
- Hegeman, J., et al. "Unraveling the Association between SSRI Use and Falls: An Experimental Study of Risk Factors for Accidental Falls in Long-Term Paroxetine Users." *Clinical Neuropharmacology* 34, no. 6 (2011): 210–15.
- Tomita, Tetsu, et al. "The Association between Sunshine Duration and Paroxetine Response Time in Patients with Major Depressive Disorder." *Journal of Affective Disorders* 136, no. 3 (2012): 1067–71.
- Zhu, H., et al. "Altered Spontaneous Neuronal Activity in Chronic Posttraumatic Stress Disorder Patients Before and After a 12-Week Paroxetine Treatment." *Journal of Affective Disorders* 174 (March 2015): 257–64.

WEBSITES

- AHFS Consumer Medication Information. "Paroxetine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a698032.html> (accessed February 26, 2015).
- National Alliance on Mental Illness. "Paroxetine (Paxil)." [http://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Paroxetine-\(Paxil\)](http://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Paroxetine-(Paxil)) (accessed February 26, 2015).
- UK National Health Service (NHS). "Paroxetine (Paroxetine 20 mg Tablets)." <http://www.nhs.uk/conditions/anxiety/pages/MedicineOverview.aspx?condition=Anxiety&medicine=Paroxetine> (accessed February 26, 2015).
- U.S. Food and Drug Administration. "Information for Healthcare Professionals: Paroxetine (Marketed as Paxil)." <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm085313.htm> (accessed February 26, 2015).

ORGANIZATIONS

- National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.
- National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

L. Fleming Fallon, Jr., MD, DrPH

REVIEWED BY KEVIN GLAZA, RPH

Pataday see **Olopatadine**

Patanol see **Olopatadine**

Paxil CR see **Paroxetine**

Pegfilgrastim

Definition

Pegfilgrastim is a long-acting injected drug that stimulates white blood cell production in patients being treated with chemotherapy for certain types of cancer. Pegfilgrastim is also called pegylated granulocyte-colony stimulating factor (G-CSF). It is in the drug classes of colony-stimulating factors and hematopoietic growth factors.

Purpose

Pegfilgrastim is used to help prevent and treat infections in cancer patients receiving high-dose chemotherapy that suppresses white blood cell production by the bone marrow (myelosuppression). In particular, pegfilgrastim is used as an adjunct treatment in patients receiving chemotherapy for cancers such as chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL). Chemotherapy drugs, as well as certain other medical treatments, can cause neutropenia—the depletion of white blood cells called neutrophils. Neutrophils are the most abundant type of white blood cell and fight off many different types of infection. Severe neutropenia and febrile neutropenia (FN)—neutropenia accompanied by fever—are serious side effects that limit chemotherapy doses for the treatment of aggressive NHL.

Pegfilgrastim stimulates white blood cell production and is a primary form of prophylaxis for preventing FN. Colony-stimulating factors such as pegfilgrastim and growth factors have replaced white blood cell or granulocyte transfusions for preventing and treating infections in chemotherapy patients. Pegfilgrastim may also help prevent serious infections in NHL patients being treated with radiation therapy.

Pegfilgrastim may be used for other conditions. It is used to reduce the frequency of infections in patients with myelodysplastic syndrome (MDS), a bone marrow disorder that is a late effect of previous cancer treatment. Pegfilgrastim is also used to stimulate the production of stem cells that will be used for stem cell or bone marrow transplants. Pegfilgrastim has orphan drug designation for treating people at risk of myelosuppression as a result of accidental radiation exposure.

Description

Pegfilgrastim is the long-acting form of the G-CSF filgrastim (Neupogen). Filgrastim and pegfilgrastim are hematopoietic growth factors that stimulate the production of neutrophils in the bone marrow to help prevent

and fight infection. They stimulate stem cells in the bone marrow to divide and mature into active neutrophils that have been depleted by chemotherapy, cancer, or other conditions. They also increase the migration of neutrophils from the bone marrow to other parts of the body and increase their ability to destroy infection-causing organisms and infected cells (cytotoxicity). Filgrastim is a laboratory version of the naturally occurring protein G-CSF. Pegfilgrastim is synthesized by attaching polyethylene glycol (PEG) to filgrastim. PEG helps keep the drug in the body longer, so that it can be injected less often than filgrastim.

Pegfilgrastim is supplied in syringes containing 6 milligrams (mg) of pegfilgrastim in 0.6 milliliters (mL) of solution for subcutaneous (SC; under the skin) injection. It may be injected by a nurse or other healthcare worker or by the patient or a family member at home.

Pegfilgrastim syringes should be kept in the refrigerator in the tightly closed carton that they are supplied in. If a syringe is accidentally frozen, it can be thawed in the refrigerator; however, if the same syringe is frozen a second time, it must be discarded. The syringes can be kept at room temperature, away from direct sunlight, for up to 48 hours.

U.S. brand names

Pegfilgrastim is sold in the United States under the brand name Neulasta.



Neulasta (pegfilgrastim). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Canadian brand names

Pegfilgrastim is sold in Canada under the brand name Neulasta.

International brand names

The most common international brand names for pegfilgrastim are Neulasta and Neulastim.

Origins

Pegfilgrastim was first approved by the U.S. Food and Drug Administration (FDA) in 2002.

Recommended dosage

Pegfilgrastim is usually given as a single, 6 mg SC injection for each cycle of chemotherapy with drugs that destroy bone marrow cells. The dose may be adjusted down for children or small adults weighing less than 100 lb. (45 kg). The dose may also be adjusted based on the results of blood tests. Pegfilgrastim is given at least 24 hours after the last dose of a chemotherapy cycle and at least 14 days before the start of the next cycle.

The medication should be removed from the refrigerator 30 minutes before injecting to allow it to reach room temperature. The solution should be examined before injection to ensure that it is not discolored and does not contain particles. The solution must not be shaken, as this can make it ineffective.

A new site should be used for each injection to help prevent soreness. Needles should be discarded in a closed needle container and returned to the healthcare facility. If a dose is missed, the doctor or pharmacist should be contacted immediately to set up a new dosing schedule.

Pediatric

For prevention of chemotherapy-induced neutropenia, the recommended dosage for children weighing less than 100 lb. (45 kg) is 100 micrograms (mcg) per kg (2.2 lb.) of body weight per chemotherapy cycle for a maximum of 6 mg per dose, given more than 14 days before and at least 24–72 hours after cytotoxic chemotherapy. For pediatric patients weighing 100 lb. or more, the dose is 6 mg once per chemotherapy cycle, administered SC at least 14 days before and at least 24 hours after chemotherapy administration.

Precautions

Precautions associated with pegfilgrastim include:

- Pegfilgrastim must never be injected into skin that is tender, red, bruised, hardened, scarred, or has stretch marks.

KEY TERMS

Chronic lymphocytic leukemia (CLL)—A slowly progressing leukemia characterized by an overabundance of mature lymphocytes, especially B cells.

Febrile neutropenia (FN)—Deficiency of neutrophils accompanied by fever.

Filgrastim—The short-acting form of pegfilgrastim.

Granulocyte-colony stimulating factor (G-CSF)—A protein that stimulates the maturation of neutrophils; pegfilgrastim is a G-CSF produced in the laboratory.

Granulocytes—White blood cells, such as neutrophils, that contain granules of immune-system chemicals.

Hematopoietic growth factor—A protein, such as granulocyte-colony stimulating factor, that promotes the proliferation and maturation of blood cells.

Myelodysplastic syndrome (MDS)—Bone marrow disorders that are late effects of cancer treatment and that may progress to acute myelogenous leukemia.

Myelosuppression—Suppression of blood cell production in the bone marrow.

Neutropenia—Deficiency of neutrophils.

Neutrophil—The major immune-system phagocytic or cytotoxic white blood cell.

Non-Hodgkin lymphoma (NHL)—Various malignant lymphomas (cancers of lymphoid tissue) that are distinct from Hodgkin lymphoma.

Orphan drug—A medication that has been developed to treat a rare disease, defined in the United States as a disease or disorder affecting fewer than 200,000 people.

Pegylated—Attachment of polyethylene glycol to a drug.

Polyethylene glycol (PEG)—A polymer attached to filgrastim to produce pegfilgrastim that lasts much longer in the body.

Stem cells—Immature cells that can give rise to differentiated cells, such as different types of blood cells in the bone marrow.

Subcutaneous (SC)—Injected under the skin.

- Periodic blood cell counts are used to monitor response and side effects.
- All doctors and laboratory personnel must be informed of pegfilgrastim use, because it can interfere with certain tests, such as bone imaging.

- Doctors and dentists must be informed of pegfilgrastim use before performing any type of surgery.
- Pegfilgrastim reduces the risk of infection but does not prevent all infections during or after chemotherapy. The doctor should be called if signs of infection develop, including fever of 100.5°F (38°C) or higher; chills; painful urination; new cough; coughing up sputum; rash; sore throat; diarrhea; or redness, swelling, or pain around a cut or sore.
- Rarely, patients receiving pegfilgrastim have developed a potentially fatal enlarged or ruptured spleen. The doctor should be informed immediately of pain or swelling under the rib cage on the left side or pain in the left shoulder area.
- In 2014, Health Canada and the pegfilgrastim manufacturer warned of the risk of capillary leak syndrome in cancer patients undergoing chemotherapy and treated with filgrastim or pegfilgrastim. Leaking of fluid from capillaries can cause potentially fatal circulatory shock. Symptoms such as swelling or puffiness, reduced urination, fatigue, or difficulty breathing require halting the treatment and closely monitoring the patient.
- Pegfilgrastim may precipitate sickle-cell crises in patients with sickle-cell disease.
- Patients should tell their doctor if they are being treated with radiation therapy or have or have ever had blood or bone marrow cancer.
- Conditions that may require close monitoring during pegfilgrastim treatment include kidney disease, liver disease (including hepatitis), heart disease, congestive heart failure, lung disease, diabetes, gout, or infections.
- Pegfilgrastim may worsen an enlarged spleen or myelodysplastic disease or cause other problems in people with these conditions.
- Rarely, patients with very low levels of white blood cells and severe blood infections (sepsis) have developed life-threatening acute respiratory distress syndrome when treated with pegfilgrastim.

Side effects

Patients should contact their doctor if side effects are severe or persistent. Side effects experienced by more than 10% of patients receiving pegfilgrastim are (in order of frequency):

- hair loss
- bone pain
- fever
- muscle pain or myalgia
- headache
- weakness
- vomiting
- peripheral edema or swelling

Less common side effects are redness, pain, itching, bumps, bruising, or swelling at the injection site. Rare side effects include:

- coughing up blood
- excess uric acid in the blood (hyperuricemia)
- elevated lactate dehydrogenase
- elevated alkaline phosphatase
- neutrophilic skin reactions or inflammation
- constipation

Patients should contact their doctor immediately if they experience any of the following serious side effects:

- pain in the left upper part of the stomach or tip of the left shoulder
- fever
- decreased urination
- swelling or puffiness of the body
- tiredness

Pregnant or breastfeeding

Pegfilgrastim is in the FDA pregnancy category C. It is not known whether it harms the fetus if used by either the male or female parent at the time of conception or during pregnancy. It should be used during pregnancy only if expected benefits outweigh potential risks to the fetus. Women should call their doctor if they become pregnant while using pegfilgrastim. Although it is not known whether pegfilgrastim passes into breast milk, it may do so and could affect the nursing infant. Women taking pegfilgrastim should discuss breastfeeding with their doctor.

Other conditions and allergies

Patients should inform their doctor and pharmacist of allergies to pegfilgrastim, filgrastim, tbo-filgrastim (Granix), any medications that are produced in the bacterium *Escherichia coli* (*E. coli*), or any other medications. The doctor and pharmacist should also be informed of any other allergies and whether the patient or another person who will inject the pegfilgrastim is allergic to latex, such as the dry natural rubber or latex needle cover of the prefilled syringes. Pegfilgrastim should not be used by patients with hypersensitivity reactions to any component of pegfilgrastim or to *E. coli*-derived proteins.

The doctor should have the patient's complete medical history. Additionally:

Other conditions and allergies

Rarely, allergic or hypersensitivity reactions may occur, especially with the first few treatments. Mild reactions may include fever, chills, skin itching, or feeling flushed. Very rare but dangerous reactions include light-headedness or severe dizziness from low blood pressure; chest tightness; shortness of breath; fast or difficult breathing; wheezing; hives; rash; sweating; back pain; fast heartbeat; flushing; or itching or swelling of the face, eyes, tongue, or throat. After treatment for such reactions, symptoms may recur in a few days and require further treatment.

Interactions

The doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by patients. Patients should not start, stop, or change the dosage of any medication without their doctor's approval. Patients should bring a list of all medications and supplements to medical appointments and carry the list with them in case of emergency.

Drugs

Pegfilgrastim should not be used in conjunction with the very similar drugs filgrastim and tbo-filgrastim. The only other known serious interactions are with lithium (Eskalith, Lithobid), which may cause excess neutrophils to enter the bloodstream.

Food and other substances

There are no known serious interactions between pegfilgrastim and foods.

Resources

BOOKS

Wilkes, Gail M. 2013 *Oncology Nursing Drug Handbook*. Sudbury, MA: Jones & Bartlett Learning, 2012.

PERIODICALS

Mullen, Ellen Catuiza. "Pegfilgrastim-Induced Pain in Patients with Lymphoma." *Oncology Nursing Forum* 41, no. 2 (2014): 212–14.

WEBSITES

"Pegfilgrastim." American Cancer Society. <http://www.cancer.org/treatment/treatmentsandsideeffects/guidetocancerdrugs/pegfilgrastim> (accessed March 1, 2015).

"Pegfilgrastim (Rx)—Neulasta." Medscape.com. <http://reference.medscape.com/drug/neulasta-pegfilgrastim-342167#91> (accessed March 1, 2015).

ORGANIZATIONS

American Cancer Society, 250 Williams Street NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org/>.

National Cancer Institute, 9609 Medical Center Drive, Bethesda, MD 20892-9760, (800) 4-CANCER (422-6237), <http://www.cancer.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY JAMES E. WAUN, MD, RPH

Pepcid see **Famotidine**

Percocet see **Oxycodone/acetaminophen**

Periactin see **Cyproheptadine**

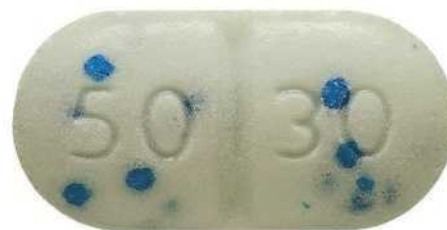
Peridex see **Chlorhexidine**

Phenergan see **Promethazine**

Phentermine

Definition

Phentermine is a medication used to help overweight people speed up their weight loss for a short time. It is in a class of drugs called central nervous system (CNS) stimulants, and its full name is phentermine hydrochloride.



Phentermine, 37.5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Hypothalamus—An area of the brain that helps control part of the nervous system, especially sleep cycles, body temperature, and appetite.

Neurotransmitter—A substance, such as a hormone, that sends nerve impulses across areas in the brain.

Purpose

Losing weight is critical to reducing the health problems that can be associated with being severely overweight or obese. Losing weight requires changes to diet and exercise habits, but weight loss takes time, and it can be difficult to stick to a weight-loss plan. Anti-obesity drugs such as phentermine are used along with diet and exercise to help boost weight loss efforts. Phentermine works by stimulating release of a hormone made in the hypothalamus region of the brain called noradrenaline or norepinephrine, which acts as a neurotransmitter and decreases appetite, causing a person to eat less food.

Description

Phentermine comes in tablet or extended-release (long-lasting) tablet form. The tablet may be taken before meals, and the extended-release form of the drug is taken in the morning. Although length of phentermine treatment varies, most people take the drug for only three to six weeks, while also dieting and exercising to lose weight.

The U.S. Food and Drug Administration (FDA) approved phentermine for use in short-term treatment of obesity in 1959. In the past, phentermine has been combined with other drugs, such as fenfluramine and dexfenfluramine, in off-label uses that were not tested for safety. Later, problems were discovered in the use of these combined drugs that included phentermine. One of the most severe side effects was heart valve disease in people who used the combination drugs. The FDA called for voluntary withdrawal of the combination drugs and the other single drugs but did not ask for withdrawal of phentermine. In fact, phentermine is one of the most popular and widely used antiobesity drugs in the United States.

In 2012, the FDA approved a new combination of phentermine with **topiramate**, a drug used to prevent seizures (anticonvulsant) that also can promote weight loss.

U.S. brand names

In the United States, phentermine is sold under the brand names Adipex-P and Ionamin. There also is a generic version of phentermine. The combination of phentermine and topiramate is sold under the brand name Qsymia.

Recommended dosage

Most patients take the extended-release capsules, which contain 37.5 milligrams (mg) of phentermine. Doctors recommend taking the capsule once a day, usually before breakfast, or one to two hours after breakfast. The medicine is most effective if taken on an empty stomach. Some patients take a smaller dose, depending on the situation, or take two small doses during the day.

The dosage for combined phentermine and topiramate is one extended-release capsule each morning. Each capsule usually consists of 3.75 mg of phentermine and 23 mg of topiramate for the first two weeks, and this dose is increased to 7.5 mg of phentermine with 46 mg of topiramate each day. If patients do not lose weight after 12 weeks, doctors may either recommend that they stop taking the medicine or increase the drug to the maximum daily dose of 15 mg of phentermine and 92 mg of topiramate per day. When stopping the medication at this dosage, patients should do so gradually.

Precautions

There are imitation medications with names that sound similar to phentermine. Patients should use caution and only take appetite suppressants either prescribed by or discussed with their healthcare provider. A rare side effect called pulmonary hypertension (high blood pressure) has been reported in some people who took combination drugs that included phentermine and in a few people who took phentermine alone. It is slightly possible that phentermine causes a serious problem with the lungs or with the heart valves.

It is important to remember that phentermine is intended for short-term use only. It is not a long-term weight-loss solution. There is a risk of drug abuse associated with long-term phentermine use.

Pediatric

The safety of phentermine has not been established in children and the drug should only be used by adults.

Geriatric

Older people taking phentermine should start at the lowest dose possible and should have their kidney function monitored while taking phentermine.

Pregnant or breastfeeding

Phentermine is a pregnancy category C drug. It is unknown whether using the drug while pregnant can harm a mother or fetus. Trials have shown that topiramate, which may be combined with phentermine, can cause harm to a fetus. Pregnant women should not take topiramate. There is a chance that use of phentermine while breastfeeding could cause serious side effects in infants, so nursing mothers should either not take phentermine or choose not to breastfeed if using phentermine.

Other conditions and allergies

Anyone who has high blood pressure should use special caution when taking phentermine.

Side effects

Phentermine can cause side effects, including:

- dry mouth or unpleasant taste in the mouth
- diarrhea or constipation
- vomiting

Some side effects of phentermine use can be severe and should be reported to a doctor immediately. These include:

- increases in blood pressure or heart rate
- restlessness or tremors
- dizziness
- problems sleeping or breathing
- chest pain
- ankle or leg swelling

Use of combined phentermine and topiramate can cause some of the same side effects, and additional effects:

- numbness or tingling of hands, feet, mouth, or face
- changes in the sense of touch
- problems concentrating, speaking, or remembering
- fatigue
- changes in how foods taste
- headache
- heartburn
- muscle tightness

More severe side effects of phentermine and topiramate should be reported to a doctor. These include:

- pounding or rapid heartbeat that lasts for minutes
- suddenly worsening vision
- red or painful eyes
- blood in the urine

- sharp and sudden pain the side or back
- rapid and shallow breathing
- hives, rash, or blisters

Interactions

Phentermine can interact with other drugs and substances. It is important to tell the doctor about any other medicines, herbal remedies, or supplements being taken before using phentermine.

Drugs

Several drugs cause major interactions with phentermine. When phentermine interacts with another drug, it can decrease the desired effects of one of the drugs or increase unwanted side effects. Drugs to be especially careful with include:

- monoamine oxidase inhibitors (MAOIs) such as isocarboxazid (Marplan), selegiline (Eldepryl, Emsam, Zelapar), and others. Using these drugs at the same time, or even within two week of phentermine, can increase risk of severe high blood pressure.
- drugs used to control insulin, weight, or depression, including **paroxetine** (Paxil) and **sertraline** (Nardil)

In addition, use of combined phentermine and topiramate with certain diuretics is not recommended.

Food and other substances

Drinking alcohol while taking phentermine can cause a severe reaction.

Resources

PERIODICALS

- Cheung, Barnard Man Yung, Tommy T. Cheung, and Nithushi R. Samaranayake. "Safety of Antiobesity Drugs." *Therapeutic Advances in Drug Safety* 4, no. 4 (2013): 171–81.
- DeBellis, Lindsay R., and Mark J. Wrobel. "Pharmacotherapeutic Options for the Treatment of Patients with Obesity." *The Journal of Pharmacy Technology* 28 (2012): 211–18.
- Smith, Steven M., Melissa Meyer, and Katy E. Trinkley. "Phentermine/Topiramate for the Treatment of Obesity." *The Annals of Pharmacotherapy* 47, no. 3 (2013): 340–49.

OTHER

- Teva Pharmaceuticals USA. "Highlights of Prescribing Information." Adipex.com. http://www.adipex.com/contents/pdf/Adipex_pi.pdf (accessed February 19, 2015).

WEBSITES

- MedlinePlus. "Phentermine." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682187.html> (accessed February 19, 2015).

MedlinePlus. "Phentermine and Topiramate." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a612037.html> (accessed February 19, 2015).

"Phentermine." Drugs.com. <http://www.drugs.com/phen/termine.html> (accessed February 19, 2015).

"What Is Phentermine?" Phentermine.com. http://www.phentermine.com/what_is_phentermine.htm (accessed February 19, 2015).

ORGANIZATIONS

American Society of Bariatric Physicians, 2821 South Parker Road, Suite 625, Aurora, CO 80014, (303) 770-2526, (303) 779-4834, <http://www.asbp.org/>.

The Obesity Society, 8757 Georgia Avenue, Suite 1320, Silver Spring, MD 20910, (301) 563-6526, (301) 563-6595, <http://www.obesity.org/>.

Teresa G. Odle, BA, ELS

REVIEWED BY GREGORY A. PRATT, RPh

Phenytoin

Definition

Phenytoin is an anticonvulsant (a drug that acts to prevent seizures).

Purpose

Phenytoin is used to control seizures (convulsions) in the treatment of epilepsy. It is also used to prevent and treat seizures that occur during brain surgery. Phenytoin may also be given to stop uncontrolled seizures. Additional uses are being studied.

Description

Phenytoin acts on areas of the brain to limit electrical discharges and stabilize cellular activity. It works by decreasing abnormal electrical activity in the brain.

U.S. brand names

In the United States, phenytoin is sold under the brand names Dilantin and Phenytek.

Recommended dosage

The dose ordered depends on blood levels of the drug determined during routine monitoring. Patients usually start on a low dose. Depending on the patient's response and drug blood levels, the dose may be increased. For seizures, patients are usually started at

100 milligrams (mg) taken three times per day. Blood is drawn to check the level of phenytoin after seven to ten days, and the dose may be adjusted accordingly.

It is very important that this drug be used exactly as directed. Patients should not crush or break extended-release drugs. Chewable tablets should be chewed before swallowing. Other pills should be swallowed whole. The medication should be taken at the same time every day. If a dose is missed, it should be taken as soon as possible, but if it is almost time for the next dose (within four hours), the missed dose is skipped. This medication should be stored in a dry place, not in the bathroom.

Different phenytoin products are absorbed by the body in different ways and cannot be substituted for one another. If patients need to switch from one phenytoin product to another, the doctor may need to adjust the dose. Patients should not change brands without the approval of the doctor.

Pediatric

Dosages for pediatric patients may be based on the patient's weight.

Geriatric

Dosages for geriatric patients may be based on the patient's weight.



Phenytoin ER (extended release), 100 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Anticonvulsant—A type of medication given to prevent seizures.

Epilepsy—A disorder of the nervous system that causes seizures.

Lymphatic system—The part of the immune system that includes lymph nodes and tissue.

Mania—The phase of bipolar disorder in which the patient is easily excited, hyperactive, agitated, and unrealistically cheerful.

Seizure—A sudden attack, spasm, or convulsion.

Precautions

Patients should not suddenly stop taking this medication. The abrupt withdrawal of phenytoin could trigger seizures.

Phenytoin may trigger disorders of the lymphatic system and cause liver damage. If the liver is not able to properly break down phenytoin, it can produce toxic effects, even at small doses. Doctors typically assess kidney and liver function prior to ordering it. The tests are repeated at regular intervals.

Patients should practice good dental hygiene to decrease the risk of gum disease. With the doctor's approval, it may be taken with food to decrease stomach upset.

Phenytoin may produce changes in the normal makeup of the blood, including high blood glucose (sugar) levels and anemia.

Geriatric

Older adults may be more prone to adverse effects than younger people.

Pregnant or breastfeeding

Phenytoin is in the FDA pregnancy category D, meaning that there is positive evidence of risk to a fetus. It has been associated with birth defects known collectively as fetal hydantoin syndrome, which causes developmental delays and abnormalities. It may also cause cleft lip and palate (underdeveloped lip and mouth) and microcephaly (underdeveloped head), as well as more severe developmental delays. Expectant mothers who are taking phenytoin to prevent seizures should not abruptly stop the drug and should discuss the risks and benefits of this medication with their doctor.

Phenytoin is excreted into breast milk, so breastfeeding mothers should not take phenytoin.

Other conditions and allergies

Phenytoin should not be taken by patients who are allergic to this drug. People with slow heart rates; certain other heart conditions; or a flaking, open skin condition should not take phenytoin.

Phenytoin may be used cautiously in patients with asthma, allergies, limited kidney or liver function, heart disease, and blood disorders. It should also be used with caution in individuals with alcoholism; diabetes mellitus; lupus; poor thyroid function; or porphyria, a rare metabolic disorder.

Side effects

Drowsiness is a common side effect of phenytoin. Patients should exercise caution when driving or operating machinery. Alcohol may increase drowsiness. Patients should not consume alcoholic beverages while taking this drug.

Other, less frequent side effects related to the central nervous system include an unsteady gait, slurred speech, confusion, and dizziness. Patients may experience depression, difficulty sleeping, nervousness, irritability, tremors, and numbness. Twitching, headache, mental health problems including psychotic episodes, and more seizure activity may occur.

This medication may also cause the following side effects:

- nausea, vomiting, stomach upset
- diarrhea, constipation
- swollen gum tissue
- rash
- hair loss (alopecia) or excessive hair growth
- vision changes
- uncontrolled eye movements
- inflammation of the surface of the eye
- chest pain
- swelling
- fever
- increase in weight
- enlarged lips
- joint or muscle pain

Patients should notify the doctor promptly of any side effects. If a skin rash develops, the doctor will instruct the patient on how to taper off and stop the drug.

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Many drugs interact with phenytoin and may increase or decrease its blood levels. Phenytoin may alter the effectiveness of other drugs. The list of interactions is long and varied. Drugs that interfere with phenytoin include:

- anticoagulants (blood thinners)
- sulfa and other antibiotics
- antifungal agents
- drugs used to treat ulcers
- **methadone**
- antidepressants
- disulfiram (used to treat alcoholism)
- corticosteroids
- estrogen hormones
- birth control pills and injections
- drugs to treat hypoglycemia
- asthma drugs
- other anticonvulsants such as **carbamazepine**
- lidocaine
- heart medications
- drugs used to treat Parkinson's disease
- anti-inflammatory drugs
- narcotic pain relievers
- anticancer drugs

Additionally, taking phenytoin with certain antidepressants may cause seizures in some patients.

Antacids can lower the effectiveness of phenytoin. These drugs should be taken two to three hours apart from phenytoin.

Herbs and supplements

Phenytoin has been reported to interact with certain herbs, including evening primrose (*Oenothera biennis*), ginkgo (*Ginkgo biloba*), wormwood (*Artemisia pontica*), and an Ayurvedic preparation known as shankhpushpi.

Patients should talk to their doctor before taking folic acid or calcium supplements, as they may interfere with this drug.

Food and other substances

Alcohol ingestion can interfere with maintaining proper blood levels of phenytoin. Patients should not drink alcoholic beverages while taking this medication, as phenytoin can accumulate to toxic levels in the bodies of noncompliant patients.

Tube feeding may decrease the amount of phenytoin absorbed. Patients should not be given tube feedings for two hours before and after taking this drug.

Resources

BOOKS

Shorvon, Simon. *Handbook of Epilepsy Treatment*. 3rd ed. Oxford, UK; Hoboken, NJ: Wiley-Blackwell, 2010.

WEBSITES

Epilepsy Foundation. "Phenytoin." <http://www.epilepsy.com/medications/phenytoin> (accessed March 9, 2015).

Genetic and Rare Diseases Information Center (GARD). "Fetal Hydantoin Syndrome." Office of Rare Diseases Research, National Center for Advancing Translational Sciences. <http://rarediseases.info.nih.gov/gard/6435/fetal-hydantoin-syndrome/resources/1> (accessed March 6, 2015).

MedlinePlus. "Phenytoin." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682022.html> (accessed March 6, 2015).

ORGANIZATIONS

Epilepsy Foundation, 8301 Professional Place East, Suite 200, Landover, MD 20785-2353, (800) 332-1000, Contact Us@efa.org, <http://www.epilepsy.com/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Pimecrolimus

Definition

Pimecrolimus (pronounced pih-MEK-ro-LIE-mus) is an immunomodulator (drug that acts on the immune system) used to treat atopic dermatitis (eczema). It is classified in the ascomycin group of macrolactam immunosuppressives. Ascomycin is a compound produced by the fermentation of *Streptomyces hygroscopicus*, a bacterium that is used to produce a number of



Elidel (pimecrolimus) cream. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

immunosuppressant medications, antibiotics, and other chemicals used in medicine. Pimecrolimus is also classified as a calcineurin inhibitor because it blocks the action of calcineurin, a protein enzyme that activates the T cells in the immune system.

Purpose

Pimecrolimus is used to treat eczema in adults and in children over two years of age.

Off-label use

Pimecrolimus is used off label for a variety of other inflammatory skin disorders. A Canadian dermatologist summarized reports of the effectiveness of pimecrolimus in treating oral lichen planus, psoriasis, and vitiligo in an article published in 2010. Other researchers have reported success in using the drug to treat seborrheic dermatitis and cutaneous lupus erythematosus.

Description

Pimecrolimus is packaged as a 1% cream in a 30-gram (1.06-ounce) tube. It should be stored at room temperature, not be allowed to freeze, and be kept tightly capped when not in use.

U.S. brand names

Pimecrolimus is sold in the United States under the brand name Elidel.

Origins

Pimecrolimus was approved by the U.S. Food and Drug Administration (FDA) in December 2001 as a new molecular entity (NME).

Pimecrolimus was originally developed by Novartis; it is marketed in the United States by Novartis and in Canada by Galderma (under the same trade name as in the United States). No generic version is presently available, as the drug will not go off patent until December 2016.

Recommended dosage

The recommended dosage in adults is to apply a thin layer of the cream to the affected area(s) of skin every 12 hours and restrict application to the affected areas. While patients should continue using the cream as long as symptoms persist, they are also advised to contact their physician if there is no improvement after six weeks.

Precautions

Pimecrolimus has been required to carry a boxed warning since 2006 regarding its potential for increasing the risk of non-melanoma skin cancer or lymphoma; however, the American Academy of Dermatology issued a report in late 2006 stating that there is no proof that pimecrolimus causes these types of cancer, and that the topical short-term application of an immunosuppressant drug seems unlikely to cause cancer. The academy's findings were reaffirmed by a study published in 2013.

Patients should observe the following precautions while using pimecrolimus:

- Apply the cream to clean, dry skin, using only the smallest amount needed to cover the affected area, and rub in gently. Do not cover the area with a bandage.
- Wash the hands after applying pimecrolimus, but do not bathe, swim, or shower immediately after applying the cream.
- Avoid getting the cream into the mouth, vagina, eyes, nose, or rectum; if the cream does get into any of those areas accidentally, rinse with water.
- Avoid exposure to direct sunlight, tanning lamps or beds, or the ultraviolet light used in phototherapy. Cover areas of skin treated with pimecrolimus with loose clothing when outdoors, but do not use sunscreen on the treated areas unless the doctor advises its use. Do not use other medications on areas of skin treated with pimecrolimus unless the doctor advises such use.
- A moisturizer may be used for dry skin at the application site(s).

KEY TERMS

Atopic dermatitis—An inflammatory, noncontagious, itchy skin disorder that is often chronic in nature. It is also known as eczema.

Boxed warning—A warning label required by the U.S. Food and Drug Administration (FDA) for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Calcineurin—A protein phosphatase that activates T cells in the immune system and can be blocked by drugs like pimecrolimus.

Eczema—A disease in which the skin becomes dry, red, itchy, and thickened.

Netherton syndrome—A rare genetic disorder of the skin characterized by red, itchy skin susceptible to infections, allergies to nuts and fish, and abnormal development of the shafts of the hair. It is named for the American dermatologist who first identified it in 1958.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the FDA. It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Oral lichen planus—A disorder of the mucous membranes lining the mouth characterized by erosive ulcers, plaque-like white patches, or a web-like pattern of white lines.

Psoriasis—An immune-mediated chronic skin disorder characterized by red, itchy, scaly lesions, papules, and plaques. It may affect only small areas of the body or completely cover the body.

Seborrheic dermatitis—An inflammatory skin disorder that produces itchy, red, scaly skin on the scalp, face, and torso. It is called cradle cap when it occurs in infants.

Topical—Referring to any drug applied to the skin, hair, nails, or other exterior surfaces of the body.

Vitiligo—A condition that causes depigmentation of areas of the skin, most commonly on the extremities. Its cause is unknown but may be related to an autoimmune disorder.

Pediatric

Pimecrolimus should not be used in children younger than two years of age.

Older children and adolescents should follow the same precautions as adults; that is, limit the application to the affected areas of skin, and consult the doctor if there is no improvement after six weeks of use.

Pregnant or breastfeeding

Pimecrolimus is a pregnancy category C drug, which means that animal studies have shown potential harm to the fetus, but there are no adequate and well-controlled studies in humans. The potential benefits of pimecrolimus may warrant the use of the drug during pregnancy despite potential risks.

It is not known whether pimecrolimus passes into breast milk. Nursing mothers should not use pimecrolimus while they are nursing.

Other conditions and allergies

Pimecrolimus is contraindicated in patients with Netherton syndrome (rare genetic skin disorder), who are immunocompromised, who have an active bacterial or viral skin infection (including herpes zoster or chickenpox), or who have a known allergy or hypersensitivity to calcineurin inhibitors.

Side effects

Common side effects with pimecrolimus include:

- warmth or burning sensations at the application site(s)
- headache
- fever
- common cold
- cough
- dry skin or mild discoloration of skin

Less common side effects include:

- diarrhea
- eye redness, tearing, or sensitivity of the eye to light
- rash on the face, scalp, or stomach
- weight loss
- difficulty sleeping
- unusual tiredness or weakness
- nausea or loss of appetite
- malaise (general feeling of discomfort or illness)

Patients should consult their doctor at once if they have any of the following side effects:

- signs of a severe allergic reaction (hives, itching, sudden and unexplained swelling of the lips, mouth, or throat, difficulty breathing)
- severe burning sensations in the areas of treated skin

- symptoms of a new viral infection in the treated area (warts, blistering or oozing, burning or tingling pain, unusual skin lesions)
- ear pain or discharge, which may indicate an ear infection
- worsening of skin symptoms in the treated area(s)
- sore throat or swollen glands
- flu-like symptoms (fever, chills, body aches)

Interactions

To avoid the risk of drug interactions, individuals should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs and supplements.

Drugs

A significant number of medications are known to interact with pimecrolimus, including:

- monoclonal antibodies (natalizumab, **adalimumab**, canakinumab, **infliximab**, etc.)
- antiretroviral medications (indinavir, atazanavir, delavirdine, ritonavir, nelfinavir, etc.)
- corticosteroids (cortisone, dexamethasone, hydrocortisone, fludrocortisone, **methylprednisolone**, **prednisone**, prednisolone, **triamcinolone**)
- antifungal medications (**fluconazole**, miconazole, ketoconazole, posaconazole)
- some antibiotics (**clarithromycin**, **erythromycin**, telithromycin)
- other immunosuppressants (**glatiramer**, anakinra, sirolimus)

However, because pimecrolimus is a topical medication rather than taken by mouth or injection, most of these interactions are mild.

Food and other substances

Pimecrolimus may produce reddening and flushing of the face, neck, or upper chest if the patient consumes alcohol while using the drug.

Resources

BOOKS

- Copeland, Robert A. *Evaluation of Enzyme Inhibitors in Drug Discovery: A Guide for Medicinal Chemists and Pharmacologists*. 2nd ed. Hoboken: Wiley, 2013.
- Hertl, Michael, editor. *Autoimmune Diseases of the Skin: Pathogenesis, Diagnosis, Management*. 3rd ed, rev. New York: Springer, 2011.

Rudikoff, Donald, Steven R. Cohen, and Noah Scheinfeld, editors. *Atopic Dermatitis and Eczematous Disorders*. Boca Raton: CRC Press/Taylor and Francis Group, 2014.

PERIODICALS

- Lin, A. N. "Innovative Use of Topical Calcineurin Inhibitors." *Dermatologic Clinics* 28, no. 3 (2010): 535–45.
- Reitamo, S., and A. Remitz. "An Update on Current Pharmacotherapy Options in Atopic Dermatitis." *Expert Opinion on Pharmacotherapy* 15, no. 11 (2014): 1517–24.
- Siegfried, E. C., J. C. Jaworski, and A. A. Hebert. "Topical Calcineurin Inhibitors and Lymphoma Risk: Evidence Update with Implications for Daily Practice." *American Journal of Clinical Dermatology* 14, no. 3 (2013): 163–78.

WEBSITES

- Mayo Clinic staff. "Pimecrolimus (Topical Route)." Mayo Clinic.org. <http://www.mayoclinic.org/drugs-supplements/pimecrolimus-topical-route/description/drg-20068138> (accessed February 21, 2015).
- Medscape Reference. "Pimecrolimus (Rx)." <http://reference.medscape.com/drug/elidel-pimecrolimus-topical-343552> (accessed February 21, 2015).
- "Pimecrolimus Topical." Drugs.com. <http://www.drugs.com/mtm/pimecrolimus-topical.html> (accessed February 21, 2015).

ORGANIZATIONS

- American Academy of Dermatology (AAD), PO Box 4014, Schaumburg, IL 60168, (847) 240-1280, (866) 503-SKIN, (847) 240-1859, <http://www.aad.org/>.
- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, 888-INFO-FDA (463-6332), <http://www.fda.gov/>.

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Pioglitazone

Definition

Pioglitazone is an oral drug for treating type 2 diabetes. It is in the drug classes of oral antidiabetics and thiazolidinediones (TZDs), also called "glitazones."



Actos (pioglitazone), 15 mg. (© Cengage Learning®.)

Purpose

Type 2 diabetes is a condition in which the body has lost its ability to respond properly to the hormone insulin, making it difficult to control blood glucose (sugar) levels. By controlling blood sugar levels, pioglitazone and other diabetes medications can help prevent life-threatening complications of high blood sugar, including heart disease and heart attacks, stroke, nerve damage, kidney failure, gum disease, and eye problems including vision loss. Pioglitazone does not cure type 2 diabetes, but, in combination with diet and exercise, it can reduce the risk of serious problems. The American Diabetes Association and the European Association for the Study of Diabetes label pioglitazone as a third-choice agent for diabetes management, after lifestyle changes and the drug metformin. Pioglitazone can:

- help keep blood glucose at target levels without causing low blood sugar (hypoglycemia), although the risk of hypoglycemia is higher if pioglitazone is used in combination with other diabetes medications such as sulfonylureas or insulin
- work longer than other diabetes medications, which often lose their effectiveness after several years
- raise levels of HDL (“good”) cholesterol slightly

- lower triglycerides (a type of blood fat) more than other diabetes drugs
- lower blood pressure slightly
- reduce liver fat and possibly even reverse fatty liver disease
- possibly help protect kidney function
- possibly reduce the risk of heart attack and stroke
- lower hemoglobin A1C by about 1 point

Pioglitazone is sometimes used alone, but it is most often used in combination with other diabetes drugs that work in different ways, such as **metformin** or **glyburide** or another sulfonylurea. Pioglitazone is not used to treat type 1 diabetes, in which the body fails to produce insulin, or diabetic ketoacidosis, a serious condition that can develop from untreated high blood sugar.

Off-label use

Pioglitazone may be prescribed for other purposes, including treatment of nonalcoholic fatty liver disease. It has also been used to treat polycystic ovary syndrome, a common cause of infertility that is linked to diabetes. In early 2015, a large study was examining whether pioglitazone could delay symptoms of Alzheimer’s disease in cognitively normal people at high risk for dementia due to age and genetics.

Description

Pioglitazone lowers blood sugar by decreasing insulin resistance and helping to restore the body’s sensitivity to insulin in muscle and fat. This enables glucose to enter cells rather than remaining in the blood. Pioglitazone also reduces the amount of glucose produced by the liver, which is often far too high in people with type 2 diabetes.

Pioglitazone is supplied as 15, 30, and 45 milligram (mg) tablets. Depending on the brand, the tablets are round or oval; white, blue, or green; and may be debossed with the dose. They should be stored in the tightly closed container they are supplied in, away from heat, light, and moisture (not in the bathroom). Pioglitazone is also available in a combination medication with metformin (Actoplus Met and Actoplus Met XR).

U.S. brand names

The U.S. brand name for pioglitazone is Actos.

Canadian brand names

The Canadian brand names for pioglitazone are Apo-Pioglitazone and Sandoz Pioglitazone.

KEY TERMS

Agonist—A drug, such as pioglitazone, that interacts with a receptor and mimics the effects of endogenous receptor-binding substances.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Congestive heart failure—A condition in which the heart is unable to maintain adequate circulation or pump out venous blood.

Diabetes mellitus, type 2—Adult-onset or non-insulin-dependent diabetes; the most common form of diabetes, most often developing in obese adults and characterized by high blood glucose (hyperglycemia) due to impaired insulin utilization.

Diabetic ketoacidosis—A condition caused by low insulin levels where the amount of sugar and ketones in the blood is high.

Hemoglobin A1C—Glycated hemoglobin; a stable binding of glucose to hemoglobin A in the blood, which can be used to determine the average blood glucose level for the previous two to three months.

High-density lipoprotein (HDL)—“Good” cholesterol; protein in the blood that includes small amounts of triglyceride and cholesterol and helps protect against heart disease.

Hypoglycemia—Low blood sugar.

Insulin—A protein hormone synthesized in the pancreas and secreted by beta cells that is required for the metabolism of carbohydrates, lipids, and proteins and that regulates blood sugar levels by facilitating the uptake of glucose into tissues; converting sugars to glycogen, fatty acids, and triglycerides; and preventing the release of glucose from the liver.

Sulfonylurea—An oral drug for treating type 2 diabetes.

Thiazolidinediones (TZDs)—A class of oral diabetes drugs, especially pioglitazone.

Triglycerides—Neutral fats; lipids formed from glycerol and fatty acids that circulate in the blood as lipoprotein; an elevated triglyceride level is a risk factor for diabetes.

International brand names

There are many international brand names for pioglitazone, of which Actos is the most common. Other common brand names are Glustin, Acpio, Pioglit, Pitazone, and Zatium.

Origins

Pioglitazone was first approved by the U.S. Food and Drug Administration (FDA) in 1999. Various generic versions have been available since 2012. Troglitazone, the first TZD, was withdrawn from the market because it caused serious liver problems in a small fraction of patients. Rosiglitazone (Avandia), the only other TZD on the U.S. market, may increase heart attack risk and is only prescribed for patients who cannot take other diabetes drugs.

Recommended dosage

The recommended initial dosage of pioglitazone for type 2 diabetes is 15–30 mg once daily with a meal, which may be increased with careful monitoring to a maximum of 45 mg once daily. It is taken at the same time each day. A missed dose is taken as soon as possible but is skipped if it is not remembered until the next day.

It can take two weeks before blood sugar begins to decrease and two to three months for pioglitazone to exert its full effects. The drug should continue to be taken exactly as prescribed, no more or less, and should not be stopped without consulting the prescribing physician.

Other conditions and allergies

Patients should contact their doctor in case of illness, infection, fever, injury, or unusual stress, because these can affect blood sugar levels and may require adjusting the pioglitazone dose. The dose should be reduced or the drug stopped in patients who develop any signs of heart failure.

Precautions

Pioglitazone carries a boxed warning that TZDs can cause or worsen congestive heart failure. After starting a TZD or increasing the dose, patients should be carefully monitored for signs and symptoms of heart failure, including:

- rapid, excessive weight gain
- shortness of breath, especially when lying down or exercising
- swelling of the hands, feet, ankles, or abdomen
- stomach pain

- dry cough or wheezing
- confusion
- fast or irregular heartbeat
- loss of appetite
- weakness
- increased tiredness

In 2011, the FDA required the addition of a pioglitazone warning label stating that the use of pioglitazone for more than one year increases the risk of bladder cancer by an estimated 40%. France has suspended pioglitazone use, and Germany has recommended against its initiation in new patients. However, a European Medicine Agency review concluded that pioglitazone's overall benefits outweigh its risks.

Additional precautions include:

- Pioglitazone can cause an average weight gain of 6–9 lb. (3–4 kg).
- Pioglitazone can cause fluid retention and swelling, especially in combination with insulin.
- Pioglitazone can affect blood sugar levels, so patients should be aware of the symptoms of high blood sugar (thirst, increased urination, confusion, drowsiness, flushing, rapid breathing, or fruity breath odor) and low blood sugar (sudden sweating, shaking, fast heartbeat, hunger, blurred vision, dizziness, or tingling hands or feet) and the appropriate responses.
- Blood sugar and glycated hemoglobin (A1C) should be checked regularly for response to pioglitazone. Other laboratory tests, such as liver function and complete blood counts, and regular eye exams are also required.
- Pioglitazone slightly increases the risk of anemia (low red blood cell counts).
- Pioglitazone can cause liver problems. Patients should stop taking the drug and call their doctor immediately if they experience nausea, vomiting, loss of appetite, pain in the upper right stomach, flulike symptoms, dark urine, yellowing of the skin or eyes, unusual bleeding or bruising, or lack of energy.
- Pioglitazone may increase the risk of broken bones, especially of the upper arms, hands, or feet, in women but not in men.
- Doctors and dentists should be informed of pioglitazone use (and all prescription and nonprescription medications, herbal products, and supplements) before performing any type of surgery.

Patients should discuss the risks of pioglitazone with their healthcare provider.

Pediatric

Pioglitazone is not recommended for pediatric patients.

Pregnant or breastfeeding

Pioglitazone is in the FDA pregnancy category C. It should be used during pregnancy only when clearly needed. The doctor may prescribe insulin during pregnancy instead. Pioglitazone can also promote ovulation, increasing the chance of pregnancy, and may decrease the effectiveness of **oral contraceptives**. It is not known whether pioglitazone passes into breast milk, but women should not breastfeed while taking it to avoid potential risks to an infant.

Other conditions and allergies

The doctor and pharmacist should be informed of allergies to pioglitazone, any ingredients in pioglitazone tablets, or any other medications. Patients with heart failure, active bladder cancer, moderate to severe liver impairment, or diabetic ketoacidosis should not take pioglitazone. Patients should tell their doctor if they have or have ever had:

- heart disease, including heart failure, heart attack, irregular heartbeat, chest pain, a congenital heart defect, or coronary artery disease
- bladder cancer
- diabetic eye disease
- kidney or liver disease
- fluid in the lungs
- swelling in the arms, hands, feet, ankles, or lower legs
- anemia
- an eye problem called macular edema
- high blood cholesterol or fats
- sleep apnea
- high blood pressure

Side effects

Although pioglitazone generally causes few side effects, potential side effects include:

- hypoglycemia and swelling
- upper respiratory infection
- headache
- heart failure
- sinus inflammation
- bone fracture
- muscle pain
- inflammation of the pharynx

Other possible side effects include:

- worsened diabetes
- diabetic macular edema
- increased cholesterol
- decreased red blood cells or hemoglobin (anemia)
- decreased vision
- difficulty breathing
- weight gain
- liver failure (rare)

Patients should consult their doctor if any of the following symptoms are severe or persistent:

- headache
- muscle pain
- pain in the arms or legs
- sore throat
- gas

Patients should call their doctor immediately if they experience:

- changes in vision or vision loss
- frequent, painful, or difficult urination
- cloudy, discolored, or bloody urine
- back or abdominal pain

Other conditions and allergies

Although serious allergic reactions to pioglitazone are rare, immediate medical help is necessary for symptoms such as:

- rash
- itching or swelling of the face, tongue, or throat
- dizziness
- difficulty breathing

Interactions

It is very important that the doctor and pharmacist be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used. Because many drugs can affect blood sugar levels, patients should not start, stop, or change doses of any medications without consulting their doctor. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Drugs

There is a risk of hypoglycemia when pioglitazone is used in combination with insulin or other oral antidiabetic drugs. When coadministered with pioglitazone,

dosages of drugs that increase insulin secretion, such as sulfonylureas, should be decreased, and insulin doses should be decreased by 10%–25%. Beta blockers, such as **metoprolol** and **propranolol**, and glaucoma eye-drops, such as **timolol**, may inhibit the fast or pounding heartbeat that usually serves as a warning symptom of hypoglycemia; other symptoms of low blood sugar, such as dizziness, hunger, or sweating, are unaffected by these drugs. Pioglitazone dosages should be limited to 15 mg per day when coadministered with a strong CYP2C8 inhibitor such as **gemfibrozil**. Rifamycins, such as **rifampin**, can also affect the removal of pioglitazone from the body. Other drugs that may require changing doses or careful monitoring for side effects include:

- **atorvastatin** (Lipitor)
- hormonal contraceptives, including birth control pills, patches, rings, implants, and injections
- **ketoconazole** (Nizoral)
- midazolam (Versed)
- **nifedipine** (Procardia)

Herbs and supplements

Patients should ask their doctor whether they should take calcium/vitamin D supplements.

Food and other substances

A healthy diet, regular exercise, and weight loss (if necessary) will improve the effectiveness of pioglitazone. Eating meals on a regular schedule helps prevent hypoglycemia. Patients should consult their doctor or pharmacist if they miss a meal. They should carry glucose tablets or gel to treat low blood sugar and inform their doctor immediately if symptoms of hypoglycemia occur. Alcohol should be limited because it can increase the risk of hypoglycemia.

Resources

BOOKS

Bhattacharya, Apurba, Rakeshwar Bandichhor, and Lokeswara Rao Madivada. "Improved and Greener Process for Pioglitazone and its Pharmaceutically Acceptable Salts." In *Scalable Green Chemistry: Case Studies from the Pharmaceutical Industry*, edited by Stefan G. Koenig. Singapore: Pan Stanford, 2013.

PERIODICALS

- Arnetz, Lisa, et al. "Gender Differences in Non-Glycemic Responses to Improved Insulin Sensitivity by Pioglitazone Treatment in Patients with Type 2 Diabetes." *Acta Diabetologica* 51, no. 2 (April 2014): 185–92.
- He, Shiyao, et al. "Pioglitazone Prescription Increases Risk of Bladder Cancer in Patients with Type 2 Diabetes: An

Updated Meta-Analysis.” *Tumor Biology* 35, no. 3 (2014): 2095–102.

Viscoli, Catherine M., et al. “Pioglitazone for Secondary Prevention after Ischemic Stroke and Transient Ischemic Attack: Rationale and Design of the Insulin Resistance Intervention after Stroke Trial.” *American Heart Journal* 168, no. 6 (2014): 823–29.

Wang, Shirley S. “Alzheimer’s Disease Fight Focuses on Preventive Treatment.” *Wall Street Journal* (July 15, 2014): D1.

WEBSITES

American Diabetes Association. “What Are My Options?” <http://www.diabetes.org/living-with-diabetes/treatment-and-care/medication/oral-medications/what-are-my-options.html> (accessed March 1, 2015).

Humphries, Andrea, et al. “Medicines for Type 2 Diabetes: A Review of the Research for Adults.” Effective Health Care Program, Agency for Healthcare Research and Quality. <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=721> (accessed March 1, 2015).

Inzucchi, Silvio, Lawrence A. Leiter, and Julio Rosenstock, eds. “Fact Sheet: Type 2 Diabetes and TZDs.” Hormone Health Network. <http://www.hormone.org/questions-and-answers/2012/type-2-diabetes-and-tzds> (accessed March 1, 2015).

MedlinePlus. “Pioglitazone.” U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699016.html> (accessed March 1, 2015).

“Pioglitazone (Rx)—Actos.” Medscape Reference. <http://reference.medscape.com/drug/actos-pioglitazone-342726#91> (accessed March 1, 2015).

U.S. Food and Drug Administration. “Women and Diabetes—Diabetes Medicines.” <http://www.fda.gov/ForConsumers/ByAudience/ForWomen/WomensHealthTopics/ucm216110.htm> (accessed March 1, 2015).

ORGANIZATIONS

Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, (301) 427-1364, <http://www.ahrq.gov/>.

American Diabetes Association, 1701 North Beauregard Street, Alexandria, VA 22311, (800) DIABETES (342-2383), <http://www.diabetes.org/>.

Endocrine Society, 2055 L Street NW, Suite 600, Washington, DC 20036, (202) 971-3636, (202) 736-9705, (888) 363-6274, hormone@endocrine.org, <http://www.endocrine.org/>.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 9000 Rockville Pike, Bethesda, MD 20892-2560, (301) 496-3583, <http://www.niddk.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY JAMES E. WAUN, MD, RPh

Plan B see **Levonorgestrel**

Plaquenil see **Hydroxychloroquine**

Plavix see **Clopidogrel**

Potassium chloride

Definition

Potassium chloride is an electrolyte that is essential for many bodily functions. Oral or intravenous potassium chloride is used to treat low potassium levels (hypokalemia). It is in the drug class of electrolyte supplements.

Purpose

Potassium chloride is used to prevent or treat hypokalemia (potassium deficiency). People normally obtain all of their required potassium from food; however, certain diseases and conditions, including kidney disease, vomiting, diarrhea, and abnormally high levels of the hormones aldosterone or insulin, can deplete potassium levels. Treatment with diuretics (“water pills”), metabolic alkalosis (high alkalinity or pH in the body), and diabetic ketoacidosis can also deplete potassium. Potassium chloride is sometimes prescribed for other purposes.



Potassium chloride ER (extended release), 20 mEq.
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KEY TERMS

Aldosterone—A steroid hormone produced by the adrenal cortex that regulates salt and water balance in the body.

Diuretic—“Water pill”; a medication that increases urine excretion and removes water and salt from the body, which helps lower blood pressure.

Electrocardiography (ECG or EKG)—Recording of the electrical potential during the heartbeat.

Electrolytes—Ions, such as potassium, calcium, sodium, and chloride, that are dissolved in bodily fluids such as blood and that regulate or affect most metabolic processes.

Hyperkalemia—Excess potassium in the blood.

Hypokalemia—Potassium deficiency.

Intravenous (IV)—Injected into a vein.

KCl—Potassium chloride.

Milliequivalent (mEq)—One-thousandth of an equivalent of an element; used for the concentration of electrolytes in a solution; 1 mEq of potassium chloride is 1 millimole or 75 mg.

Parenteral—Administered inside the body but outside the digestive tract.

Description

Potassium is the major cation (positively charged ion) in intracellular fluid. Among other functions, potassium is essential for:

- conduction of nerve impulses in the heart, brain, and skeletal muscle
- contraction of the heart, skeletal, and smooth muscles
- maintenance of kidney function
- maintenance of acid-base balance in the body
- carbohydrate metabolism
- gastrointestinal secretions

Potassium is ingested in food and beverages and excreted in the urine. It is readily absorbed in the upper digestive tract and actively transported from extracellular fluids into cells. Potassium levels are measured with a blood test, usually as milliequivalents (mEq) of potassium chloride (KCl) per liter (L), which is the same as millimoles (mmol) of KCl per L. One mEq of KCl is 75 milligrams (mg). The normal range of KCl in adult blood serum or plasma is 3.5–5.1 mEq/L. In children, the normal range is 3.4–4.7 mEq/L depending on age. Higher

or lower levels increase the risk of an irregular heartbeat and other problems. Potassium levels are affected by various factors, such as aldosterone, a hormone produced by the adrenal glands, and sodium levels—potassium levels increase as sodium levels decrease. However, potassium levels in the blood represent only 2% of the potassium in the body. Most potassium is inside of cells.

Potassium supplementation may be supplied alone or as a component of combination drugs or solutions. Oral potassium chloride comes in many forms—liquids, powders, granules, regular tablets, effervescent tablets (tablets that break up in contact with liquid and release carbon dioxide), microcapsules, and extended-release tablets and capsules. Oral potassium is always taken with a full glass of water or fruit juice. Liquids are added to water. Powders, granules, and effervescent tablets are dissolved in cold water or fruit juice according to the specific instructions and mixed well just before drinking. Cold liquids help disguise the unpleasant taste. Solutions should be clear and used within 24 hours. Long-acting (extended-release) and wax-matrix tablets are swallowed whole, not dissolved in the mouth, crushed, or chewed. Oral potassium chloride is generally taken two to four times per day, with or immediately following meals. It is kept in the tightly closed container it is supplied in, at room temperature, and away from excess heat and moisture (not in the bathroom).

Oral potassium chloride dosage forms include:

- 20 or 40 mEq/15 mL as 120 mL or 480 mL oral solutions (flavored or unflavored, with or without alcohol or sugar)
- 20 mEq or 25 mEq packets of powder for oral solutions (unflavored or fruit flavored and/or sugar free)
- 8 mEq (600 mg) or 10 mEq (800 mg) wax-matrix tablets
- 10 mEq (800 mg) film-coated tablets
- 8 mEq (600 mg), 10 mEq (800 mg), or 15 mEq (1,125 mg) microcapsules
- 20 mEq (1,500 mg) scored microcapsules
- 8 mEq (600 mg), 10 mEq (800 mg), or 20 mEq (1,500 mg) extended-release tablets
- 10 mEq (800 mg) wax-matrix, film-coated, slow-release tablets
- 10 mEq (800 mg) extended-release capsules

Parenteral potassium chloride is diluted or supplied as a premixed solution and injected or incorporated into maintenance intravenous (IV) fluids for infusion. The maximum concentration for a peripheral line is 80 mEq/L and for a central line is 150 mEq/L or 15 mEq/100 mL.

U.S. brand names

There are various brand-name and generic potassium chloride products available in the United States, including:

- Glu-K
- K+ 8
- K+ 10
- Kaochlor 10%
- Kaon Elixir
- Kaon-Cl-10
- Kay Ciel
- K-Dur 10
- K-Lor
- Klor-Con 10
- Klotrix
- K-Lyte Effervescent Tablets
- K-Tab Filmtab
- Micro-K
- Quic-K
- Rum-K
- Slow-K
- Tri-K
- Twin-K

Canadian brand names

Canadian brand names for potassium chloride include:

- Apo-K
- K-10
- K-Dur
- K-Lor
- K-Lyte/Cl
- Micro-K Extencaps
- Roychlor
- Slow-K

International brand names

Among the more common of the many international brand names for potassium chloride are:

- Addex-Kaliumklorid
- Apo-K
- Kaldyum
- Kaleorid
- Kalii Chloridi
- Kalij klorid Jadran
- Kaliumchlorid B. Braun
- Kay-Cee-L

- KCl-retard Zyma
- Slow-K
- Span-K

Recommended dosage

Recommended dosages vary depending on serum potassium levels, but the usual oral or IV requirements for adults are 40–80 mEq per day.

- For treating hypokalemia, oral doses are 20–40 mEq 2–4 times per day.
- For IV treatment of hypokalemia with intermittent infusion, the usual dose is 5–10 mEq per hour, with a maximum of 40 mEq per hour and 400 mEq in 24 hours.
- At serum (blood) potassium levels above 2.5 mEq/L, the maximum infusion rate is 10 mEq/hour to a maximum concentration of 40 mEq/L and a maximum 24-hour dose of 200 mEq.
- For potassium levels below 2.5 mEq/L, the initial oral dose may be up to 40–60 mEq, with further doses based on laboratory values.
- For serum potassium levels below 2.5 mEq/L, the maximum infusion rate is 40 mEq/hour to a maximum concentration of 80 mEq/L and a maximum 24-hour dose of 400 mEq.
- For preventing hypokalemia, the initial oral dose is generally 20 mEq per day.
- For preventing hypokalemia during diuretic therapy, the usual oral dosage is 20–40 mEq per day in one or two divided doses.

A missed oral dose is taken as soon as it is remembered, with the day's remaining doses taken at evenly spaced intervals. Double doses are not taken to compensate for a missed dose.

Pediatric

For treating hypokalemia, the usual pediatric dose is 0.5–2 mEq per kilogram (kg) of body weight orally every 12 hours or 0.5 mEq per kg per hour IV for 1–2 hours with close monitoring. Other dosing schedules include:

- premature infants: 2–6 mEq per kg body weight per 24 hours
- full-term infants aged 0–24 hours: 0–2 mEq/kg/24 hours
- infants older than 24 hours: 1–2 mEq/kg/24 hours
- children: initially 1–2 mEq/kg orally, then as needed, or 2–3 mEq/kg/day
- children with severe or ongoing potassium loss: initially 1 mEq/kg IV over 1–2 hours, then repeated as needed, with a maximum of 40 mEq per hour or 3 mEq/kg/day

- for prevention during diuretic therapy in children: 1–2 mEq/kg/day orally in 1 or 2 divided doses

Other conditions and allergies

Solid oral forms of potassium are not administered to patients with conditions that would cause its passage through the gastrointestinal tract to be delayed or halted. Oral liquid preparations are used for patients with esophageal compression or delayed stomach-emptying times.

Precautions

Potassium chloride administration requires blood tests to determine serum potassium concentrations and correct dosages and may require electrocardiography (ECG) to monitor heart activity. Doctors and dentists should be told of potassium administration before performing any type of surgery.

Potassium chloride should be taken only as prescribed, never more or less than prescribed or more often. However, potassium chloride is the fourth most common medication involved in drug administration errors (after insulins, **albuterol**, and **morphine**). Symptoms of potassium overdose include:

- heart electrical abnormalities and arrhythmias
- muscle weakness
- paralysis

Pregnant or breastfeeding

Potassium chloride is in the FDA pregnancy category C, meaning that it should be used cautiously only if benefits outweigh risks to the fetus. Women should call their doctor if they become pregnant while taking potassium. Potassium chloride's effects on breast milk are not known. Nursing mothers should consult with their physician.

Other conditions and allergies

Patients should tell their doctor and pharmacist if they are allergic to potassium or any other medications. Caution is required when administering potassium to patients who have or have ever had cardiovascular disease, Addison's (adrenal gland) disease, or kidney impairment. Potassium should only be used for severe depletion in patients who are undergoing ECG monitoring. Potassium should not be administered to patients with:

- hypersensitivity to potassium
- severe kidney impairment or kidney failure
- untreated Addison's disease
- heat cramps

- hyperkalemia (high serum potassium)
- severe tissue trauma

Side effects

More than 10% of patients taking potassium chloride experience gastrointestinal upset, including diarrhea, nausea, stomach pain, flatulence, and vomiting. Patients should consult their doctor if these symptoms are severe or persistent. Side effects affecting 1%–10% of patients are:

- slow heartbeat (bradycardia)
- hyperkalemia
- pain or skin reactions at the site of injection
- weakness
- labored breathing

Side effects affecting less than 1% of patients but that require immediately calling the physician are:

- increased alkalinity of the blood and tissues (alkalosis)
- irregular heart rhythm (arrhythmia)
- chest pain
- heart block
- hypotension (low blood pressure)
- mental confusion
- pricking, creeping, or tingling skin sensations (paresthesia)
- burning, tightness, or pulling sensations in the arms, hands, legs, or feet
- heaviness or weakness in the legs
- paralysis
- inflammation of a vein (phlebitis)
- rash
- throat pain
- listlessness
- cold, pale, gray skin
- unusual stomach bulging
- black stools

Interactions

The doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Drugs

Potassium should not be taken by patients taking amiloride (Midamor), **spironolactone** (Aldactone), or

triamterene (Dyrenium). Other drugs that can cause serious or life-threatening interactions with potassium and require the use of alternative medications or close monitoring are:

- drosiprenone
- eplerenone
- **oxybutynin**
- potassium acid phosphate
- potassium citrate
- IV potassium chloride and potassium phosphates

At least 106 other medications have significant interactions with potassium and require close monitoring. Potassium-sparing diuretics and angiotensin-converting enzyme (ACE) inhibitors, such as captopril (Capoten), **enalapril** (Vasotec), and **lisinopril** (Prinivil, Zestril), used for treating high blood pressure can increase potassium levels or the effects of potassium. Drugs that can cause potassium loss include beta-adrenergic agonists such as isoproterenol, alpha-adrenergic antagonists such as **clonidine**, antibiotics such as gentamicin and carbenicillin, and the antifungal agent amphotericin B. Low urine potassium levels may result from the use of glucocorticoids or nonsteroidal anti-inflammatory drugs (NSAIDs).

Food and other substances

Plenty of fluids and/or food should be administered with potassium to reduce stomach irritation and discomfort. Patients should tell their doctor if they use salt substitutes, because many of these contain potassium and should be considered when determining potassium dosages. Patients may be advised to eat potassium-rich foods, such as bananas, prunes, raisins, and milk.

Resources

PERIODICALS

Ingelfinger, Julie R., and Julian L. Seifter. "Disorders of Fluids and Electrolytes: Integration of Acid-Base and Electrolyte Disorders." *New England Journal of Medicine* 371, no. 19 (2014): 1821–31.

WEBSITES

Lerma, Edgar V. "Potassium." Medscape.com. <http://emedicine.medscape.com/article/2054364-overview#showall> (accessed March 1, 2015).

MedlinePlus. "Potassium." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601099.html> (accessed March 1, 2015).

"Potassium Chloride." Health Library, University of Maryland Baltimore Washington Medical Center. <http://www.mybwmc.org/library/41/103795> (accessed March 1, 2015).

"Potassium Chloride (Rx)." Medscape.com. <http://reference.medscape.com/drug/kdur-slow-k-potassium-chloride-344450#0> (accessed March 1, 2015).

ORGANIZATIONS

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Pradaxa see **Dabigatran**

Pramipexole

Definition

Pramipexole dihydrochloride, or simply pramipexole, is a prescription medication used to treat movement disorders. It is in a class of medications called dopamine agonists. Dopamine is a substance in the brain that affects movement.



Mirapex (pramipexole), 1 mg. (© Cengage Learning®.)

KEY TERMS

Dopamine—A neurotransmitter in the brain that influences many of the brain's functions, including movement, areas of thinking, pleasure, and control of hormones.

Neurotransmitter—A chemical in the brain that can affect the activity of neurons, or nerve cells.

Parkinson's disease—A chronic, progressive disease that begins when the brain fails to develop enough dopamine, which affects the coordination of the body's movement.

Purpose

People who have Parkinson's disease experience progressively worse symptoms such as tremors, or slight shakiness, while the person is at rest. They also have slow movement, rigid limbs, and problems with balance and walking, along with some pain, fatigue, and other symptoms. Pramipexole can help individuals with Parkinson's disease move easier and provide some relief of other symptoms. Pramipexole dihydrochloride acts on the central nervous system (CNS) in place of dopamine to help improve Parkinson's disease symptoms.

Pramipexole is also prescribed to some people who have a condition known as restless legs syndrome (also called Willis-Ekbom disease) that causes them to have discomfort in their legs, especially when sitting or lying down. The discomfort is accompanied by an urge to move the legs.

Description

Pramipexole comes as a tablet taken by mouth or as an extended-release (long-acting) tablet, also taken by mouth. The timing and number of times pramipexole is taken per day depends on the reason for the drug's use. Although the medicine can help manage symptoms of Parkinson's disease and restless legs syndrome, it is not considered a cure for either disease.

U.S. brand names

In the United States, pramipexole is sold under the brand name Mirapex.

Recommended dosage

Pramipexole adult dosage is usually started at 0.125 milligrams (mg) three times a day (for a total of 0.375 mg) for treatment of Parkinson's disease

symptoms, and gradually increased to a maximum of 1.5 mg taken three times a day, or 4.5 mg of pramipexole a day. The extended-release tablets come in dosages of 0.375 mg and are taken once a day. Extended-release therapy also is increased gradually, however, to reach this average dose. Patients who are taking the immediate-release tablets may switch the next day to an extended-release formula of the same dose, though some may require dose adjustment once they begin taking the long-acting tablets.

For treatment of restless legs syndrome, patients usually begin at 0.125 mg and increase the dose by the same amount every four to seven days until the medicine becomes effective. Once they are taking the medicine for maintenance of the condition, they generally take 0.5 mg once a day. When taking pramipexole for restless legs syndrome, the medicine should always be taken two to three hours before bedtime.

Precautions

Pramipexole should always be started and discontinued gradually. Pramipexole may cause sudden sleepiness (including while driving or performing other activities) and a sudden drop in blood pressure when standing after sitting or lying down. Some people who take pramipexole and similar medications experience problems controlling impulses, which can lead to compulsive use of the medication, gambling problems, compulsive shopping, and similar behaviors.

Pramipexole can cause jerky motions in some people. Hallucinations also have been reported by some people who have taken pramipexole.

Pediatric

Pramipexole has not been evaluated for safety or effectiveness in children.

Geriatric

Risk of some side effects, such as hallucinations, increases with age. Older people who take pramipexole should also be aware of the possibility of low blood pressure upon standing because it can increase risk of falls and fractures.

Pregnant or breastfeeding

Pramipexole is a pregnancy category C drug. It has only been tested in animals, and women who are pregnant should only take the medication if the potential benefits clearly outweigh possible risks. Women who are nursing should discontinue use of pramipexole or choose not to breastfeed to avoid problems associated with pramipexole and nursing.

Other conditions and allergies

Anyone who has kidney disease or poor kidney function should discuss the condition with the doctor before taking pramipexole.

Side effects

Pramipexole can cause many side effects, including:

- abnormal body movements
- nausea and loss of appetite
- heartburn, constipation, and diarrhea
- dizziness
- weakness and drowsiness
- sleep problems
- memory or thinking problems
- confusion and strange thoughts or dreams
- urgent or frequent need to urinate
- pain or problems when urinating

Some side effects of pramipexole use can be severe and should be reported to a doctor right away. These include:

- visual or aural hallucinations
- changes to vision
- chest pain and problems breathing
- urine that darkens or turns red
- muscle weakness, pain, or stiffness

Interactions

Some drugs or substances can interfere with the effectiveness of prescription drugs or cause side effects to worsen. It is important to tell the doctor about any medications, herbal remedies, or other supplements being taken before starting pramipexole.

Drugs

It is especially important to discuss with a doctor any medicines that also affect dopamine, such as drugs called dopamine antagonists. Some antidepressant medicines may slightly affect how well the body processes pramipexole dihydrochloride. Other medications that tend to interact with pramipexole include various antipsychotics, cimetidine, central nervous system depressants, **diltiazem**, levodopa, and **metoclopramide**.

Resources

PERIODICALS

Fernandez, Hubert H. "Updates in the Medical Management of Parkinson Disease." *Cleveland Clinic Journal of Medicine* 79, no. 1 (2012): 28–35.

Garcia-Ruiz, Pedro J., et al. "Impulse Control Disorder in Patients with Parkinson's Disease under Dopamine Agonist Therapy: A Multicentre Study." *Journal of Neurology, Neurosurgery, and Psychiatry* 85, no. 8 (2014): 841–45.

Patel, Tejal, and Feng Chang. "Parkinson's Disease Guidelines for Pharmacists." *Canadian Pharmacists Journal* 147, no. 3 (2014): 161–70.

WEBSITES

Boehringer Ingelheim Pharmaceuticals, Inc. "About Mirapex." https://www.mirapexer.com/about_mirapex/index (accessed February 21, 2015).

MedlinePlus. "Pramipexole." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a697029.html> (accessed February 21, 2015).

"Pramipexole." Drugs.com. <http://www.drugs.com/cdi/pramipexole.html> (accessed February 21, 2015).

ORGANIZATIONS

The Michael J. Fox Foundation for Parkinson's Research, Grand Central Station, PO Box 4777, New York, NY 10163-4777, (800) 708-7644, <https://www.michaeljfox.org/>.

Parkinson's Disease Foundation, 1359 Broadway, Suite 1509, New York, NY 10018, (212) 923-4700, (212) 923-4778, <http://www.pdf.org/en/index>.

Teresa G. Odle, BA, ELS

REVIEWED BY GREGORY A. PRATT, RPh

Prasugrel

Definition

Prasugrel is an oral medication for treating blood-clotting disorders and preventing blood clots in people with coronary heart disease. It is an antiplatelet agent in the drug class of adenosine diphosphate (ADP) receptor antagonists. It is in the thienopyridine class of platelet activation and aggregation inhibitors.

Purpose

Prasugrel is used in combination with **aspirin** to help prevent further serious or life-threatening cardiovascular events in patients who have already had a heart attack or severe chest pain (unstable angina) from lack of oxygen to the heart and in patients who have been treated with angioplasty to open the blood vessels that supply blood to the heart. Prasugrel can help prevent another heart attack, stroke, blood clots after angioplasty, and death. Prasugrel may be prescribed for other purposes.



Effient (prasugrel), 10 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

Platelets are a type of blood cell involved in normal blood clotting. However, platelets are also involved in forming blood clots that can block an artery or a stent and cause a heart attack or stroke. Prasugrel hydrochloride is a prodrug that is rapidly metabolized in the intestines to a thiolactone that is converted to the active drug in a single step. This active metabolite binds irreversibly to a subtype of ADP receptors on the surfaces of platelets. Normal ADP interaction with these receptors promotes the activation and aggregation (clumping) of platelets to form blood clots. As an ADP-receptor antagonist, prasugrel binding to these receptors blocks ADP interaction with the receptors, thereby preventing the aggregation or sticking together of platelets to form a clot.

Within one hour, a 60-milligram (mg) loading dose of prasugrel inhibits platelet aggregation by at least 50% in about 90% of patients. Maximum inhibition of platelet aggregation is about 80%. After the 60 mg loading dose, 10 mg daily of prasugrel inhibits platelet aggregation by an average of about 70% within three to five days. After discontinuing the drug, platelet aggregation gradually returns to baseline levels over five to nine days as a result of new platelet production.

Prasugrel is supplied as 5 mg yellow tablets imprinted with “5” and “5121” and as 10 mg beige

tablets imprinted with “10” and “5123”. The tablets are elongated hexagonal-shaped, film-coated, and non-scored. They are supplied in blister packs or bottles of 30 tablets.

The tablets are taken by mouth, usually once a day and at about the same time each day, with or without food. The medication should be kept in the tightly closed container in which it is supplied. The container includes a gray cylinder to keep out moisture, which should be left in place. The container is stored at room temperature away from excess heat and moisture (not in the bathroom).

U.S. brand names

The U.S. brand name for prasugrel is Effient.

Canadian brand names

The Canadian brand name for prasugrel is Effient.

International brand names

The major international brand name for prasugrel is Efient.

Origins

Prasugrel hydrochloride, produced by Eli Lilly and Company, was originally approved by the U.S. Food and Drug Administration (FDA) in 2009.

Recommended dosage

Prasugrel treatment is initiated with a 60 mg loading dose, followed by 10 mg doses once daily. Patients also take 75–325 mg of aspirin. The prasugrel tablet is swallowed whole, without splitting, crushing, or chewing. A missed dose should be taken as soon as possible, unless it is almost time for the next dose, in which case it should be skipped and the normal dosing schedule resumed.

Patients weighing less than 132 lb. (60 kg) may be prescribed 5 mg once daily because of increased exposure to the active drug and increased risk of bleeding.

Other conditions and allergies

No dosage adjustment is necessary for patients with renal (kidney) impairment or mild-to-moderate liver impairment, although patients with end-stage renal disease or severe liver disease are generally at higher risk for bleeding.

KEY TERMS

Adenosine diphosphate (ADP)—A nucleotide with a variety of essential functions in the body, including activation and aggregation of platelets for blood-clot formation.

Angioplasty—Repair or opening of a blood vessel.

Antagonist—A drug, such as prasugrel, that blocks the action of a substance by binding to its receptor.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Clopidogrel—Plavix; an antiplatelet medication similar to prasugrel.

Platelets—Small cell-like bodies in the blood that are necessary for blood-clot formation.

Prodrug—A drug that is converted to its active form by an enzyme in the body.

Receptor—A molecule, usually a protein inside or on the surface of a cell, that binds to a specific substance, such as adenosine diphosphate, to control specific processes in the body.

Stent—A metal or plastic tube or mesh placed in a blood vessel to hold it open.

Stroke—The obstruction (ischemic) or rupture (hemorrhagic) of a blood vessel in the brain.

Thrombotic thrombocytopenic purpura (TTP)—A rare disorder in which clots form in small blood vessels throughout the body, which can occur with prasugrel.

Transient ischemic attack (TIA)—Occlusion (blockage) of a smaller blood vessel in the brain that can produce stroke-like symptoms for a few minutes to 24 hours but does not usually cause permanent damage.

Precautions

Prasugrel comes with a boxed warning regarding bleeding risk:

- Prasugrel can cause significant and sometimes fatal bleeding.
- Prasugrel should not be used by patients with active bleeding or a history of transient ischemic attack (TIA) or stroke.

- Prasugrel is not recommended for patients aged 75 and older.
- Prasugrel should be discontinued at least seven days before any surgery and should not be initiated in patients who are likely to undergo coronary artery bypass graft surgery.
- Additional risk factors include patients of small stature, a tendency to bleed, and the use of other medications that increase bleeding risk.
- Bleeding should be suspected in patients who have low blood pressure and have recently undergone surgical interventions.
- If possible, bleeding should be managed without discontinuing prasugrel because of increased risk of cardiovascular events when stopping the drug.

In 2014, the FDA added an additional boxed notice that it was evaluating preliminary clinical-trial data. The data indicated that 30 months of treatment with aspirin plus prasugrel or **clopidogrel** (Plavix), although decreasing the risk of heart attacks and clot formation in stents, increased the overall risk of death compared with 12 months of the dual-medication treatment. However, the FDA was not currently recommending changes to prasugrel prescribing practices.

Patients should discuss the risks of prasugrel with their doctor.

- Prasugrel should be taken exactly as directed, no more or less and no more often. It must not be stopped without consulting the doctor because stopping prasugrel increases the risk of a heart attack, a blood clot in a stent, or death.
- Patients should get immediate medical help for symptoms of a stroke or TIA, including sudden slurring of speech, weakness or numbness in a part of the body, sudden blurred vision, or sudden severe headache. The doctor will probably instruct the patient on how to safely discontinue prasugrel.
- Patients should talk to their prescribing doctor before having any type of surgery or invasive procedure, and doctors and dentists should be told of prasugrel use before performing any type of surgery. It is usually necessary to discontinue prasugrel at least seven days before surgery.
- Patients should call their doctor immediately if they fall or are injured, especially if they hit their head.

Because prasugrel interferes with blood clotting, patients usually bleed and bruise more easily and longer than usual and often experience nosebleeds. The doctor should be called immediately if any of the following symptoms occur:

- unexplained, severe, long-lasting, or uncontrollable bleeding
- pink or brown urine
- red or black, tarry stools
- vomit that is bloody or looks like coffee grounds
- coughing up blood or blood clots
- unexplained or enlarging bruises

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening condition in which blood clots can form in blood vessels throughout the body. It sometimes develops in less than two weeks after initiating treatment with prasugrel and requires immediate hospital treatment. Symptoms can include:

- purplish spots called purpura on the skin or mucous membranes (such as on the mouth) from bleeding under the skin
- paleness or jaundice (a yellowish color of the skin or eyes)
- weakness or fatigue
- fever
- fast heart rate or shortness of breath
- headache, speech changes, confusion, stroke, seizure, or coma
- low amounts of urine or urine that is pink-tinged or contains blood
- abdominal pain, nausea, vomiting, or diarrhea
- visual changes

Pediatric

It is not known whether prasugrel is safe and effective for children.

Geriatric

Prasugrel is usually not recommended for patients aged 75 or older because of increased risk of fatal bleeding or bleeding in the brain. Elderly patients have a 1% risk of fatal bleeding events compared to a 0.1% risk for similar patients taking clopidogrel. Furthermore, the effectiveness of prasugrel in patients aged 75 and older is uncertain, except for high-risk patients with diabetes and a history of heart attack, in whom the drug appears to confer greater benefit.

Pregnant or breastfeeding

Prasugrel is in the FDA pregnancy category B, meaning that although there have been no adequate studies in pregnant women, animal studies have shown no evidence of fetal harm. Nevertheless, prasugrel should only be used during pregnancy if the potential benefit to the mother outweighs possible risk to the fetus. Women

should call their doctor if they become pregnant while taking prasugrel. It is not known whether prasugrel is excreted in human milk, but it should be used while nursing only if the potential benefit to the mother outweighs possible risk to the infant.

Other conditions and allergies

Patients should tell their doctor and pharmacist if they are allergic to prasugrel or any of its ingredients or to any other medications, especially clopidogrel or ticlopidine hydrochloride (Ticlid), have ever had kidney disease, or are planning to have surgery or a dental procedure. Patients are usually not prescribed prasugrel if they:

- are likely to have heart bypass surgery soon
- have ever had a condition that causes easy bleeding
- have abnormal bleeding, such as stomach or intestinal bleeding or bleeding in the head
- have ever had a stomach ulcer or any condition that could cause intestinal bleeding, such as polyps or diverticulitis
- have had a TIA or stroke
- have had recent surgery or an injury
- have liver disease

Bleeding risk may be higher in patients who weigh less than 132 lb. (60 kg), take other medications that increase bleeding risk, or who have:

- had surgery, an accident, or other trauma
- recent or recurrent stomach or intestinal bleeding or a stomach ulcer
- severe liver problems
- moderate to severe kidney problems

Side effects

Patients should tell their doctor if they have any severe or persistent side effects, including:

- dizziness
- excessive tiredness
- pain in the back, arms, or legs
- cough

Patients should call their doctor immediately if they experience signs of bleeding or:

- slow, fast, or irregular heartbeat
- slow or difficult speech
- sudden weakness of an arm or leg
- swelling of the eyes, face, mouth, lips, tongue, throat, arms, hands, feet, ankles, or lower legs
- rash

Other conditions and allergies

Serious allergic reactions are possible with prasugrel, especially in patients who have had serious allergic reactions to clopidogrel or ticlopidine. Symptoms that require immediate medical assistance include:

- swelling or hives on the face or lips or in or around the mouth or throat
- difficulty breathing or swallowing
- chest pain or pressure
- dizziness or fainting

Interactions

The doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

Drugs that can increase the risk of bleeding in combination with prasugrel include:

- anticoagulants (blood thinners) such as **warfarin** (Coumadin)
- medications containing heparin
- other medications to prevent or treat blood clots
- daily or regular use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as **ibuprofen** (Advil, Motrin) and naproxen (Aleve), or long-lasting NSAIDs such as **indomethacin** (Indocin) and piroxicam (Feldene)

Resources

BOOKS

Serebruany, Victor L., and Dan Atar. *Antiplatelet Therapy in ACS and A-Fib*. New York: Karger, 2012.

PERIODICALS

“Blood Thinners.” *Journal of the American Medical Association* 310, no. 23 (2013): 2579.

Cornel, Jan H., et al. “Impact of Smoking Status on Platelet Function and Clinical Outcomes with Prasugrel vs. Clopidogrel in Patients with Acute Coronary Syndromes Managed Without Revascularization: Insights from the TRILOGY ACS Trial.” *American Heart Journal* 168, no. 1 (2014): 76–87.e1.

Huber, Kurt, et al. “Antiplatelet and Anticoagulation Agents in Acute Coronary Syndromes: What is the Current Status and What Does the Future Hold?” *American Heart Journal* 168, no. 5 (2014): 611–21.

Matteau, Alexis, and Deepak L. Bhatt. “Recent Advances in Antithrombotic Therapy after Acute Coronary Syndrome.”

Canadian Medical Association Journal 186, no. 8 (2014): 589–96.

Parodi, Guido, et al. “Comparison of Double (360 mg) Ticagrelor Loading Dose with Standard (60 mg) Prasugrel Loading Dose in ST-Elevation Myocardial Infarction Patients: The Rapid Activity of Platelet Inhibitor Drugs (RAPID) Primary PCI 2 Study.” *American Heart Journal* 167, no. 6 (2014): 909–14.

Winslow, Ron. “New Thinking on Clot Risk—Study: Longer Blood-Thinner Use by Stent Patients Limits Future Heart Attacks.” *Wall Street Journal* (November 17, 2014): A3.

OTHER

“Antiplatelet Drugs: Do You Need One to Help Prevent a Heart Attack or Stroke?” *Consumer Reports*. <http://www.consumerreports.org/health/resources/pdf/best-buy-drugs/Antiplatelets-2paggers-FINAL.pdf> (accessed March 2, 2015).

Daiichi Sankyo, Inc. and Eli Lilly and Company. “Prescribing Information.” U.S. Food and Drug Administration. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022307s010lbl.pdf (accessed March 2, 2015).

WEBSITES

MedlinePlus. “Prasugrel.” U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a609027.html> (accessed March 2, 2015).

U.S. Food and Drug Administration. “FDA Drug Safety Communication: FDA Reviews Long-Term Antiplatelet Therapy as Preliminary Trial Data Shows Benefits but a Higher Risk of Non-Cardiovascular Death.” <http://www.fda.gov/Drugs/DrugSafety/ucm423079.htm> (accessed March 2, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Pravachol see **Pravastatin**

Pravastatin

Definition

Pravastatin is an oral drug used to treat high blood cholesterol levels and heart disease. It is a lipid-lowering agent in the drug class known as statins or HMG-CoA reductase inhibitors.



Pravastatin, 10 mg. (*U.S. National Library of Medicine, Pillbox*)

Purpose

The purpose of pravastatin is to reduce fatty substances in the blood—low-density lipoprotein (LDL or “bad” cholesterol) and triglycerides—while increasing high-density lipoprotein (HDL or “good” cholesterol). Cholesterol and fat accumulation in the walls of the arteries—atherosclerosis—decreases blood flow and oxygen supply to the heart, brain, and other parts of the body. Along with diet, weight loss, and exercise, statins such as pravastatin can lower cholesterol and triglyceride levels and help prevent heart disease, angina (chest pain), stroke, and heart attack. Statins can reduce the need for heart surgery in people with heart disease or at risk for developing heart disease and may help prevent cardiovascular events even in at-risk patients who have normal cholesterol levels. Pravastatin may sometimes be prescribed for other purposes.

The 20-year West of Scotland Coronary Prevention Study (WOSCOPS) demonstrated that five years of pravastatin treatment consistently increased protection against cardiovascular events over a period of two decades: initiating LDL-lowering treatment with pravastatin at about age 50 added five additional years of protection. Pravastatin lowered LDL cholesterol by 26% and total cholesterol by 20%. After 20 years, heart failure had been reduced by 31%, death from coronary heart disease had been reduced by 27%, and death from all causes was reduced by 13%. Pravastatin treatment had no effect on the incidence of stroke.

In 2013, the American Heart Association (AHA) and the American College of Cardiology (ACC) issued new guidelines for statin use, based on additional benefits for heart health beyond lowering LDL cholesterol levels. Under the new guidelines, almost 13 million additional adults in the United States are eligible for statins. Among healthy adults aged 40–75, statins are recommended for

anyone with at least a 7.5% risk of heart attack or stroke in the next ten years, with the risk determined by an equation based on age, gender, race, total cholesterol, blood pressure, diabetes, and smoking history. The guidelines call for statin use by those:

- aged 40–75 without cardiovascular disease but with at least a 7.5% risk of a heart attack or stroke within the next ten years
- with a history of heart attack, stroke, angina, peripheral artery disease, transient ischemic attack, or coronary or other arterial revascularization
- aged 21 or older with very high LDL cholesterol (190 mg/deciliter of blood or higher)
- aged 40–75 with type 1 or type 2 diabetes

Description

Statins are inhibitors of the enzyme HMG-CoA reductase. This enzyme controls the rate-limiting step in cholesterol biosynthesis by the body. Inhibition by statins slows this production. Pravastatin begins to take effect about two weeks after it is started and reaches its peak effect about four weeks after initiation. Most people continue to take statins for many years.

There are seven different statins approved by the U.S. Food and Drug Administration (FDA), five of which, including pravastatin, are available in generic forms. Statins all lower LDL cholesterol and reduce the risk of plaque development, but they vary in the degree to which they lower LDL and reduce the risk of cardiovascular disease. Pravastatin is a low-intensity statin, which means that it is used for patients who need to lower their LDL cholesterol by less than 30%. The statins may also differ in their side effects.

Pravastatin is available as 10, 20, 40, and 80 milligram (mg) oral tablets. Pravastatin should be kept in its original container, tightly closed, at room temperature and away from excess heat and moisture (not in the bathroom).

U.S. and Canadian brand names

The U.S. and Canadian brand name for pravastatin is Pravachol. Various generic pravastatins are available in both countries.

International brand names

There are many brand-name and generic pravastatins available internationally. Some of the more common brand names include:

- Elisor
- Lipostat
- Mevalotin

KEY TERMS

Atherosclerosis—The process in which the inner layer of the arteries thicken and harden due to the accumulation of plaque, a primary cause of coronary artery disease.

Cholesterol—A fat-soluble steroid alcohol (sterol) found in animal fats and oils and in egg yolks. The human body needs cholesterol to produce vitamin D, but too much cholesterol may contribute to cardiovascular disease.

HDL cholesterol—High-density lipoprotein, or “good” cholesterol. A lipoprotein in the blood that is primarily protein with small amounts of triglyceride and cholesterol that helps protect against heart disease.

LDL cholesterol—Low-density lipoprotein, or “bad” cholesterol. A lipoprotein in the blood with a high proportion of cholesterol. High levels of LDL increase the risk of coronary heart disease.

Plaque—A deposit of fatty and other substances that accumulate in the linings of the artery walls.

Statins—HMG-CoA reductase inhibitors are drugs, such as pravastatin, that lower LDL cholesterol and help protect against cardiovascular disease and heart attacks.

Triglycerides—Neutral fats are lipids formed from glycerol and fatty acids that commonly circulate in the blood as lipoprotein. Elevated triglyceride levels contribute to the development of atherosclerosis.

- Pralip
- Pratin
- Pravachol
- Pravacol
- Pravalip
- Pravapres
- Pravastatina
- Pravastatine
- Pravastatinenatrium
- Pravatin
- Sanaprav

Origins

Pravastatin as Pravachol was first approved by the FDA in 1991.

Recommended dosage

The usual pravastatin dosage is 10–80 mg taken once a day, with or without food, at about the same time each day. The maximum dosage is 80 mg per day. Pravastatin is usually initiated at a low dose, according to baseline LDL cholesterol levels, and gradually increased no more often than once every four weeks. Patients generally use the lowest effective dose, since higher doses increase the risk of serious side effects, including muscle, kidney, and liver problems. A missed dose should be taken as soon as it is remembered unless it is almost time for the next dose, in which case it should be skipped and the normal schedule resumed.

If pravastatin is coadministered with an immunosuppressant such as cyclosporine, it should be started at 10 mg per day at bedtime, with a maximum of 20 mg per day. When coadministered with clarithromycin (Biaxin), pravastatin should not exceed 40 mg per day.

Pediatric

Pravastatin may be used in children with heterozygous familial hypercholesterolemia, a hereditary condition of high blood cholesterol. The dosage for children ages 8 through 13 is 20 mg once per day. The dosage is 40 mg once a day for children ages 14 through 18, depending on baseline LDL cholesterol levels. Dose adjustments should be made no more often than every four weeks. If coadministered with **cyclosporine** (Neoral, Sandimmune), starting dosage should be 10 mg once a day at bedtime, not to exceed 20 mg per day.

Other conditions and allergies

For patients with kidney impairment, pravastatin should be initiated at 10 mg once per day.

Precautions

Some precautions while taking pravastatin include:

- Patients should have liver function tests before starting pravastatin, and further lab tests may be required, especially if symptoms of liver damage occur.
- Patients should tell doctors and lab personnel about pravastatin use before having any laboratory tests or if hospitalized for serious injury or infection. They should tell their doctors and dentists that they are taking pravastatin before having any type surgery.
- Patients should not stop taking pravastatin without consulting their doctor.
- Symptoms of pravastatin overdose may include peripheral neuropathy (nerve pain), diarrhea, high potassium levels, muscle pain, muscle tissue degeneration, acute

kidney failure, elevated liver enzyme levels, and eye lens opacity.

Geriatric

Under the new AHA and ACC guidelines, everyone aged 64 and older meets the criteria for treatment with statins, regardless of cholesterol levels or other risk factors. However, it is not known whether statins help prevent heart attacks in otherwise healthy older adults with normal cholesterol levels.

Pregnant or breastfeeding

Pravastatin is in the FDA pregnancy category X—it should never be used during pregnancy. Women who could become pregnant while taking pravastatin should discuss their birth control methods with their doctor. Pravastatin enters breast milk and should not be used while breastfeeding.

Other conditions and allergies

Patients should tell their doctor and pharmacist if they are allergic to pravastatin, any ingredients in pravastatin, or any other medications. Pravastatin should not be used by people with active liver disease or people who may be developing liver disease or who have unexplained persistently high levels of serum transaminases. Patients should inform their doctors if they drink more than two alcoholic beverages per day and if they have or have ever had:

- liver disease
- low blood pressure
- muscle aches or weakness
- seizures
- thyroid or kidney disease

Side effects

Side effects from statins are uncommon. Most people do not experience side effects, and any potential side effects may be reversible. Studies have found that pravastatin and **simvastatin** have the fewest side effects among the seven statins on the U.S. market, especially in low to moderate doses. Statins may cause muscle pain and raise blood sugar levels, and there may be a 9% increased risk of diabetes from statin use. Statins are not linked to increased cancer risk. Although there is a risk of usually reversible increased liver enzymes, the rate of liver toxicity is very low. Patients should tell their doctor if any of the following symptoms are severe or persistent:

- heartburn
- headache

- forgetfulness or memory loss
- confusion

Muscle aches, pain, or weakness could be a sign of dangerous muscle tissue breakdown, and the doctor should be called immediately. Other side effects that require immediately notifying the doctor or obtaining emergency medical help are:

- lack of energy
- fever
- yellowing of the skin or eyes
- pain in the upper-right stomach
- nausea
- extreme tiredness
- weakness
- unusual bleeding or bruising
- dark-colored urine
- loss of appetite
- flulike symptoms
- rash
- hives
- itching
- hoarseness
- difficulty breathing or swallowing
- swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs

Interactions

The doctor and pharmacist should be informed of all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used or planning to be used by the patient. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Drugs

The antidepressant **paroxetine** (Paxil) can raise blood glucose levels when taken with pravastatin. Cholestyramine (Questran) or colestipol (Colestid) should be taken four hours before or one hour after pravastatin. The following drugs may require changing dosages or carefully monitoring for side effects when coadministered with pravastatin:

- antacids
- antifungals such as **fluconazole** (Diflucan) and **ketoconazole** (Nizoral)
- boceprevir (Victrelis)
- cimetidine (Tagamet)

- **clarithromycin**
- **colchicine** (Colcris)
- cyclosporine
- **digoxin** (Lanoxin)
- **diltiazem** (Cardizem, Cartia, Taztia, Tiazac)
- **erythromycin** (E.E.S., E-Mycin, Erythrocin)
- other cholesterol-lowering medications such as **fenofibrate** (Tricor), **gemfibrozil** (Lopid), and niacin (nicotinic acid, Niacor, Niaspan)
- ritonavir (Norvir) taken with darunavir (Prezista)
- **spironolactone** (Aldactone)
- verapamil (Calan, Covera, Verelan)
- **warfarin** (Coumadin)

Food and other substances

Patients may be instructed to follow a low-fat, low-cholesterol diet. Drinking a quart or more of grapefruit juice every day may interact with statins. Alcohol can increase the risk of serious side effects; patients should discuss the safe use of alcohol with their doctors.

Resources

BOOKS

- Cordes, Eugene H. *Hallelujah Moments: Tales of Drug Discovery*. Oxford: Oxford University, 2014.
- Roberts, Barbara H. *The Truth About Statins: Risks and Alternatives to Cholesterol-Lowering Drugs*. New York: Gallery, 2012.

PERIODICALS

- Greenwood, Veronique. "Drive Data." *New York Times Magazine* (October 5, 2014): 16–17.
- Rosenthal, Elisabeth. "Lawmakers Look for Ways to Provide Relief for High Cost of Drugs." *New York Times* (November 25, 2014): A17.

WEBSITES

- American Heart Association. "New Heart Disease and Stroke Prevention Guidelines Released." <http://blog.heart.org/new-heart-disease-and-stroke-prevention-guidelines-released> (accessed February 21, 2015).
- "Choosing a Statin to Lower Cholesterol." *Consumer Reports Health Best Buy Drugs*. <http://www.consumerreports.org/health/resources/pdf/best-buy-drugs/StatinsUpdate-2pager-Feb07.pdf> (accessed February 21, 2015).
- Go Red for Women/American Heart Association. "Statins Use: Side Effects are Rare." American Heart Association. https://www.goredforwomen.org/about-heart-disease/heart_disease_research-subcategory/statins-use-side-effects-are-rare (accessed February 21, 2015).
- MedlinePlus. "Pravastatin." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a692025.html> (accessed February 21, 2015).

Medscape. "Pravastatin (Rx)—Pravachol." <http://reference.medscape.com/drug/pravachol-pravastatin-342460> (accessed February 21, 2015).

O'Riordan, Michael. "WOSCOPS at 20 Years: Study Shows Lifetime Benefit with 5 Years of Statin Therapy." Medscape Reference. <http://www.medscape.com/viewarticle/835238> (accessed February 21, 2015).

U.S. Food and Drug Administration. "High Cholesterol—Medicines To Help You." <http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118595.htm> (accessed February 21, 2015).

ORGANIZATIONS

- American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.
- National Heart, Lung, and Blood Institute (NHLBI), PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbinfo@nhlbi.org, <http://www.nhlbi.nih.gov/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Prednisone

Definition

Prednisone is a synthetic corticosteroid that is classified both as an anti-inflammatory drug and as an immunosuppressant. Also known as deltacortisone and deltadehydrocortisone, prednisone is sometimes described as a prodrug, which means that it is inactive until it has been administered to the patient and is converted into its active form (prednisolone) in the liver. Prednisone has been used since the mid-1950s to treat a wide variety of diseases and disorders ranging from allergic conditions to cancer.

Purpose

Systemic prednisone is used to treat many different conditions and disorders that are responsive to treatment with corticosteroids. These conditions include asthma, adrenocortical insufficiency, lupus, chronic obstructive pulmonary disease (COPD) and other breathing disorders, hives, poison ivy, psoriasis and other skin conditions, Ménière's disease, rheumatic disorders, advanced tuberculosis, ulcerative colitis, and flare-ups of multiple sclerosis. Prednisone is also given to patients following organ transplantation to lower the risk of transplant rejection, and it may be given together with

other anticancer drugs to treat patients with acute lymphoblastic leukemia, non-Hodgkin lymphomas, Hodgkin lymphoma, multiple myeloma, and other tumors that are sensitive to hormones.

Off-label use

Prednisone is used off label to treat the following conditions in humans:

- autoimmune hepatitis
- Crohn's disease
- *Pneumocystis jiroveci* pneumonia in patients with AIDS

Description

Prednisone is available as standard tablets, extended-release tablets, a standard oral solution, and a concentrated oral solution. Standard prednisone tablets are available in six dosages: 1, 2.5, 5, 10, 20, and 50 milligrams (mg). The delayed-release formulation is available as 1 mg, 2 mg, and 5 mg tablets. Standard prednisone tablets are round, with the lower dosages white and the 20 mg and higher dosages colored orange. The delayed-release tablets are white in the 1 mg dosage, pale yellow in the 2 mg dosage, and true yellow in the 5 mg dosage. Liquid prednisone is available as a 5 mg per 5 milliliter (mL) solution flavored with peppermint and vanilla, and as a concentrated 5 mg/1 mL solution.



Prednisone, 5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

U.S. brand names

Prednisone is sold in the United States under the brand names PredniSONE IntenSol, Prednicot, Rayos, Sterapred, and Sterapred DS.

Canadian brand names

Prednisone is sold in Canada under the brand names Winpred and Apo-Prednisone.

International brand names

International brand names for prednisone include Apo-Prednisone, Bersen, Cortancyl, Cortiprex, Cutason, Dacortin, Decortin, Decortisyl, Dehydrocortison, Deltacortene, Deltasone, Deltison, Encorton, Meticorten, Panafcort, Pehacort, Predeltin, Predicorten, Prednicort, Prednidib, Prednisona Alonga, Prednisona, Prednison acsis, Prednisona L.CH., Prednison-Armedica, Prednison, Prednison Dak, Prednisone, Prednison Galen, Prednison Galepharm, Prednison Hexal, Prednison-ratiopharm, Prednison Streuli, Predni Tablinen, Prednitone, Predson, Pronison, Rectodelt, Sone, Uniao Prednisona, and Winpred.

Origins

Prednisone was developed in the early 1950s by Arthur Nobile (1920–2004), a microbiologist who worked for the Schering Corporation (later Schering-Plough). Nobile found that the natural steroid hormone known as cortisone could be oxidized by a bacterium called *Corynebacterium simplex* to form prednisone. Prednisone was first put on the U.S. market in 1955 by Schering under the brand name Medicorten and by Upjohn under the brand name Deltasone.

Prednisone went off patent in 1972 and has been manufactured by a large number of pharmaceutical companies worldwide. The first liquid formulation of prednisone was approved by the U.S. Food and Drug Administration (FDA) in 1982; the first delayed-release tablet was approved by the FDA in July 2012.

Recommended dosage

There are few universal guidelines for recommended dosages of prednisone because the drug is prescribed for such a wide range of conditions. The prescribing physician will take into account not only the specific condition to be treated but also its severity; the patient's age, sex, and general health; other medications the patient is taking; and any concurrent medical or psychiatric disorders that the patient may have. The patient's dosage needs may change in the event of severe emotional stress, serious illness or infection, fever, scheduled surgery, or a medical emergency.

KEY TERMS

Addisonian crisis—A condition of severe adrenal insufficiency marked by convulsions, fever, fainting, low blood pressure, severe nausea, vomiting, and dehydration, confusion and slurred speech, and severe pain in the legs or lower back. It can result from the sudden withdrawal of prednisone in a patient who has become dependent on the drug, as well as from known adrenal insufficiency or sudden trauma to the adrenal glands.

Corticosteroids—A class of compounds that includes the steroid hormones produced in the cortex of the adrenal gland of humans and other vertebrates, and synthetic analogues of these compounds.

Cushing syndrome—A disorder caused by prolonged exposure to high levels of the hormone cortisol. Symptoms include upper body obesity, rounded “moon” face, increased fat around the neck, thin arms and legs, fatigue, weakness, high blood pressure, and mood disorders. It is named for Harvey Cushing (1869–1939), the American physician who first described the syndrome in 1932.

Giant cell arteritis—An inflammatory disorder that affects the large- and medium-sized arteries in the head. It may result in sudden blindness as well as ringing in the ears, severe headache, and pain in the jaw and tongue when chewing.

Hypokalemia—An abnormally low level of potassium in the blood.

Idiopathic thrombocytopenic purpura (ITP)—A bleeding disorder in which the patient has a low platelet count in the absence of other causes of this condition. ITP is characterized by a purple skin rash and an increased tendency to bleed.

Immunosuppressant—Any agent that decreases the response of the immune response of an individual.

Nephrotic syndrome—A kidney disorder characterized by edema (swelling), ascites (fluid accumulation in the abdomen), high levels of protein in the urine, and low levels of albumin in the blood.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Prednisolone—A corticosteroid that is the active metabolite of prednisone. Prednisone is converted to prednisolone in the liver.

Prodrug—A medication that is administered in an inactive or partially active form and is converted to its active form by a normal metabolic process in the body.

Recommended dosages for some specific indicated conditions in adults are as follows:

- Conditions responsive to glucocorticoids: 5–60 mg per day, either in a single daily dose or in divided doses taken every 6 or 12 hours.
- Acute asthma: 40–60 mg per day in a single daily dose or divided doses every 12 hours for three to ten days.
- Giant cell arteritis: 40–60 mg per day for one to two years.
- Idiopathic thrombocytopenic purpura (ITP): 1–2 mg per kilogram (kg) of body weight per day.
- Allergic conditions: The typical initial dose is 30 mg on the first day of treatment, divided into four doses; 25 mg on the second day, divided into four doses; 20 mg on the third day, divided into four doses; 15 mg on the fourth day, divided into three doses; 10 mg on the fifth day, divided into two doses; and on the sixth day, one 5 mg dose taken at breakfast.
- Rheumatoid arthritis (RA): Patients taking disease-modifying antirheumatic drugs (DMARDs) are prescribed immediate-release prednisone tablets in a dosage either equal to or less than 10 mg per day. Patients prescribed delayed-release tablets should take 5 mg by mouth initially, then gradually lessen (taper) to the lowest dose that maintains a clinical response to RA.
- Advanced tuberculosis: 40–60 mg per day, tapered over a period of four to eight weeks.

Prednisone should always be taken with a meal or snack, as it can irritate the stomach.

Patients taking the liquid form of prednisone should use a dose-measuring spoon or medicine cup rather than a kitchen teaspoon or tablespoon to measure the dose.

Patients taking the extended-release prednisone tablets should not chew, bite, or crush the tablets, but should swallow them whole.

All forms of prednisone should be kept away from pets and children and stored at room temperature away from heat and direct light.

Pediatric

Recommended dosages for children and adolescents are as follows:

- Inflammation: 0.5–2 mg/kg/day in a single daily dose, or in divided doses taken every 12 hours; total dose should not exceed 80 mg/day.
- Acute asthma: Children 12 years or younger should take 1–2 mg/kg per day in a single daily dose, or in divided doses every 12 hours for three to ten days; the total dose should not exceed 80 mg per day. Children and adolescents over 12 years can take 40–60 mg per day in a single daily dose, or in divided doses every 12 hours for three to ten days.
- Nephrotic syndrome: 2 mg/kg/day; total dose should not exceed 80 mg per day.

Precautions

Patients who are treated with systemic prednisone for longer than seven days may become dependent on the drug, as the adrenal cortex will begin to slow down its production of natural corticosteroids like cortisol. If prednisone use is stopped too quickly, the patient may undergo a potentially life-threatening condition of adrenal insufficiency known as an Addisonian crisis. Each patient's doctor will need to decide how rapidly and how substantially to reduce the dose of prednisone on a case-by-case basis. In general, the drug is withdrawn gradually in patients who are unlikely to relapse, have received more than 40 mg of prednisone per day for longer than a week, have been given repeat doses in the evening, have received the drug for longer than three weeks, or have taken a short course of prednisone therapy within one year of stopping long-term prednisone therapy. The dose may be reduced rapidly to about 7.5 mg per day in adults and then reduced more slowly.

Additional precautions for prednisone include the following:

- Avoid close contact with others who have active infections while taking prednisone.
- Take the medication exactly as directed by the doctor.
- Do not discontinue the drug suddenly without consulting the doctor.
- Wear a medical alert tag or carrying a card indicating prednisone use, as this is important information for emergency medical personnel.

- Avoid vaccination with any vaccine made from a live virus, and avoid close contact with others who have recently received such vaccines.

Pediatric

Children taking prednisone should be monitored for normal growth, as the drug can slow the growth of the long bones and cause other bone problems in children who receive high doses of the drug over long periods of time.

Geriatric

Older adults with kidney or liver disorders may require adjustment of the standard adult dosages of prednisone and more frequent blood tests and blood pressure monitoring.

Pregnant or breastfeeding

The risk of harm to the fetus cannot be ruled out for prednisone, although there are no controlled data for human pregnancies. Most doctors recommend using prednisone during pregnancy only when there are no alternatives and the benefit to the mother outweighs the risk to the fetus.

Prednisone is known to pass into human breast milk. Although the American Academy of Pediatrics considers prednisone safe for use by breastfeeding mothers, the drug's manufacturers recommend cautious use of the drug by nursing women.

Other conditions and allergies

People with a known allergy to prednisone or who have fungal infections anywhere in the body should not use prednisone at all.

People with any of the following conditions should inform their doctors before taking prednisone:

- a recent history of any kind of infection
- stomach ulcers, ulcerative colitis, a history of stomach bleeding, or any illness that causes diarrhea
- myasthenia gravis or other muscle disorder
- osteoporosis
- heart disease, high blood pressure, or hypokalemia (low blood levels of potassium)
- liver disease, including cirrhosis
- kidney disease
- thyroid disorders
- history of mental illness or depression
- history of malaria
- glaucoma, cataracts, or a herpes infection of the eye
- tuberculosis

Side effects

Prednisone can cause both short-term and long-term side effects.

Common short-term side effects include:

- stomach irritation
- mood changes, often irritability or aggression
- headaches
- insomnia
- agitation or anxiety
- decrease in urine output
- fast, slow, pounding, or irregular heartbeat
- increased appetite and weight gain
- blurred vision
- swelling of the hands, feet, or lower legs
- numbness or tingling sensations in the arms or legs
- acne

Long-term side effects of prednisone, particularly at higher dosages, may include:

- osteoporosis
- Cushing syndrome
- type 2 diabetes
- glaucoma and cataracts
- steroid dementia syndrome (memory loss, difficulty paying attention, drop in academic or occupational performance); reverses once the drug is stopped
- weight gain around the trunk of the body

Patients taking prednisone who notice any of the following side effects should contact their doctor at once:

- sharp rise in blood glucose levels in patients with diabetes
- signs of a severe allergic reaction, including hives, difficulty breathing, or swelling of the face, lips, tongue, or throat
- symptoms of glaucoma, which include blurred vision, eye pain, or seeing halos around lights
- symptoms of pancreatitis, which include severe pain in the upper stomach spreading to the back, nausea and vomiting, and fast heart rate
- symptoms of severe edema (fluid retention), which include rapid weight gain, feeling short of breath, and swelling
- symptoms of hypokalemia, which include mental confusion, uneven heart rate, extreme thirst, increased urination, leg discomfort, and muscle weakness
- symptoms of dangerously high blood pressure, which include severe headache, blurred vision, buzzing or

ringing in the ears, anxiety, confusion, chest pain, shortness of breath, uneven heartbeat, and seizures

- symptoms of depression or another mood disorder, which include feelings of extreme happiness or sadness, severe depression, rapid mood changes, and other changes in personality or behavior
- blood in the stools, tarry-looking stools, or coughing up blood (hemoptysis)

Interactions

Individuals should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs and supplements, before taking prednisone.

Drugs

Known drug interactions with prednisone include:

- Barbiturates (phenobarbital, secobarbital, butalbital, amobarbital, etc.) reduce effectiveness of prednisone.
- The dosages of diabetes medications, both insulins and oral diabetes medications, may need to be adjusted as prednisone increases blood sugar levels in some patients.
- Statins (**lovastatin**, **atorvastatin**, **simvastatin**, etc.) reduce effectiveness of prednisone.
- Monoclonal antibodies (golimumab, natalizumab, **infliximab**, adalimumab, etc.) increase the risk of infection.
- Diuretics (**hydrochlorothiazide**, **furosemide**, ethacrynic acid, **torsemide**, metolazone, etc.) increase risk of hypokalemia.
- Estrogens (hormone replacement therapy, birth control pills) increase the effects of prednisone.
- Mifepristone (abortifacient) is contraindicated (should not be used) in patients taking prednisone.

Other drugs known to interact with prednisone include:

- fluoroquinolone antibiotics (**ciprofloxacin**, ofloxacin, norfloxacin, **levofloxacin**, etc.)
- other medications containing cortisone (cortisone, hydrocortisone, fludrocortisone, etc.)
- nonsteroidal anti-inflammatory drugs (**ibuprofen**, naproxen, ketorolac, **ketoprofen**, **celecoxib**, etc.)
- **methadone**
- rifamycin antibiotics (**rifampin**, rifabutin, rifapentine)
- antifungal medications (posaconazole, itraconazole, voriconazole, etc.)
- **warfarin**
- **phenytoin**

- tricyclic antidepressants (clomipramine, **nortriptyline**, desipramine, **doxepin**, **amitriptyline**, **imipramine**, etc.)
- salicylates (**aspirin**, diflunisal, salsalate)

Patients taking prednisone should not receive vaccines made from live viruses, including measles, mumps, influenza (nasal flu vaccine), poliovirus (oral form), rotavirus, rabies, anthrax, yellow fever, zoster, chickenpox, smallpox, bacille Calmette-Guérin, and rubella. Patients should also not receive diphtheria-tetanus toxoids, hepatitis B vaccine, human papillomavirus (HPV) or acellular pertussis vaccine. Patients taking prednisone should not only not receive any of these vaccines, but they should also avoid close contact with anyone who has recently received one of them.

Herbs and supplements

Patients taking prednisone should avoid the use of herbal preparations including St. John's wort, as it decreases the effectiveness of prednisone.

Food and other substances

Patients taking prednisone should avoid smoking marijuana or ingesting food products made with it, as it increases the effects of prednisone. They should also avoid grapefruit and grapefruit juice for the same reason.

Resources

BOOKS

- Rice, Peter J. *Understanding Drug Action: An Introduction to Pharmacology*. Washington, DC: American Pharmacists Association, 2014.
- Turley, Susan M. *Understanding Pharmacology for Health Professionals*. 5th ed. Upper Saddle River, NJ: Pearson Education, 2014.

PERIODICALS

- Briot, K., et al. "2014 Update of Recommendations on the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis." *Joint, Bone, Spine* 81, no. 6 (2014): 493–501.
- Curtis, G., and A. C. Lewis. "Treatment of Severe Poison Ivy: A Randomized, Controlled Trial of Long versus Short Course Oral Prednisone." *Journal of Clinical Medical Research* 6, no. 6 (2014): 429–34.
- Czaja, A. J. "Diagnosis and Management of Autoimmune Hepatitis." *Clinics in Liver Disease* 19, no. 1 (2015): 57–79.
- Judd, L. L., et al. "Adverse Consequences of Glucocorticoid Medication: Psychological, Cognitive, and Behavioral Effects." *American Journal of Psychiatry* 171, no. 10 (2014): 1045–51.
- Rau, R. "Glucocorticoid Treatment in Rheumatoid Arthritis." *Expert Opinion on Pharmacotherapy* 15, no. 11 (2014): 1575–83.

WEBSITES

- AHFS Consumer Medication Information. "Prednisone." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601102.html> (accessed March 5, 2015).
- Medscape Reference. "Prednisone (Rx)." <http://reference.medscape.com/drug/prednisone-intensol-342747> (accessed February 21, 2015).
- Micromedex. "Prednisone (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/prednisone-oral-route/description/drg-20075269> (accessed February 21, 2015).
- Physicians' Desk Reference. "Prednisone." PDR Health. <http://www.pdrhealth.com/drugs/prednisone> (accessed March 5, 2015).
- "Prednisone." Drugs.com <http://www.drugs.com/prednisone.html> (accessed February 21, 2015).

ORGANIZATIONS

- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rebecca J. Frey
REVIEWED BY KEVIN GLAZA

Pregabalin

Definition

Pregabalin (pronounced pre-GAH-bah-lin) is an oral anticonvulsant and neuropathic pain medication used to treat epilepsy, neuropathy (nerve pain), and fibromyalgia.

Purpose

Pregabalin is approved in the United States for the treatment of the following conditions in adults:

- epilepsy
- diabetic neuropathy
- postherpetic neuralgia
- fibromyalgia
- neuropathic (nerve) pain following spinal cord injury

The reason for pregabalin's effectiveness in treating these conditions is not yet fully understood, but it is thought to be related to its selective binding to specific portions of calcium channels in the central nervous system. Pregabalin is not a cure for the conditions it is approved to treat; it is given to control partial seizures in



Lyrical (pregabalin), 75 mg. (© Cengage Learning®.)

patients with epilepsy and to relieve pain in patients diagnosed with the other four disorders.

Off-label use

Pregabalin is used off label in the United States to treat generalized anxiety disorder (GAD) and other anxiety disorders; it is formally approved in the European Union and in Russia for this purpose. Its other off-label use in the United States is for treatment of moderate pain following tooth extraction and similar dental procedures.

Description

Pregabalin is available as white oval tablets or as a liquid formulation. It should be stored in a closed container away from moisture, heat, and direct light, and kept at temperatures above freezing. It should be kept away from children and pets, and discarded when its expiration date has passed. The oral solution should be used within 45 days of opening the bottle.

U.S. brand names

Pregabalin is marketed by Pfizer in the United States under the trade name Lyrical.

International brand names

Pregabalin is sold under the brand name Nervalin in the European Union and in Asia.

Origins

Pregabalin was formulated in the early 2000s as a more potent successor to **gabapentin** (Neurontin), and it was approved by the U.S. Food and Drug Administration (FDA) in 2004 for the treatment of epilepsy, postherpetic neuralgia, fibromyalgia, and diabetic peripheral neuropathy.

Recommended dosage

Pregabalin is available in 25, 50, 75, 100, 150, 200, 225, and 300 milligram (mg) capsules; and as a 20 mg per milliliter (mL) oral solution. It is usually taken in divided doses two or three times daily. If the patient forgets a dose, he or she should take it as soon as he or she remembers, unless it is almost time for the next dose. Patients should never take a double dose of pregabalin to make up for a missed dose.

Recommended dosages of pregabalin in adults include:

- **epilepsy:** initial dose of 150 mg per day divided into two or three daily doses; may be increased after one week to 600 mg per day (divided into two or three daily doses) for maintenance
- **diabetic neuropathy:** 50 mg every eight hours; may be increased to 100 mg every eight hours within one week but should not exceed 300 mg per day
- **postherpetic neuralgia:** 150–300 mg per day as the initial dose, divided into two or three daily doses; may be increased after one week to 300 mg per day (divided into two or three daily doses)
- **fibromyalgia:** initial dose of 150 mg per day divided into two daily doses; may be increased after one week to 300–450 mg per day (divided into two daily doses) for maintenance
- **neuropathic pain following spinal cord injury:** initial dose of 150 mg per day divided into two daily doses, later increased within one week to 300 mg per day (divided); if needed, dose may be increased to 600 mg per day (divided into two daily doses)

Patients may take pregabalin either with or without food, as they prefer, but they should take their daily doses at the same times every day. Patients who are prescribed the liquid formulation of pregabalin should use a marked measuring spoon, an oral syringe, or a medicine cup to measure the dose, as ordinary household teaspoons vary in the amount of liquid they hold and so may not provide an accurate dose.

KEY TERMS

Angioedema—A condition marked by sudden and rapid swelling of subcutaneous tissues and mucous membranes, often as an allergic reaction to some foods or drugs.

Anticonvulsant—Any drug given to control seizures. Anticonvulsants are also called antiepileptic drugs or AEDs.

Diabetic neuropathy—A complication of diabetes in which damage to the capillaries in the circulatory system leads to nerve damage. The patient may feel tingling or burning sensations along the nerve endings, or may lose sensation in such areas as the lower legs and feet.

Epilepsy—A brain disorder with symptoms that include seizures.

Fibromyalgia—A condition characterized by widespread muscle pain, heightened sensitivity to pressure, fatigue, and joint stiffness.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Partial seizure—A seizure that affects only one hemisphere of the brain.

Postherpetic neuralgia—Nerve pain caused by the varicella zoster virus (shingles).

Seizure—A sudden attack, spasm, or convulsion.

Withdrawal—Physical symptoms and psychological discomforts experienced after a person suddenly stops using a drug on which he or she has become dependent.

Geriatric

Elderly patients known to have age-related kidney problems or who experience side effects from pregabalin such as dizziness, confusion, or clumsiness may require some adjustment in the dosage of this drug.

Other conditions and allergies

The recommended dosages of pregabalin are sharply reduced (by 50% or more) in patients with impaired kidney function. The extent of the reduction depends on

the size of the dose the patient was previously taking, with higher dosages cut the most sharply.

Precautions

Patients taking pregabalin should not stop taking the medication without consulting their physician, as abrupt discontinuation of the drug may result in a withdrawal syndrome marked by seizures, headache, insomnia, sweating, anxiety, and diarrhea. The dosage of the drug should be tapered over a period of at least a week to prevent withdrawal syndrome.

Patients taking pregabalin should not drive or operate hazardous machinery until they know how the drug affects them, as drowsiness and loss of coordination are common side effects.

Individuals who feel the need to take larger or more frequent doses of the drug should report this to their healthcare provider. While pregabalin is considered to have a low risk of addiction, some patients may become dependent on it. Pregabalin is classified as a Schedule V (low potential for abuse but may lead to limited psychological or physical dependence) drug by the Controlled Substances Act of 1970.

Pediatric

The safety and efficacy of pregabalin have not been established for use in children, and its use in children is not recommended.

Pregnant or breastfeeding

Pregabalin is a pregnancy Category C drug, which means that animal studies have shown potential harm to a fetus, but there are no adequate and well-controlled studies in humans. The potential benefits of pregabalin may warrant the use of the drug during pregnancy despite potential risks.

There are no controlled studies of the risks of pregabalin to the infants of breastfeeding women. Lactating women should discuss the benefits and potential risks of the drug with their physicians.

Other conditions and allergies

Patients with any of the following conditions should consult their doctor before taking pregabalin:

- known hypersensitivity to pregabalin or history of angioedema
- history of bleeding disorders
- history of depression or behavioral changes
- thrombocytopenia (low level of platelets in the blood)

PATIENT PROFILE

Pregabalin (Lyrica) was prescribed for a 42-year-old woman who had been diagnosed with fibromyalgia several months after suffering physical trauma in an automobile accident. Fibromyalgia is a chronic autoimmune disease that manifests as generalized pain in various locations in the body, usually accompanied by extreme fatigue. The patient was experiencing moderate but constant pain day and night, primarily in her neck and shoulders and in her arms and legs on both sides of her body. The constant pain kept her from reporting to work each day, and she had to take a leave of absence in order to seek treatment. Although she was now staying at home every day, she was not able to care properly for her 5-year-old daughter in the hours after school or to perform normal household chores. Her doctor explained that the widespread pain characteristic of fibromyalgia is believed to be amplified by the way the brain processes pain sensations. He advised the patient that pregabalin is appropriate for treating fibromyalgia because it alters the release of certain neurotransmitters in the brain and spine, blocking nervous system communication channels and moderating the perception of pain. Pregabalin is used mainly to treat different types of neuropathic pain, and studies have shown that it works well for fibromyalgia.

Pregabalin is available in oral capsules ranging from 25 mg to 300 mg. The initial dosage of pregabalin for this patient was a 100 mg capsule to be taken three times a day, with or without food. When it was clear that she was able to tolerate the initial dosage, the doctor recommended increasing the dosage to 200 mg three times daily. At that dosage, her body aches and pains were much relieved. However, at her first follow-

up visit four weeks after beginning treatment, the patient reported sleeping frequently during the day and feeling dizzy when she was standing. Her vision was somewhat blurred and she could not drive her car. She was also having difficulty walking and felt as though she were stumbling. She reported falling recently when going down the stairs in her home. The doctor noted that the patient appeared to be somewhat lethargic and observed that her walking gait seemed to be unbalanced.

After confirming that the patient was not taking any other pain medications or tranquilizers that might increase the side effects of pregabalin, the doctor attributed the patient's symptoms to drug side effects and recommended that it be discontinued. Instead, he prescribed milnacipran (Savella), which works differently than pregabalin for treating fibromyalgia. Milnacipran is a serotonin and norepinephrine reuptake inhibitor (SNRI) that is used mainly for treating depression and other psychiatric disorders. Although it is an antidepressant, milnacipran works for fibromyalgia by balancing neurotransmitters in the brain that carry signals to the rest of the body. In this way, signals indicating nerve pain in multiple body parts are interrupted. The doctor prescribed 50 mg tablets as the initial dose, to be taken orally three times a day with meals. This was increased to 100 mg three times a day when the patient responded well to the drug in terms of both pain control and tolerability. No adverse reactions occurred at the higher dosage after one month of treatment, and the patient continued taking milnacipran long-term, regaining her ability to function and her quality of life.

- history of kidney disease or edema (fluid retention)
- abnormal heart rhythm, particularly a prolonged PR interval

Side effects

Common side effects of pregabalin include (in order of frequency):

- dizziness
- drowsiness
- problems with coordination
- weight gain
- dry mouth
- infections
- headaches
- tremor
- fatigue

- water retention in arms and legs

Less common side effects include:

- memory loss or difficulty concentrating
- constipation
- increased appetite
- vomiting
- back pain
- flulike symptoms (body aches and chills)
- feeling giddy or drunk
- anxiety
- joint pains and muscle cramps

The following side effects should be reported to a doctor immediately:

- symptoms of angioedema, which include sudden swelling of the face, arms, legs, eyes, lips, or tongue and problems with swallowing or breathing
- symptoms of congestive heart failure, which include difficulty breathing or water retention in the hands, legs, and feet
- unusual bruising or bleeding
- suicidal thinking or behavior
- changes in vision
- irregular heartbeat

Interactions

As with all prescription medications, patients prescribed pregabalin for any of its uses should inform their physicians of any other medications they are taking, including over-the-counter medications, nutritional supplements, and herbal preparations as well as other prescription drugs. They should also inform their healthcare providers of any known allergies to foods, preservatives, or dyes.

Drugs

Pregabalin interacts with a large number of prescription drugs, including:

- benzodiazepine tranquilizers (**alprazolam**, **diazepam**, **chlorthalidone**, **lorazepam**, **temazepam**, etc.)—intensify the effects of pregabalin
- barbiturates (amobarbital, phenobarbital, secobarbital, etc.)—intensify the effects of pregabalin
- dental, general, and local anesthetics
- opioid (narcotic) pain relievers (**fentanyl**, **oxycodone**, morphine, codeine, hydrocodone, etc.)
- sedatives and sleeping medications
- orlistat, an antiobesity drug with notable gastrointestinal side effect—inhibits proper absorption of pregabalin
- **ketorolac**, an NSAID used to treat moderate to severe pain

ACE inhibitors (medications given to control high blood pressure) such as enalapril, **fosinopril**, **lisinopril**, **captopril**, and others should not be used with pregabalin because of the risk of angioedema and increased toxicity.

Herbs and supplements

Patients taking pregabalin should not use over-the-counter antihistamines, cold medicines, cough syrups, or sleeping medications without consulting their doctor, as many of these preparations contain alcohol or other compounds that intensify drowsiness and similar side effects of pregabalin.

Food and other substances

Patients taking pregabalin should not drink alcoholic beverages, because alcohol intensifies the effects of the drug, particularly drowsiness and loss of coordination.

Resources

BOOKS

Patsalos, Philip N. *The Epilepsy Prescriber's Guide to Antiepileptic Drugs*. 2nd ed. New York: Cambridge University Press, 2014.

Pohlmann-Eden, Bernd, and Bernhard J. Steinhoff; translated by Klaus C. Hofer. *Understanding Antiepileptic Drugs: Guiding You Through the Maze of Options*. Oxford: Oxford University Press, 2014.

Smith, Howard S., and Marco Pappagallo. *Essential Pain Pharmacology: The Prescriber's Guide*. New York: Cambridge University Press, 2012.

PERIODICALS

Arnst, Catherine. "Feds Hit Pfizer with a \$2.3 Billion Fine." *Business Week*, September 2, 2009.

Frampton, J. E. "Pregabalin: A Review of Its Use in Adults with Generalized Anxiety Disorder." *CNS Drugs* 28, no. 9 (2014): 835–54.

Johnson, R. W., and A. S. Rice. "Clinical Practice: Postherpetic Neuralgia." *New England Journal of Medicine* 371, no. 16 (2014): 1526–33.

Moulin, D., et al. "Pharmacological Management of Chronic Neuropathic Pain: Revised Consensus Statement from the Canadian Pain Society." *Pain Research and Management* 19, no. 6 (2014): 328–35.

Muñana, Karen R. "Update: Seizure Management in Small Animal Practice." *Veterinary Clinics of North America: Small Animal Practice* 43, no. 5 (2013): 1127–47.

WEBSITES

"Pregabalin." Drugs.com. <http://www.drugs.com/ppa/pregabalin.html> (accessed February 21, 2015).

Medscape Reference. "Pregabalin (Rx)." <http://reference.medscape.com/drug/lyrica-pregabalin-343368> (accessed February 21, 2015).

Micromedex. "Pregabalin (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/pregabalin-oral-route/description/drg-20067411> (accessed February 21, 2015).

ORGANIZATIONS

American Academy of Neurology (AAN), 201 Chicago Avenue, Minneapolis, MN 55415, (612) 928-6000, Fax: (612) 454-2746, (800) 879-1960, memberservices@aan.com, <http://www.aan.com/>.

American Academy of Pain Medicine, 8735 West Higgins Road, Suite 300, Chicago, IL 60631-2738, (847) 375-4731, (847) 375-6477, info@painmed.org, <http://www.painmed.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Premarin see **Conjugated estrogens**

Prevacid see **Lansoprazole**

Prilosec see **Omeprazole**

Prinivil see **Lisinopril**

Pristiq see **Desvenlafaxine**

Proair HFA see **Albuterol**

Procardia XL see **Nifedipine**

Progestin/estrogen see **Oral contraceptives**

Prograf see **Tacrolimus**



Promethazine hydrochloride, 25 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Promethazine

Definition

Promethazine is a drug used to help relieve problems such as motion sickness. It is in a class of drugs called phenothiazines, which are designed to block the action of certain receptors in the brain.

Purpose

When someone has an allergic reaction, motion sickness, or nausea from causes such as medication reactions, the cause is a complex relationship among the brain, nerves, and other systems of the body. For example, motion sickness occurs when input from the eyes, inner ears, and other receptors appears to conflict. Promethazine can block dopamine, histamine and other receptors or chemicals to help ease the symptoms related to motion sickness, nausea, and allergies or allergic reactions.

Description

Promethazine comes in several forms, including tablets that can be taken by mouth. For treating severe motion sickness or nausea, patients may receive a suppository or injected form of the medicine.

U.S. brand names

In the United States, promethazine once was sold under the trade name Phenergan, but is no longer

available under that name. Generic alternatives are available for promethazine.

Recommended dosage

For adults taking promethazine to relieve allergy symptoms, the recommended dose usually is a 25 milligram (mg) tablet before bedtime. Adults also can split the dose into 12.5 mg before a meal and 12.5 mg at bedtime. Adults taking promethazine for motion sickness usually take 25 mg by mouth 30 to 60 minutes before their trip or expected cause of motion, repeated every 8–12 hours as needed. On later travel days that may cause motion sickness, adults can take 25 mg of promethazine each morning and evening as needed. Doctors may recommend promethazine for nausea and vomiting at a dosage of 12.5 to 25 mg every four to six hours as needed, either by mouth or suppository.

When allergic reactions or nausea are severe, promethazine may be injected into a patient's vein (given intravenously) by a health care professional. When a patient is too sick to keep medicine down, or otherwise unable to swallow a tablet, doctors may recommend use of promethazine in suppository form. Rectal doses generally are equivalent to doses taken by mouth.

Pediatric

Promethazine is not considered appropriate for infants for allergy control, and its use for all children as an allergy

KEY TERMS

Dopamine—A neurotransmitter, or chemical, in the brain that influences many of the brain's functions, including movement, areas of thinking, pleasure, and control of hormones.

Rectal—Referring to the rectum, the lowest part of the intestine, from the colon to the anus.

Suppository—A small cylinder or cone that melts when it comes in contact with normal body temperature, designed to be inserted into a body cavity such as the rectum to deliver medication.

relief medicine is not approved by the U.S. Food and Drug Administration (FDA). The medication may be used for severe allergic reactions in children, however, at a dose of 0.1 mg per kilogram (kg, or 2.2 lb.) of the child's body weight every 6 hours during the day. A larger dose of 0.5 mg per kg of body weight is given at bedtime as needed. For motion sickness in children, doctors usually recommend 12.5 to 25 mg of promethazine 30 to 60 minutes before expected travel and every 8–12 hours as needed, or 0.5 mg per kg of the child's body weight every 12 hours as needed.

Precautions

Promethazine has caused respiratory, or lung, failure in young children and severe injury to tissue around the area where it is injected in some patients. It should not be given to people who already have breathing problems, such as asthma. Promethazine can cause drowsiness and affect the ability to drive or perform other activities requiring concentration. The drug has also caused problems with heart rhythm in some patients.

Patients should never chew the oral tablet, but instead swallow it whole. The suppository is for rectal use only, and should be used according to doctor, pharmacist, and package insert instructions. Some people are allergic to promethazine and should inform the doctor of any known allergic reactions or any symptoms that are unusual that occur as soon as they take the drug.

Pediatric

Promethazine should never be given to children of infants younger than two years old and should always be used with caution in all children. Promethazine can cause severe breathing problems and even lung failure in children, especially children younger than two years old.

The FDA issued a boxed warning for the drug's use in children in 2009, particularly as an intravenous medication.

Geriatric

Older people are more vulnerable to the side effects of promethazine than are younger adults. Doctors often start patients older than 65 on lower doses of the drug to monitor its effects.

Pregnant or breastfeeding

Promethazine is a category C drug. It should be used during pregnancy only if the potential benefit to the mother outweighs possible risks to the fetus.

It is not known whether promethazine can harm nursing infants, but a mother who wants to breastfeed her infant should not take promethazine while nursing or should choose not to breastfeed while taking the drug.

Other conditions and allergies

People who have heart and blood vessel disease, such as coronary artery disease, or who have problems with liver disease or liver function should use promethazine with caution.

Side effects

Promethazine can cause several side effects, including:

- drowsiness
- dizziness
- dry mouth
- nausea and vomiting
- vision problems
- sleep problems and nightmares
- loss of coordination
- nervousness or restlessness
- itching and stuffy nose

Some side effects of promethazine use are severe and should be reported to a doctor immediately. These include:

- breathing that slows or stops for a short time
- wheezing
- fever and sweating
- stiff muscles
- rapid or irregular heartbeat and pulse
- feeling faint or less alert
- stiff muscles
- confusion and hallucinations
- seizures
- uncontrollable shaking or eye movements

Interactions

Some drugs and other substances can interact with one another, causing one drug to be less effective or worsening side effects of a drug. It is important to tell the doctor about all medications, herbal remedies, and supplements being taken before starting promethazine.

Drugs

Taking promethazine along with other drugs that affect the central nervous system can increase the effects of the drugs, causing sleepiness or sedation. Examples are barbiturates, narcotic analgesics, and antidepressants such as **amitriptyline** (Elavil) and nortriptyline (Pamelor). Some allergy and cold medicines also add to the sedating effects of promethazine.

Food and other substances

Drinking alcohol while taking promethazine increases the sedating effect of the drug and should be avoided.

Resources

PERIODICALS

Furyk, Jeremy S., Robert Meek, and Suzanne McKenzie. "Drug Treatment of Adults with Nausea and Vomiting in Primary Care." *British Medical Journal* 349 (2014): 1–6.

WEBSITES

Brainard, Andrew. "Motion Sickness." Medscape. <http://emedicine.medscape.com/article/2060606-overview> (accessed February 21, 2015).

MedlinePlus. "Promethazine." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682284.html> (accessed February 21, 2015).

Peck, Peggy. "FDA Orders Black Box Warning for Antinausea Drug." <http://www.medpagetoday.com/ProductAlert/Prescriptions/16002> (accessed February 21, 2015).

"Phenergen (Promethazine HCL)." Rxlist.com. <http://www.rxlist.com/phenergan-drug.htm> (accessed February 21, 2015).

"Promethazine." Drugs.com. <http://www.drugs.com/promethazine.html> (accessed February 21, 2015).

ORGANIZATIONS

American Academy of Allergy, Asthma & Immunology, 555 E. Wells Street, Suite 1100, Milwaukee, WI 53202, (414) 272-6071, <http://www.aaaai.org/home.aspx>.

American Academy of Neurology (AAN), 201 Chicago Avenue, Minneapolis, MN 55415, (612) 928-6000, Fax: (612) 454-2746, (800) 879-1960, memberservices@aan.com, <http://www.aan.com/>.

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REVIEWED BY GREGORY A. PRATT, RPh

Propranolol

Definition

Propranolol is a drug classified as a beta-blocker.

Purpose

Propranolol is approved by the U.S. Food and Drug Administration (FDA) for the treatment of hypertension (high blood pressure), angina, certain types of cardiac arrhythmias, certain types of cardiac output diseases, a sympathetic nervous system disorder known as pheochromocytoma, hyperthyroid conditions, heart attack, infantile hemangiomas, and tremors of a variety of origins. It is also used in the prevention of migraine headaches.

Off-label use

On occasion, propranolol is prescribed to treat medication-induced movement disorders, which are caused by some antipsychotic drugs, and for certain anxiety states in people suffering from a specific form of social phobia. Beta-blockers such as propranolol are not useful for people with general social phobia who are anxious in most social situations; instead, propranolol may be more useful for people who are anxious about specific performance situations, such as presenting a speech before an audience.



Propranolol, 40 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

Beta-blockers block specific sites in the central nervous system known as beta-adrenergic receptor sites. When these sites are blocked, heart rate and blood pressure are reduced, and patients become less anxious. Because of this, propranolol is useful in treating chest pain, high blood pressure, and excessive nervousness. Unfortunately, propranolol often makes breathing disorders (such as asthma) worse because it tends to constrict breathing passages and sometimes causes fluid buildup in the lungs if the heart rate drops too low.

Propranolol is available in 10, 20, 40, 60, and 80 milligram (mg) tablets; in 60, 80, 120, and 160 mg long-acting capsules; and in an injectable form containing 1 mg per milliliter (mL). It is also combined with the diuretic **hydrochlorothiazide** in tablets and extended-release capsules.

U.S. brand names

Propranolol is sold in the United States under the brand name Inderal, Inderal LA (long acting), InnoPran, and InnoPran XL (extended release). When combined with the diuretic hydrochlorothiazide, it is sold under the brand name Inderide. Propranolol also is produced as a generic product by a number of generic manufacturers.

Recommended dosage

Dosage varies depending on the condition being treated. Examples include:

- Patients with hypertension are started at 40 mg taken twice per day. This is gradually adjusted to a maintenance dose of 120–240 mg per day, though some patients require higher doses.
- Angina is dosed at 80–320 mg per day, divided into two to four doses throughout the day.
- Individuals with atrial fibrillation may take 10–30 mg in three to four doses (30–120 mg daily).
- The dose for migraine prevention is started at 80 mg per day. This is gradually increased to 120–240 mg per day.
- For the treatment of performance anxiety or stage fright, a single dose of 10–40 mg may be administered 20–30 minutes before the event.
- For the treatment of tremors, doses range from 80 to 160 mg per day, administered in two or three divided doses.
- For the treatment of movement disorders secondary to antipsychotic drug therapy, doses range from 10–30 mg, taken three times daily.

KEY TERMS

Arrhythmia—A variation in the normal rhythm of the heartbeat. Atrial fibrillation and flutter are two types of arrhythmia.

Beta-blocker—Drugs that block beta-adrenergic receptors on neurons in the central nervous system. When these sites are blocked, heart rate, blood pressure, and anxiety levels decrease.

Diuretic—An agent that increases the amount of urine; often used to decrease fluid retention in bodily tissues.

Epinephrine—A hormone produced by the adrenal medulla. It is important in the response to stress and partially regulates heart rate and metabolism. It is also called adrenaline.

Hypertension—High blood pressure.

Norepinephrine—A hormone released by nerve cells and the adrenal medulla that causes constriction of blood vessels.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to prescribe these drugs, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Pheochromocytoma—A tumor of specialized cells of the adrenal gland.

Precautions

Individuals taking propranolol should never suddenly stop taking the drug because of the risk of chest pain or heart attack in some people who do so. Instead, the dosage should be gradually decreased.

Pregnant or breastfeeding

Propranolol is classified as pregnancy category C. The drug has caused adverse fetal effects in animal studies, but there is no human data. The drug also passes through breast milk. Pregnant or nursing women should consult with their healthcare provider regarding the risks of taking propranolol.

Other conditions and allergies

Precautions should be taken when administering propranolol to individuals with liver or kidney failure, prior to a glaucoma screening test, or to patients with a

history of an immediate allergic reaction (known as anaphylaxis) to a beta-blocker of any kind.

Side effects

The following side effects have been observed with propranolol. Most effects are mild and rarely require the withdrawal of therapy:

- cardiovascular: slow heart rate (bradycardia), congestive heart failure, hypotension (low blood pressure), Raynaud's syndrome
- central nervous system: light-headedness, mental depression, insomnia, vivid dreams, disorientation, memory loss
- gastrointestinal: nausea, vomiting, abdominal pain, cramping, diarrhea, constipation, bowel ischemia
- allergic: fever, rash, laryngospasm, thrombocytopenia (low blood platelets)
- respiratory: bronchospasm
- hematologic: bone marrow suppression, bleeding under the skin

Interactions

Individuals should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs and supplements, to avoid the risk of interactions.

Drugs

Interactions with drugs that deplete the body of the neurotransmitters **epinephrine** and norepinephrine have been reported with concomitant propranolol. This group includes reserpine and guanethidine. Fainting, hypotension, dizziness, and slow heart rate have occurred under these circumstances. Drugs known as calcium channel blockers may decrease the pumping ability of the heart and lead to the development of cardiac arrhythmias. Nonsteroidal anti-inflammatory agents (e.g., **ibuprofen** and naproxen) may blunt the blood pressure-lowering effects of propranolol. Aluminum hydroxide antacids greatly reduce the rate of absorption of propranolol, as does alcohol. Interactions have also been reported with the drugs **phenytoin**, **rifampin**, phenobarbital, chlorpromazine, lidocaine, thyroxine, cimetidine, and theophylline.

Resources

PERIODICALS

- Püttgen, K. B. "Evidence and Nuances of Propranolol Safety." *British Journal of Dermatology* 172, no. 2 (2015): 319–20.

OTHER

- U.S. Food and Drug Administration. "Inderal [prescribing information]." http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016418s080,016762s017,017683s_0081bl.pdf (accessed February 26, 2015).
- U.S. Food and Drug Administration. "InnoPran XL [prescribing information]." http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021438s0161bl.pdf (accessed February 26, 2015).

WEBSITES

- AHFS Consumer Medication Information. "Propranolol Oral." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682607.html> (accessed February 26, 2015).
- American Heart Association. "About High Blood Pressure." http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressure/About-High-Blood-Pressure_UCM_002050_Article.jsp (accessed February 26, 2015).
- American Heart Association. "Cardiac Medications." http://www.heart.org/HEARTORG/Conditions/HeartAttack/PreventionTreatmentofHeartAttack/Cardiac-Medications_UCM_303937_Article.jsp (accessed February 26, 2015).
- UK National Health Service (NHS). "Propranolol (Propranolol 80 mg Modified-Release Capsules)." <http://www.nhs.uk/Medicine-Guides/Pages/MedicineOverview.aspx?condition=Anxiety&medicine=Propranolol> (accessed February 26, 2015).
- U.S. National Library of Medicine. "Inderal LA (Propranolol Hydrochloride) Capsule, Extended Release." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=6143> (accessed February 26, 2015).

ORGANIZATIONS

- American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Revised by Emily Jane Willingham, PhD

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Proscar see **Finasteride**

Protonix see **Pantoprazole**

Protopic see **Tacrolimus**

Provera see **Medroxyprogesterone**

Provigil see **Modafanil**

Prozac see **Fluoxetine**

Pulmicort see **Budesonide**

Q

Quetiapine

Definition

Quetiapine (quetiapine fumarate) is a second-generation antipsychotic drug, also referred to as an atypical antipsychotic drug, used to treat symptoms of schizophrenia. It works by changing the activity of certain natural substances in the brain.

Purpose

Quetiapine tablets and extended-release tablets (quetiapine XR) are used to treat the symptoms of schizophrenia and are used alone or with other medications to treat or prevent episodes of mania or depression in patients with bipolar disorder. The extended-release tablets are also used along with other medications to treat depression. Quetiapine may be used as part of a program to treat bipolar disorder and schizophrenia in children.

Description

Quetiapine is a crystalline powder prepared in tablets as a fumarate salt. Chemically, quetiapine is a dibenzothiazepine, which differs from earlier or first-generation antipsychotics, which are phenothiazines. Quetiapine is chemically related to another second-generation antipsychotic agent, **clozapine**.

In the brain, maintaining the proper levels of the brain chemicals dopamine and serotonin helps to achieve and maintain mental well-being. Quetiapine is thought to modify the actions of chemicals in the brain known as dopamine and serotonin and is therefore considered a dopamine and serotonin antagonist. It may also be an antagonist to other brain chemicals, which may explain certain other effects of the drug. Antagonism to histamine receptors on cell surfaces may explain sleepiness in patients taking the drug.

Quetiapine accumulates with multiple dosing. The drug is metabolized in the liver and then distributed widely throughout the body. The action in adults and children is similar even with differences in dosage.

Second-generation antipsychotic drugs, including quetiapine and others (e.g., clozapine, **olanzapine**, **risperidone** and **ziprasidone**) have been compared with first-generation phenothiazine antipsychotic drugs (e.g., perphenazine) in several important studies. The effectiveness of quetiapine and its side effects were evaluated in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Study in 2006, which found that more patients (80%) discontinued treatment with quetiapine due to adverse side effects than with other second-generation antipsychotics (e.g., olanzapine and risperidone) in the treatment of schizophrenia. A review study found that second-generation drugs had similar efficacy to first-generation drugs but improved both psychopathologic symptoms and quality of life to a limited extent. However, patients taking the second-generation drugs, including quetiapine, self-reported improved well-being/quality of life while taking these drugs. Researchers have concluded that no single antipsychotic drug is best for all schizophrenia patients, since individual responses differ considerably.

U.S. brand names

Quetiapine is available by prescription under the trade name Seroquel.

Recommended dosage

Quetiapine is available as tablets in doses of 25, 50, 100, 200, 300, and 400 milligrams (mg), which are distinguished by color. Initially, a dosage of 25 mg is taken twice a day. Dosage is then increased by 25–50 mg increments every three to four days until achieving a target dose of 300–400 mg per day, administered in two or three divided doses. It is not known whether doses higher than 800 mg per day are safe.



Seroquel (quetiapine), 100 mg. (© Cengage Learning®.)

Precautions

Children and adults up to age 24 are at increased risk of developing suicidal thoughts and actions while taking quetiapine.

Quetiapine has the potential to produce a serious side effect called tardive dyskinesia. This syndrome consists of involuntary, uncoordinated movements that may appear late in therapy and not disappear even after the drug is stopped. Tardive dyskinesia involves involuntary movements of the tongue, jaw, mouth, face, or other groups of skeletal muscles. The incidence of tardive dyskinesia increases with age and with dosage of quetiapine. Women are at greater risk than men for developing tardive dyskinesia. No known effective treatment is available for tardive dyskinesia, although gradual (but rarely complete) improvement may occur over a long period.

Quetiapine users may be at risk for potentially fatal heart arrhythmias, especially when taken in combination with other drugs that carry the risk of arrhythmia.

Quetiapine may increase cholesterol levels and contribute to the formation of cataracts. Regular monitoring of cholesterol levels is recommended, and yearly eye exams should be performed.

Because quetiapine is metabolized exclusively by the liver, it may cause liver damage. Patients should

notify their healthcare providers if they experience signs of liver problems such as flu-like symptoms, yellowing of the skin or eyes, or abdominal pain, especially in the right upper abdomen. Liver function should be assessed periodically.

Neuroleptic malignant syndrome may develop in rare cases. This is a complicated and potentially fatal condition characterized by muscle rigidity, high fever, alterations in mental status, and cardiac symptoms such as irregular pulse or blood pressure, sweating, tachycardia (rapid heartbeat), and arrhythmias (irregular heartbeat). People who think they may be experiencing side effects from taking this or any other medication should talk to their physicians promptly.

Quetiapine may alter thyroid gland function, and patients taking medications for low thyroid function may require dosage adjustments.

Quetiapine may cause extreme drowsiness and should be used carefully by people who need to be mentally alert to operate machinery or vehicles of any type.

Geriatric

Quetiapine is associated with an increased risk of death when used in elderly patients with dementia. Manufacturers of quetiapine (and other antipsychotic drugs) are required by the U.S. Food and Drug Administration (FDA) to add a warning label to their packaging stating this risk. Studies have shown that most deaths are related to either cardiovascular complications or infection-related complications. Quetiapine is not approved by the FDA for the treatment of behavior problems in older adults with dementia, and patients in this category (or caregivers of patients in this category) are advised to consult a physician about the risks associated with taking quetiapine.

Pregnant or breastfeeding

The drug should not be taken by women who are pregnant, trying to become pregnant, or breastfeeding. Babies born to mothers who took quetiapine during pregnancy may develop extrapyramidal symptoms (EPS) and withdrawal symptoms, including agitation, trouble breathing, and difficulty feeding.

Other conditions and allergies

Caution should be used in patients with heart disease because the drug may cause blood pressure to fall too low, resulting in dizziness, rapid heartbeat, or fainting.

The drug should be used cautiously in people with a history of liver disease or alcoholic cirrhosis. Quetiapine should also be used carefully by those with a history of

seizure disorders, as it may increase the tendency to have seizures.

Side effects

Relatively common side effects that accompany quetiapine usage include drowsiness, dizziness, rash, dry mouth, insomnia, fatigue, muscular weakness, anorexia, blurred vision, orthostatic hypertension, some loss of muscular control, and amenorrhea (lack of menstruation) in women.

Dystonia (difficulty walking or moving) may occur with quetiapine use. This condition may subside in 24–48 hours, even when patients continue to take the drug, and it usually disappears when quetiapine is discontinued.

Quetiapine use may lead to the development of symptoms that resemble Parkinson's disease. These symptoms may include a tight or mask-like expression on the face, drooling, tremors, pill-rolling motions in the hands, cogwheel rigidity (abnormal rigidity in muscles characterized by jerky movements when the muscle is passively stretched), and a shuffling gait. Taking the anti-Parkinson's drugs **benztropine** mesylate or trihexypenidyl hydrochloride along with the quetiapine usually controls these symptoms.

Interactions

Individuals should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs and supplements, before starting treatment with quetiapine.

Drugs

Quetiapine may be less effective when it is taken with drugs like **carbamazepine** (Tegretol), **phenytoin** (Dilantin), **rifampin** (Rifadin), barbiturates, thioridazine (Mellaril), or corticosteroids such as prednisolone, **methylprednisolone**, **prednisone**, and dexamethasone, because these drugs increase the breakdown of quetiapine in the liver, causing lower-than-normal levels of the drug.

Antifungal drugs, such as **fluconazole** (Diflucan) or **ketoconazole** (Nizoral); antibiotics, such as **erythromycin** or **clarithromycin** (Biaxin); and cimetidine (Tagamet) may decrease the breakdown of quetiapine in the liver, causing higher-than-normal levels of the drug.

Any drug that causes drowsiness may lead to decreased mental alertness and impaired motor skills when taken with quetiapine. Some examples include antidepressants such as **imipramine** (Tofranil) or **paroxetine** (Paxil), antipsychotics such as thioridazine (Mellaril), and some antihistamines.

KEY TERMS

Bipolar disorder—A mood disorder marked by alternating episodes of extremely low mood (depression) and exuberant highs (mania). Also known as manic-depressive disorder.

Extrapyramidal symptoms—A group of side effects associated with antipsychotic medications that are characterized by involuntary muscle movements, including contraction and tremor.

Insomnia—Waking in the middle of the night and having difficulty returning to sleep, or waking too early in the morning.

Schizophrenia—A severe mental illness in which a person has difficulty distinguishing what is real from what is not real. It is often characterized by hallucinations, delusions, and withdrawal from people and social activities.

Seizure—A convulsion, or uncontrolled discharge of nerve cells that may spread to other cells throughout the brain.

Food and other substances

Alcohol increases the sedative effects of quetiapine.

Resources

BOOKS

- Albers, Lawrence J., Rhoda K. Hahn, and Christopher Reist. *Handbook of Psychiatric Drugs*. Laguna Hills: Current Clinical Strategies Publishing, 2010.
- American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda: American Society of Health-System Pharmacists, 2015.
- Holland, Leland Norman, and Michael Patrick Adams. *Core Concepts in Pharmacology*. 3rd ed. New York: Prentice Hall, 2011.
- Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland: New Harbinger Publications, 2013.

PERIODICALS

- Foussias, G., and G. Remington. "Antipsychotics and Schizophrenia: From Efficacy and Effectiveness to Clinical Decision-Making." *Canadian Journal of Psychiatry* 55, no. 3 (2010): 117–25.
- Kasper, S., et al. "Treatment of Depressive Symptoms in Patients with Schizophrenia: A Randomized, Open-Label, Parallel-Group, Flexible-Dose Subgroup Analysis of Patients Treated with Extended-Release Quetiapine Fumarate or Risperidone." *International Clinical Psychopharmacology* 30, no. 1 (2015): 14–22.

- Naber, D., and M. Lambert. "The CATIE and CUtLASS Studies in Schizophrenia: Results and Implications for Clinicians." *CNS Drugs* 23, no. 8 (2009): 649–59.
- Naber, D., et al. "Subjective Well-Being in Schizophrenia: A Randomised Controlled Open-Label 12-Month Non-Inferiority Study Comparing Quetiapine XR with Risperidone (RECOVER)." *European Neuropsychopharmacology* 23, no. 10 (2013): 1257–69.

WEBSITES

AHFS Consumer Medication Information. "Quetiapine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a698019.html> (accessed March 12, 2015).

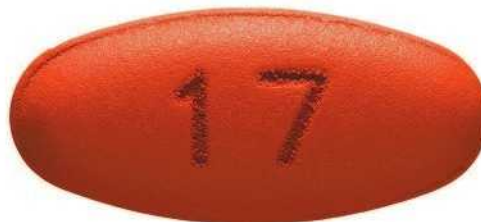
ORGANIZATIONS

- American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.
- Mental Health America, 2000 N. Beauregard Street, 6th Floor, Alexandria, VA 22311, (703) 684-7722, (800) 969-6642, Fax: (703) 684-5968, <http://www1.nmha.org/>.
- National Alliance on Mental Illness (NAMI), 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.
- National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 8184, MSC 9663, Bethesda, MD 20892, (301) 443-4513, (866) 615-6464, Fax: (301) 443-4279, nimhinfo@nih.gov, <http://www.nimh.nih.gov/index.shtml>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Quinapril, 40 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Quinapril may also be given to people with a high likelihood of developing coronary artery disease, helping them to feel less tired and short of breath. Since ACE inhibitors are used to control and prevent conditions of the heart, they are usually prescribed for the long term. ACE inhibitors are often recommended for individuals with diabetes and hypertension, because they may help delay the progression of diabetic nephropathy (kidney damage).

Some other common ACE inhibitors include:

- **captopril** (Capoten)
- **enalapril** (Vasotec)
- **lisinopril** (Zestril, Prinivil)
- **benazepril** (Lotensin)
- **ramipril** (Altace)

Description

Quinapril is available as a tablet and is to be taken by mouth (orally). It may be used alone or in combination with other medications for the management of high blood pressure (hypertension) and for the management of congestive heart failure (CHF).

U.S. brand names

Quinapril is sold under the brand name Accupril. It is offered by prescription only.

Quinapril

Definition

Quinapril is a medication used for the management of high blood pressure and heart failure.

Purpose

Quinapril is an ACE inhibitor. The term ACE stands for angiotensin-converting enzyme. An ACE inhibitor blocks the conversion of angiotensin I to angiotensin II by inhibiting the angiotensin-converting enzyme, which prevents tightening (constriction) of blood vessels. When the blood vessels are not constricted, the heart can pump blood more freely and effectively throughout blood vessels.

KEY TERMS

Angiotensin-converting enzyme (ACE) inhibitor—A drug that lowers blood pressure by interfering with the breakdown of a protein-like substance involved in blood pressure regulation.

Carotid artery—Major artery leading to the brain, blockages of which can cause temporary or permanent strokes.

Carotid artery disease—A condition in which the arteries in the neck that supply blood to the brain become clogged, causing the danger of a stroke.

Congestive heart failure—Also called heart failure; a condition in which a damaged or overworked heart cannot pump enough blood to meet the oxygen and nutrient needs of the body. People with heart failure may find it hard to exercise due to insufficient blood flow, but many people live a long time with this condition.

Coronary artery disease—Also called atherosclerosis; a buildup of fatty matter and debris in the coronary artery wall that causes narrowing of the artery.

Recommended dosage

The initial dose of quinapril for adults for the treatment of hypertension is a 10- or 20-milligram (mg) tablet taken once a day. Later, a maintenance dose of 20 to 80 mg may be prescribed. Patients who are on diuretics may be prescribed a lower initial or lower maintenance dose by their physician, or the diuretic may be discontinued.

The dose of quinapril may vary for patients taking it for the treatment of heart failure. In this case, the initial dose may be 5 mg taken two times per day (for a total of 10 mg), and a maintenance dose of 20 to 40 mg divided into two doses per day.

Whether taken for hypertension or for heart failure, patients taking quinapril will be monitored closely to ensure that the drug is well tolerated; if so, they may progress to a higher maintenance dosage.

Geriatric

Dosing should be done conservatively in seniors. As the body ages, it becomes less efficient at eliminating drugs, which can lead to increased risk of side effects and an increased risk of overdose. The usual dose for hypertension or for heart failure is 10 mg daily. Seniors

should be monitored closely and given the lowest effective dosage.

Precautions

This medication affects blood pressure, so it is advised that patients who are taking quinapril move from lying to standing positions slowly to avoid becoming dizzy or falling.

Quinapril may cause a change in kidney function, increasing serum creatinine and blood urea nitrogen levels, so special caution should be taken for use in patients who have poor liver or kidney (renal) function, especially patients with diabetes.

Quinapril tablets should be taken whole and not crushed, broken, or chewed. Breaking down the pill can result in an inconsistent or unpredictable amount of the medication entering the bloodstream at one time.

All patients taking quinapril should be monitored closely, and the dosage should be re-evaluated regularly.

Pediatric

Quinapril is not used for treatment in children.

Geriatric

Seniors are at an increased risk of side effects from quinapril and should be monitored closely. Seniors may take a number of other medications that may interact poorly with quinapril, so the use of all medications and supplements should be discussed with their healthcare provider.

Pregnant or breastfeeding

Quinapril is considered a class D pregnancy drug, which means that evidence of serious risks to a fetus exist. Quinapril should not be taken by anyone who is pregnant or plans to become pregnant. This drug can pass into breast milk, so it should not be taken if a mother is breastfeeding her baby.

Side effects

In some cases, allergic reactions to quinapril have occurred. Any patient who experiences symptoms of an allergic reaction, including swelling of the lips, throat, mouth, or face; difficulty breathing; hives; or rash, should seek emergency medical attention immediately.

High potassium may occur while taking quinapril. Symptoms of high potassium include weakness, a slow or weak pulse, and tingling in limbs. Patients should seek medical treatment if these side effects occur. Patients

should seek emergency medical assistance if any of the following symptoms occur:

- feeling like you may faint or pass out
- swelling of the face, lips or tongue (angioedema)
- difficulty swallowing
- confusion
- abdominal pain
- signs of dehydration such as little or no urine output
- sudden weakness

Common but less serious side effects include:

- cough
- headache
- dizziness
- fatigue

Interactions

Many medications can cause serious interactions with quinapril. Individuals should tell their doctor and pharmacist about all prescription medications, over-the-counter medications, vitamins, herbs, and supplements that they are taking. It may be necessary to stop taking some medications or switch to different medications to reduce the chance of interactions with quinapril.

Drugs

Patients taking diuretics or potassium supplements should take quinapril with caution and only after discussion with their doctor.

Quinapril should not be used by individuals with diabetes who are also taking aliskiren (Tekturna).

Food and other substances

Patients taking quinapril should not consume alcohol. Alcohol may increase or mimic potential side effects of quinapril such as dizziness or light-headedness.

Resources

BOOKS

Mann, Douglas, et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 10th ed. Philadelphia: Saunders, 2014.

Resources

PERIODICALS

Kaufman, Michele B. "ACE Inhibitor-Related Angioedema: Are Your Patients at Risk?" *Pharmacy and Therapeutics* 38, no. 3 (2013): 170–72.

Sunny, A., et al. "Risk-Benefit Analysis and Risk Minimization of Quinapril: A Review." *American Journal of Pharmacology & Toxicology* 9, no. 1 (2014): 68–74.

Resources

WEBSITES

Mayo Clinic staff. "Heart Failure." MayoClinic.org. <http://www.mayoclinic.com/health/heartfailure/DS00061> (accessed March 11, 2015).

U.S. National Library of Medicine. "Accupril—Quinapril Hydrochloride Tablet, Film Coated." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=63cf5651-d52c-4d27-9fd4-ed9cd9724dff> (accessed January 26, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.

Heart Foundation, 80 William Street, Level 3, East Sydney NSW 2011, Australia, +61 02 9219 2444, 300 36 27 87, <http://www.heartfoundation.org.au/>.

National Heart, Lung, and Blood Institute (NHLBI), PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbinfo@nhlbi.org, <http://www.nhlbi.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Laura Jean Cataldo, RN, EdD

REVIEWED BY GREGORY A. PRATT, RPh

R

Rabeprazole

Definition

Rabeprazole is a medication designed to help relieve heartburn and other symptoms of gastroesophageal reflux disease (GERD). GERD is a condition that allows some acid from the stomach to return back up to the esophagus, the tube that leads from the throat to the stomach. Rabeprazole belongs to a class of drugs called proton pump inhibitors and is available only with a prescription.

Purpose

Heartburn is a hallmark symptom of GERD, and is a burning sort of pain near the breast bone, especially when a person lies down or bends over. Although GERD may seem harmless, the constant reflux of stomach acid can eventually harm the thin lining of the esophagus. Rabeprazole and other proton pump inhibitors reduce the amount of acid made in the stomach, which helps control symptoms of GERD. The medicine also helps the esophagus heal if it has been damaged by GERD and can be used to treat ulcers in the stomach, esophagus, or duodenum (the first part of the small intestine). Combining rabeprazole with certain antibiotics can eliminate the bacteria called *Helicobacter pylori* that is responsible for nearly all stomach ulcers.

Description

Rabeprazole comes in a delayed-release tablet that is swallowed whole. The delayed release keeps the tablet from being broken down by stomach acids. There also is a capsule with granules that can be sprinkled on soft food for children or anyone else who cannot swallow a tablet.

U.S. brand names

In the United States, rabeprazole is sold under the brand name AcipHex. The U.S. Food and Drug Administration (FDA) approved a generic version of

the drug for treating GERD in people age 12 and older in November 2013.

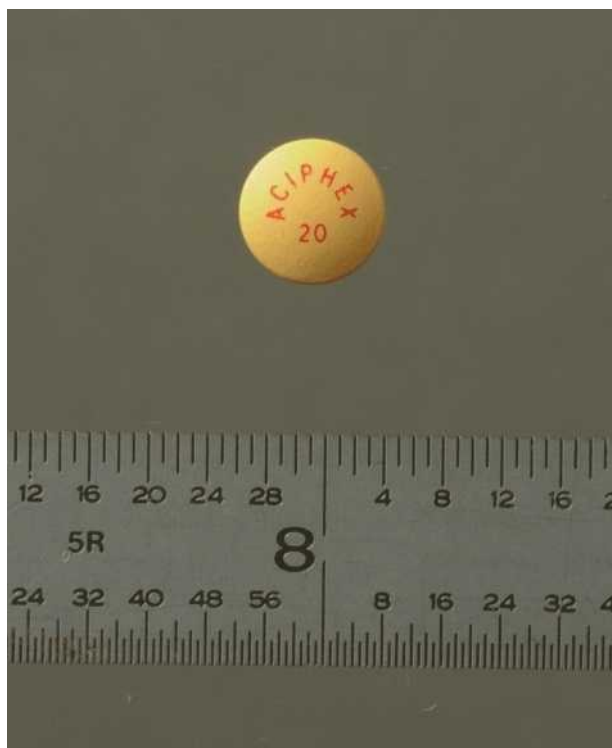
Recommended dosage

Dosage depends on the reason for use of rabeprazole and age. Unless otherwise noted, the medicine is taken after a morning meal. To treat the symptoms of GERD, the recommended adult dose is 20 mg once a day for four to eight weeks, depending on when symptoms improve. If rabeprazole is being taken to heal ulcers caused by GERD, doctors recommend 20 mg once a day for four to eight weeks, and continuing the therapy if signs or symptoms return. Adults should take 20 mg of rabeprazole a day to treat or prevent duodenal ulcers, with the doctor determining how long to continue the medication. No studies have been done on continuing rabeprazole for duodenal ulcers for longer than one year. To eliminate *H. pylori* infection, a 20 mg dose of rabeprazole is combined with either amoxicillin or **clarithromycin** and taken two times a day for seven days.

Children age 12 and older can take 20 mg once a day after their morning meal for eight weeks to treat GERD. If less than age 12, dosage is based on weight. Children aged 1 to 11 who weigh less than 15 kg should take 5 mg of sprinkled rabeprazole by mouth once a day with food. Doctors can increase the dose to 10 mg a day if the 5 mg dose fails to relieve symptoms. If a child weighs more than 15 kg, recommended dose is 10 mg of the sprinkled rabeprazole by mouth once a day for up to 12 weeks.

Precautions

Some people are allergic to rabeprazole, and anyone who has had an allergic reaction or high sensitivity to another proton pump inhibitor should inform the doctor. Doctors and patients should be aware that some stomach cancers can cause similar symptoms to GERD, and clearly distinguish symptoms before assuming that rabeprazole's effectiveness rules out the possibility of



AcipHex (rabeprazole), 20 mg. (© Cengage Learning®.)

cancer. Long-term use of rabeprazole can increase risk of fractures from osteoporosis. Use of rabeprazole and other proton pump inhibitors may increase risk of severe diarrhea caused by stomach bacteria.

Pediatric

Studies show that rabeprazole is not recommended for use in children less than 12 months old.

Pregnant or breastfeeding

Rabeprazole is a pregnancy category B drug, and could harm a fetus. It should only be used by pregnant women if clearly needed. The medication could be passed from mother to infant through breastfeeding. A mother who wants to nurse her baby should discuss with her doctor whether the medication is important enough to continue. If so, she should not breastfeed while taking rabeprazole.

Side effects

Rabeprazole can cause side effects, including:

- sore throat
- headache
- nausea and vomiting
- gas and constipation

KEY TERMS

Gastroesophageal reflux disease—Abbreviated GERD, this condition involves the passage of stomach acid back into the esophagus through the small opening and muscle that normally allow food to travel down from the esophagus into the stomach. GERD can cause heartburn and lead to ulcers in the esophagus.

Osteoporosis—A chronic and progressive disease that leads to bone weakening and brittleness.

Proton pump inhibitor—These medicines reduce how much acid is made by glands that are located in the stomach's lining. When less acid is made, less makes its way back into the esophagus, and the symptoms of gastroesophageal reflux disease are eased.

Ulcer—A sore or break in the skin or lining of an organ.

Some side effects are more severe and should be reported to the doctor immediately, including:

- skin that peels or blisters
- hives and rash
- problems with breathing or swallowing
- rapid or irregular heartbeat
- extreme fatigue
- dizziness
- muscles spasms or shaking that won't stop

Interactions

Drugs can interact with one another, reducing the effects of one drug or increasing side effects. It is important to tell the doctor about any medications, herbal remedies, or vitamin supplements being taken before starting rabeprazole therapy.

Drugs

Rabeprazole interacts with some antiretroviral drugs used to treat AIDS, including atazanavir (Reyataz), making the antiretroviral drug work less effectively. Rabeprazole interacts with blood thinners such as warfarin (Coumadin), and with **clopidogrel** (Plavix), which is used to prevent severe problems in people with heart and blood vessel disease. Rabeprazole also may increase levels of **methotrexate** (Rheumatrex), a drug used to treat psoriasis.

Herbs and supplements

Rabeprazole may interfere with how the body absorbs certain vitamins and supplements, including iron.

Resources

PERIODICALS

- Hussain, Nazia, and Narra Nailah. "Peptic Ulcer Disease." *InnovAIT* 7, no. 7 (2014): 404–12.
- Kelly, Kristin J. "Generic Aciphex Approved for GERD." *NEJM Journal Watch* (November 12, 2013): FW108145.

WEBSITES

- "AcipHex." Rxlist.com. <http://www.rxlist.com/aciphex-drug.htm> (accessed February 21, 2015).
- "Delayed-release Tablets, Rabeprazole." Drugs.com. <http://www.drugs.com/cdi/delayed-release-tablets.html> (accessed February 21, 2015).
- Eisai, Inc. "AcipHex." Aciphex.com. <http://www.aciphex.com/> (accessed February 21, 2015).
- MedlinePlus. "Rabeprazole." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699060.html> (accessed February 21, 2015).

ORGANIZATIONS

- American Gastroenterological Association, 4930 Del Ray Avenue, Bethesda, MD 20814, (301) 654-2055, Fax: (301) 654-5920, <http://www.gastro.org/>.
- North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, 1501 Bethlehem Pike, Flourtown, PA 19031, (215) 233-0808, naspgan@naspgan.org, <http://www.gikids.org/>.

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Raloxifene

Definition

Raloxifene (Evista) is an oral medication classified as a selective estrogen receptor modulator (SERM). This classification means that its action on the estrogen receptor is different in various tissues, allowing it to selectively inhibit or stimulate estrogen-like action in different tissues of the body. It stimulates the action of estrogen on the bones but blocks the effects of estrogen on breast and uterine tissues.

Purpose

Raloxifene is a hormone therapy drug that protects against bone loss (osteoporosis) in postmenopausal



Evista (raloxifene), 60 mg. (© Cengage Learning®.)

women. In 2007, the FDA approved raloxifene as a treatment to reduce the risk of invasive breast cancer in postmenopausal women diagnosed with osteoporosis. However, raloxifene is not indicated for the treatment of invasive breast cancer, and it cannot be used to prevent the recurrence of breast cancer or reduce the risk of noninvasive breast cancer.

Description

Estrogen is a steroid hormone secreted by the granulosa cells of a maturing follicle within the female ovary. Depending on the target tissue, estrogen can stimulate the growth of female reproductive organs and breast tissue, play a role in the female menstrual cycle, and protect against bone loss by binding to estrogen receptors on the outside of cells within the target tissue.

Raloxifene selectively inhibits the effects of estrogen on breast tissue and uterine tissue, while selectively mimicking the effects of estrogen on bone (by increasing bone mineral density). Its effects on breast and uterine tissue are thought to make raloxifene an excellent therapeutic agent against the risk of breast cancer and uterine cancer by depriving potential tumors of the estrogen they need to grow.

Raloxifene is available in tablet form.

KEY TERMS

Cancer—A disease caused by uncontrolled growth of the body's cells.

Estrogen—A female hormone produced by the ovaries that stimulates the growth of the lining of the uterus.

Estrogen receptors—A group of proteins found inside cells that are activated by the sex hormone estrogen.

Granulosa cells—Cells that form the wall of the ovarian follicle and produce various steroid hormones.

Menopause—The end of a woman's menstrual periods when a woman can no longer conceive a child.

Osteoporosis—The excessive loss of calcium from the bones, causing the bones to become fragile and break easily. Postmenopausal women are especially vulnerable to this condition because estrogen, a hormone that protects bones against calcium loss, decreases drastically after menopause.

Ovarian follicle—Several layers of cells that surround a maturing egg in the ovary.

Postmenopausal—A term referring to the time period following menopause.

Selective estrogen receptor modulator (SERM)—A drug that has estrogenic effects in some body tissues and antiestrogenic effects in other tissues.

Thromboembolism—A blood clot that blocks a blood vessel in the cardiovascular system.

Origins

Raloxifene was approved by the U.S. Food and Drug Administration (FDA) for the prevention of osteoporosis in postmenopausal women in 1997 and for the treatment of osteoporosis in postmenopausal women in 1999.

U.S. brand name

Raloxifene is marketed under the brand name Evista.

Recommended dosage

The standard dose of raloxifene for any of its indications is one 60 milligram (mg) tablet by mouth daily. It can be taken with or without food, but patients should take it at the same time each day. Postmenopausal

women prescribed raloxifene to reduce the risk of invasive breast cancer should take the drug at this 60 mg daily dosage for five years. If a dose is missed, patients should not double the next dose. Instead, they should go back to their regular schedule and contact their doctor.

Raloxifene should be kept at room temperature, tightly capped, away from children, and away from excess heat and moisture (not in the bathroom).

Precautions

Women taking raloxifene should make sure to eat foods that are rich in calcium and vitamin D or take calcium and vitamin supplements.

Women with coronary heart disease (CHD) are at increased risk of stroke if they take raloxifene, and others not presently diagnosed with CHD are at increased risk of developing it. Raloxifene can cause a higher risk of developing blood clots.

Patients taking raloxifene should stop taking the drug and call their doctor at once if they notice any of the following symptoms:

- swelling of the hands, feet, ankles, or lower legs
- sudden chest pain
- shortness of breath
- coughing up blood
- loss of vision or blurred vision
- sensations of warmth in the lower legs
- pain in the legs

Pregnant or breastfeeding

Although raloxifene is approved for use only by women past their childbearing years, researchers emphasize that it is not recommended for women who are pregnant or breastfeeding. In test animals, raloxifene caused birth defects and miscarriages. Although it is not known whether raloxifene is present in breast milk, it is possible that its presence may be toxic to infants.

Other conditions and allergies

Patients at risk for the formation of deep venous thrombosis or pulmonary thromboembolisms should use raloxifene with caution. Those with past episodes of venous thrombosis should not use the drug at all. Women with kidney or liver disease should use raloxifene with caution. Patients should tell their doctor if they have ever smoked, been treated for high blood pressure, had a stroke or transient ischemic attack (TIA), or been diagnosed with an irregular heartbeat.

PATIENT PROFILE

A generally healthy, postmenopausal woman aged 60 was diagnosed with reduced bone mass (osteopenia) and weakened bones, a condition known as osteoporosis. Although it was too late to prevent osteoporosis, the patient's gynecologist advised that the patient should be taking medication to reduce the progression of osteoporosis and to restore bone mass as much as possible. The doctor explained that increased bone resorption and accelerated bone loss were common in postmenopausal women due to decreases in estrogen levels after menopause. In some women, certain bone cells are also altered as a result of normal aging, which may also tend to decrease bone mass. All of these changes can lead to spontaneous bone fractures, but risk of fracture can be reduced and bone mass increased to some extent by taking certain medications that have been shown to restore normal bone quality.

The doctor suggested that raloxifene (Evista) was the first-line treatment and prevention method for osteoporosis in postmenopausal women. It is also used to reduce risk of invasive breast cancer in postmenopausal women with known osteoporosis. Raloxifene is a selective estrogen receptor modulator (SERM) that works for osteoporosis by binding to estrogen receptors, which activates certain estrogen pathways and blocks others. This, in turn, decreases resorption of bone, restoring levels of bone turnover to premenopause levels and increasing bone mineral density. Raloxifene is supplied in tablet form for oral administration, with each tablet containing 60 mg of raloxifene hydrochloride. For this

patient, the doctor prescribed raloxifene 120 mg to be taken once a day.

Initially, the patient tolerated raloxifene well, and the doctor increased the dosage to 180 mg per day. The patient had no noticeable symptoms or side effects after the first two to three months of treatment at this higher dosage. However, at her six-month follow-up visit, she reported that she had been having hot flashes, sweating, and leg cramps during the night, symptoms of menopause that had diminished within a year or so after menopause was over. She expressed that she did not want to endure the recurrence of those symptoms. She also complained of weight gain and slight pain and swelling in her legs. However, since a bone density test and laboratory tests for bone turnover rates (alkaline phosphatase, osteocalcin, and collagen breakdown products) at that time showed a modest increase in density and no signs of osteopenia, the doctor was reluctant to discontinue treatment. Instead, he reduced the dosage of raloxifene to 60 mg per day as taken initially and urged the patient to also begin a regular walking schedule to help limit weight gain and also to increase calcium levels. As an adjunctive treatment for osteoporosis, the doctor recommended taking supplemental calcium and vitamin D daily in addition to a multivitamin. After another month of taking the lower dosage of raloxifene, the patient reported that the hot flashes and leg cramps had diminished. She continued taking raloxifene long term without significant side effects.

Side effects

Although raloxifene is usually well tolerated by patients, it has been associated with some adverse effects. Commonly reported side effects include mild nausea, vomiting, hot flashes, weight gain, bone pain, and hair thinning, which are not severe enough to stop therapy. Other side effects include leg cramps, flu-like symptoms, insomnia, joint pain, and heavy sweating.

Interactions

Patients should make their healthcare providers aware of all medications they are currently taking, including over-the-counter drugs and supplements.

Drugs

The usefulness of raloxifene can be diminished if patients also are on hormone replacement therapy (HRT) or the cholesterol-lowering drug cholestyramine

(Questran). Cholestyramine decreases the absorption of raloxifene into the blood, while estrogen supplements increase the amount of estrogen competing with raloxifene for binding sites on target cells' estrogen receptors. Raloxifene also interacts with diazepam (Valium), lidocaine, colestipol, and diazoxide (Proglycem, used to treat low blood sugar). Patients should tell their doctor if they are taking any of these medications or if they are likely to require local anesthesia for dental work or minor surgery.

Raloxifene interferes with the anticoagulant (clot-preventing) effect of **warfarin** with severe consequences and even death. Patients using warfarin should make sure their physician is aware prior to commencing treatment with raloxifene.

Resources

BOOKS

Huang, Xianhai, and Robert G. Aslanian, eds. *Case Studies in Modern Drug Discovery and Development*. Hoboken, NJ: John Wiley and Sons, 2012.

Jordan, V. Craig, ed. *Estrogen Action, Selective Estrogen Receptor Modulators, and Women's Health: Progress and Promise*. Hackensack, NJ: World Scientific, 2013.

PERIODICALS

Gizzo, S., et al. "Update on Raloxifene: Mechanism of Action, Clinical Efficacy, Adverse Effects, and Contraindications." *Obstetrical and Gynecological Survey* 68 (June 2013): 467–81.

Komm, B. S., and S. Mirkin. "An Overview of Current and Emerging SERMs." *Journal of Steroid Biochemistry and Molecular Biology* 143C (September 2014): 207–22.

Moyer, C. A., and the U.S. Preventive Services Task Force (USPSTF). "Medications to Decrease the Risk for Breast Cancer in Women: Recommendations from the U.S. Preventive Services Task Force Recommendation Statement." *Annals of Internal Medicine* 159 (November 19, 2013): 698–708.

Pinkerton, J. V., and S. Thomas. "Use of SERMs for Treatment in Postmenopausal Women." *Journal of Steroid Biochemistry and Molecular Biology* 142 (July 2014): 142–54.

Reimers, L., and K. D. Crew. "Tamoxifen vs. Raloxifene vs. Exemestane for Chemoprevention." *Current Breast Cancer Reports* 4 (September 1, 2012): 207–15.

Visvanathan, K., et al. "Use of Pharmacologic Interventions for Breast Cancer Risk Reduction: American Society of Clinical Oncology Clinical Practice Guideline." *Journal of Clinical Oncology* 31 (August 10, 2013): 2942–62.

OTHER

U.S. Food and Drug Administration (FDA). "Medication Guide: Evista." <http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088593.pdf> (accessed February 26, 2015).

WEBSITES

MedlinePlus. "Raloxifene." U.S. National Library of Medicine. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a698007.html> (accessed February 26, 2015).

"Raloxifene Hydrochloride." Drugs.com. <http://www.drugs.com/monograph/raloxifene-hydrochloride.html> (accessed February 26, 2015).

Susan G. Komen. "Risk-Lowering Drugs." <http://ww5.komen.org/BreastCancer/RiskLoweringDrugs.html> (accessed February 26, 2015).

U.S. Food and Drug Administration (FDA). "FDA Approves New Uses for Evista." <http://www.fda.gov/newsevents/newsroom/pressannouncements/2007/ucm108981.htm> (accessed February 26, 2015).

ORGANIZATIONS

National Cancer Institute, 9609 Medical Center Drive, BG 9609 MSC 9760, Bethesda, MD 20892-9760, (800) 4-CANCER (422-6237), <http://www.cancer.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Revised by Rebecca J. Frey, PhD

REVIEWED BY KEVIN GLAZA, RPH

Ramelteon

Definition

Ramelteon is an oral drug used to treat sleep-onset insomnia in adults. It is in the drug classes known as melatonin receptor agonists, hypnotics, sleep medications, sedatives, and miscellaneous anxiolytics.

Purpose

Insomnia generally causes people to sleep poorly or to not get enough sleep. Insomnia can interfere with daytime functioning and quality of life and is associated with an increased need for healthcare services. Approximately one-third of the general population experiences occasional insomnia, and 10%–15% of adults suffer from chronic insomnia. The elderly and people with other medical conditions are more likely to suffer from insomnia.

Ramelteon is most effective for people who have difficulty falling asleep—sleep-onset insomnia—and it can help them fall asleep faster. Ramelteon is not generally used for insomnia that makes it difficult to stay asleep or that causes early awakening and the inability to fall back asleep. However, there is evidence that ramelteon does increase total sleep time. Unlike some other sleep medications, ramelteon does not usually cause morning sleepiness, nor is it habit-forming. However, a 2014 meta-analysis of 13 trials reported that although ramelteon is associated with some improvement



Zozerem (ramelteon), 8 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Agonist—A drug, such as ramelteon, that binds to specific receptors, with resulting activities that are similar to the binding of an endogenous substance.

Anxiolytic—An anxiety-relieving drug.

Circadian rhythm—A 24-hour cycle of physiological and behavioral activity, including the sleep/wake cycle under the control of melatonin.

Delirium—A disturbance of consciousness marked by confusion, agitation, inattention, delusions, and/or hallucinations.

Hormone—A substance, such as melatonin, that is produced in one area of the body and travels through the bloodstream to another part of the body where it has its effects.

Hypnotic—A drug that induces sleep.

Insomnia—Prolonged or abnormal inability to obtain adequate sleep.

Melatonin—A hormone involved in regulation of the sleep-wake cycle and other circadian rhythms.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Pineal gland—A small endocrine gland in the brain that produces melatonin.

Receptor—A molecule, usually a protein, inside or on the surface of a cell, that binds a specific substance to initiate a series of events.

Sedative—A drug that calms or tranquilizes nervousness or excitement.

Serotonin—A neurotransmitter found in the brain and blood; a melatonin precursor.

Suprachiasmatic nucleus (SCN)—A pair of nerve clusters in the hypothalamus of the brain that receives light input from the retina via the optic nerve and regulates circadian rhythms.

in sleep parameters in adults with insomnia, its effects appear to be relatively small.

Off-label uses

Although ramelteon is only approved by the U.S. Food and Drug Administration (FDA) for treating insomnia, it is sometimes prescribed for other purposes.

It is being studied for its ability to reduce the frequency of migraine headaches. Furthermore, a 2014 study found that it may help prevent delirium in elderly patients hospitalized with acute illnesses. The study found that it reduced the risk of delirium from 32% to 3% compared with a placebo. Melatonin—the naturally occurring hormone that is similar to ramelteon—and melatonin agonists, such as ramelteon, are also being studied for blood pressure lowering and other cardiovascular effects, and they may have a potential role in treating major depression and irritable bowel syndrome.

Description

Ramelteon represents the newest class of hypnotics—drugs that induce partial loss of consciousness or sleep. Unlike other hypnotics and sedatives used to treat insomnia, ramelteon affects the melatonin system in the brain. Ramelteon is the only approved sleep medication that does not have a direct sedating effect on the central nervous system; rather, it acts directly on sleep regulating mechanisms in the suprachiasmatic nucleus (SCN) of the brain. The SCN regulates the production and release of melatonin by the pineal gland in the brain. Melatonin is involved in the regulation of circadian rhythms—the body's sleep/wake cycle—and is required for sleep. It is produced from serotonin, a neurotransmitter in the brain, and is secreted especially in response to darkness. Melatonin is widely used as an over-the-counter (nonprescription) sleep aid. Ramelteon is similar in structure to melatonin and binds with high affinity to the melatonin receptors MT1 and MT2 in the SCN. Its binding to the receptors is similar to that of melatonin itself. Ramelteon is called a selective melatonin receptor agonist, because upon binding melatonin receptors, it initiates the same sequence of events as melatonin binding. MT1 binding promotes sleep onset. MT2 binding reinforces or shifts the timing of the circadian system. This is in contrast to sedatives, which treat insomnia by slowing down nerve transmissions in the central nervous system. Insomnia usually improves within seven to ten days of initiating ramelteon treatment.

Ramelteon is available as 8 milligram (mg) oral tablets. It should be stored in the tightly closed container that it is supplied in, at room temperature and away from excess heat and moisture (not in the bathroom).

U.S. brand names

Rozerem is the brand name for ramelteon in the United States.

Canadian brand names

Ramelteon is available in Canada under its generic name.

International brand names

Rozerem is sold in the Philippines. Ramelteon is approved in Japan and some other countries but not in Europe.

Origins

Ramelteon was first approved by the FDA in 2005. It was the first sleep medication to target melatonin receptors and the first that was not a controlled substance. Generic ramelteon was approved in 2013.

Recommended dosage

The recommended ramelteon dosage is 8 mg once per day, within 30 minutes of going to bed. It should only be taken when the person is ready to go to sleep and can remain asleep for at least seven or eight hours. If it was not taken at bedtime, and the person is unable to fall asleep, ramelteon may be taken as long as the patient is able to remain in bed for the subsequent seven to eight hours. The tablets are swallowed whole—not split, chewed, or crushed. There are no limitations to the duration of treatment with ramelteon.

Precautions

Some precautions to be taken with ramelteon include:

- No more than the prescribed dose of ramelteon should be taken.
- Ramelteon should be taken no sooner than 30 minutes before going to bed. Sleepiness may occur soon after taking ramelteon, so patients should be prepared to go to bed and sleep for seven to eight hours.
- Ramelteon can cause daytime drowsiness: people should not drive a car or operate machinery until they know how the drug affects their daytime activities.
- Patients should call their doctor if insomnia does not improve or worsens while taking ramelteon.
- Ramelteon should not be taken by people who drink alcohol or take other medications that cause sleepiness.
- Some people taking ramelteon have gotten out of bed and sleepwalked, drove their cars (“sleep-driving”), prepared and eaten food, engaged in sex, made phone calls, or performed other activities while partially asleep. Upon waking, they usually do not remember having gotten up in the night. The risk of such activities is higher after consuming alcohol or taking other medications that induce sleepiness along with ramelteon. The doctor should be called immediately if patients find they have gotten up while asleep.
- People taking ramelteon have experienced unexpected changes in mental health, although it is unclear whether

these changes were caused by ramelteon or by other conditions. Family members should be aware of serious mental health symptoms so that they can call the doctor if patients are unable to call the doctor on their own.

Pediatric

Ramelteon is not to be used by children.

Pregnant or breastfeeding

Ramelteon is in the FDA pregnancy category C—it is not known whether it is safe during pregnancy and should only be used, with caution, if benefits outweigh potential risks to the fetus. Although no clinical studies have been performed on breastfeeding while taking ramelteon, its use is not recommended.

Other conditions and allergies

Patients should tell their doctor and pharmacist if they are allergic to ramelteon, any ingredients in ramelteon tablets, or any other medications. Patients with liver disease should not take ramelteon. Patients should tell their doctors if they have or have ever had:

- suicidal thoughts or plans or suicide attempts
- depression
- mental illness
- chronic obstructive pulmonary disease (COPD) or other lung diseases
- sleep apnea (frequent, brief pauses in breathing during the night) or other breathing problems
- liver disease

Side effects

The most common side effects of ramelteon are drowsiness lasting into the next day, fatigue, and dizziness. Headache, sleepiness, and sore throat occur in fewer than 1% of patients taking ramelteon. Patients should notify their doctor if drowsiness, tiredness, or dizziness is severe or persistent.

Patients should contact their doctor immediately if they experience any of the following symptoms:

- agitation, anxiety, or frenzied or abnormally excited mood
- hallucinations
- nightmares
- memory problems
- new or worsening depression
- suicidal thoughts or behaviors
- getting out of bed while not fully awake and performing activities that they are unaware of

Ramelteon can decrease testosterone levels and increase prolactin levels in the blood. Symptoms of these hormonal effects include:

- decreased interest in sex
- fertility problems
- irregular menstrual periods or missed menstrual periods
- milky discharge from the nipples in a woman who is not lactating

Other conditions and allergies

Ramelteon can cause severe allergic reactions. Symptoms—including swelling of the tongue or throat, difficulty swallowing or breathing, a sensation that the throat is closing, and nausea and vomiting—require emergency medical assistance.

Interactions

Many different medications may interact with ramelteon. The doctor and pharmacist should be informed of all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used or planning to be used by the patient. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

Ramelteon should not be taken by anyone taking **fluvoxamine** (Luvox). Patients must be closely monitored if they are taking **donepezil** or **doxepin**, because these drugs can increase body-wide (systemic) exposure to ramelteon. Other drugs that may require changing doses or carefully monitoring for side effects if taken in conjunction with ramelteon include:

- certain antifungals such as **fluconazole** (Diflucan), itraconazole (Sporanox), and **ketoconazole** (Nizoral)
- cimetidine (Tagamet)
- **clarithromycin** (Biaxin, in Prevpac)
- fluoroquinolones including **ciprofloxacin** (Cipro, Proquin XR), gemifloxacin (Factive), **levofloxacin** (Levaquin), **moxifloxacin** (Avelox), norfloxacin (Noroxin), ofloxacin (Floxin), others
- HIV protease inhibitors including indinavir (Crixivan), nelfinavir (Viracept), and ritonavir (Norvir, in Kaletra)
- medications for anxiety, pain, or seizures
- nefazodone
- **rifampin** (Rifadin, in Rifamate, in Rifater, Rimactane)
- sedatives
- other sleeping pills

- ticlopidine (Ticlid)
- tranquilizers

Other drug interactions are possible.

Food and other substances

Ramelteon should not be taken with or shortly after a meal, especially a high-fat meal. Alcohol should not be consumed while taking ramelteon, since it can worsen side effects. Patients should talk to their doctor about eating grapefruit or drinking grapefruit juice while taking ramelteon.

Resources

BOOKS

- Julien, Robert M., Claire D. Advokat, and Joseph E. Comaty. *Primer of Drug Action: A Comprehensive Guide to the Actions, Uses, and Side Effects of Psychoactive Drugs*. 13th ed. New York: Worth, 2014.
- Kuhn, Cynthia, et al. *Buzzed: The Straight Facts about the Most Used and Abused Drugs from Alcohol to Ecstasy*. 4th ed. New York: W. W. Norton, 2014.
- Stahl, Stephen M. *Stahl's Essential Psychopharmacology: Prescriber's Guide*. 5th ed. New York: Cambridge University, 2014.

PERIODICALS

- Adams, Katie S., and Ericka L. Breden Crouse. "Melatonin Agonists in the Management of Sleep Disorders: A Focus on Ramelteon and Tasimelteon." *Mental Health Clinician* 4, no. 2 (March 2014): 48.
- "FDA-Approved Drugs to Treat Sleep Disorders." *Journal of Psychosocial Nursing & Mental Health Services* 52, no. 10 (2014): 11–12.
- Hatta, K., et al. "Preventive Effects of Ramelteon on Delirium: A Randomized Placebo-Controlled Trial." *Journal of the American Medical Association Psychiatry* 71, no. 4 (2014): 397–403.
- Jaoko, Japheth. "Insomnia Treatment." *Journal of Sociological Research* 5, no. 1 (2014): 47–52.
- Laudon, Moshe, and Anat Frydman-Marom. "Therapeutic Effects of Melatonin Receptor Agonists on Sleep and Comorbid Disorders." *International Journal of Molecular Sciences* 15, no. 9 (2014): 15924–50.

OTHER

- Takeda Pharmaceuticals America, Inc. "Medication Guide Rozerem (Ramelteon)." U.S. Food and Drug Administration. <http://www.fda.gov/downloads/drugs/drugsafety/ucm143463.pdf> (accessed February 21, 2015).

WEBSITES

- Bonnet, Michael H., and Donna L. Arand. "Patient Information: Insomnia Treatments (Beyond the Basics)." UpToDate.com. <http://www.uptodate.com/contents/insomnia-treatments-beyond-the-basics?view=print> (accessed February 21, 2015).

- Cassels, Caroline. "Melatonin Agonist Cuts Delirium Risk." Medscape. <http://www.medscape.com/viewarticle/820795> (accessed February 21, 2015).
- MedlinePlus. "Medicines for Sleep." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/ency/patientinstructions/000758.htm> (accessed February 21, 2015).
- Medscape Reference. "Ramelteon (Rx)—Rozerem." <http://reference.medscape.com/drug/rozerem-ramelteon-342928> (accessed February 21, 2015).
- Reuters. "Clinical Benefits of Ramelteon for Insomnia Small, Hints New Meta-Analysis." Medscape. <http://www.medscape.com/viewarticle/821259> (accessed February 21, 2015).

ORGANIZATIONS

- National Sleep Foundation, 1010 N. Glebe Road, Suite 310, Arlington, VA 20221, (703) 243-1697, nsf@sleepfoundation.org, <http://sleepfoundation.org/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY KEVIN GLAZA, RPh

Ramipril

Definition

Ramipril is a medication used for the management of high blood pressure, for patients experiencing heart failure after a heart attack, and to reduce the risk or likelihood of a cardiovascular event such as a heart attack or stroke.

Purpose

Ramipril is an ACE inhibitor. The term ACE stands for angiotensin-converting enzyme. An ACE inhibitor blocks the conversion of angiotensin I to angiotensin II by inhibiting the angiotensin-converting enzyme, which prevents tightening (constriction) of blood vessels. When the blood vessels are not constricted, the heart can pump blood more freely and effectively throughout blood vessels.

Ramipril may also be given to people with a history of peripheral vascular disease, diabetes, or coronary artery disease (CAD), or if they have had a stroke. Individuals with these conditions who also have high blood pressure or high cholesterol may benefit from this drug to reduce their likelihood of experiencing a cardiovascular event such as a heart attack or stroke.



Altace (ramipril), 5 mg. (© Cengage Learning®.)

For patients experiencing heart failure following a heart attack, ramipril may help decrease worsening heart failure and the risk of death associated with this condition.

Since ACE inhibitors are used to control and prevent conditions of the heart, they are usually prescribed for the long term.

Description

Ramipril is available as a tablet or capsule and is to be taken by mouth (orally). It may be used alone or in combination with other medications for the management of high blood pressure (hypertension) and congestive heart failure (CHF) and to reduce the risk of a fatal or nonfatal cardiovascular event such as a heart attack or stroke.

Ramipril may be used alone or in conjunction with other medication such as diuretics, antiplatelet drugs, or cholesterol-lowering drugs.

Some other common ACE inhibitors include:

- **captopril** (Capoten)
- **enalapril** (Vasotec)
- **lisinopril** (Zestril, Prinvil)
- **benazepril** (Lotensin)
- **quinapril** (Accupril)

KEY TERMS

Angiotensin-converting enzyme (ACE) inhibitor—A drug that lowers blood pressure by interfering with the breakdown of a protein-like substance involved in blood pressure regulation.

Carotid artery—Major artery leading to the brain, blockages of which can cause temporary or permanent strokes.

Carotid artery disease—A condition in which the arteries in the neck that supply blood to the brain become clogged, causing the danger of a stroke.

Congestive heart failure—Also called heart failure; a condition in which a damaged or overworked heart cannot pump enough blood to meet the oxygen and nutrient needs of the body. People with heart failure may find it hard to exercise due to the insufficient blood flow, but many people live a long time with this condition.

Coronary artery disease—Also called atherosclerosis; a build-up of fatty matter and debris in the coronary artery wall that causes narrowing of the artery.

Diuretic—A drug designed to encourage excretion of urine in people who accumulate excess fluid such as individuals with high blood pressure or heart conditions.

Heart attack—Also called myocardial infarction; myocardial means heart muscle and infarction means death of tissue from lack of oxygen.

Peripheral vascular disease—Narrowing or occlusion of arteries usually due to atherosclerosis.

U.S. brand names

Ramipril is sold under the brand name Altace. It is offered by prescription only.

Recommended dosage

The initial dose of ramipril for adults for the treatment of hypertension is 2.5 milligrams (mg) taken once a day. Later, a maintenance dose of 2.5–20 mg may be prescribed. Patients who are on diuretics may be prescribed a lower initial or lower maintenance dose by their physician, or the diuretic may be discontinued.

The dose of ramipril may vary for patients taking it for the treatment of heart failure. In this case, the initial dose may be 2.5 mg to be taken two times per day (for a

total of 5 mg), and a maintenance dose of 5 mg to be taken twice a day (to total 10 mg daily).

The dosing regimen of ramipril when taken to reduce the risk of heart attack or stroke is a bit different than when it is taken for hypertension or heart failure. The initial dose usually begins at 2.5 mg once a day for three weeks, then the dose is slowly increased to a total of 10 mg daily taken in either a single or divided dose.

Dose adjustments may need to be made for patients who have poor kidney function (renal failure), for patients who have chronic heart failure, or for patients taking diuretics. For these patients, an overall lower daily dose (2.5–5 mg) is usually prescribed.

Whether taken for hypertension, heart failure, or for reducing the risk of heart attack or stroke, patients taking ramipril will be monitored closely to ensure the drug is well tolerated; if so, they may progress to a higher maintenance dosage.

Geriatric

Dosing should be done conservatively in seniors. As the body ages, it becomes less efficient at eliminating drugs, which can lead to increased risk of side effects and an increased risk of overdose. Seniors should be monitored closely and given the lowest effective dosage.

Precautions

This medication affects blood pressure, so it is advised that patients who are taking it move from lying to standing positions slowly to avoid becoming dizzy or falling.

Ramipril may cause a change in kidney function, increasing serum creatinine and blood urea nitrogen levels, so special caution should be taken for use in patients who have poor liver or kidney (renal) function, especially patients with diabetes.

Ramipril should be taken whole, and not crushed, broken, or chewed. Breaking down the pill can result in an inconsistent or unpredictable amount of the medication entering the bloodstream at one time.

All patients taking ramipril should be monitored closely, and the dosage should be re-evaluated regularly.

Pediatric

Ramipril is not used for treatment in children.

Geriatric

Seniors are at an increased risk of side effects from ramipril and should be monitored closely. Seniors may take a number of other medications that may interact

poorly with ramipril, so the use of all medications and supplements should be discussed with their doctor.

Pregnant or breastfeeding

Ramipril is considered a class D pregnancy drug, which means that evidence of serious risks to a fetus exist. Ramipril should not be taken by anyone who is pregnant or plans to become pregnant. This drug may pass into breast milk, so it should not be taken if a mother is breastfeeding her baby.

Side effects

In some cases allergic reactions to ramipril have occurred. Any patient who experiences symptoms of an allergic reaction, including swelling of the lips, throat, mouth or face; difficulty breathing; hives; or rash, should seek emergency medical attention immediately.

High potassium may occur while taking ramipril. Symptoms of high potassium include weakness, a slow or weak pulse, and tingling in limbs. Patients should seek medical treatment if these side effects occur.

Patients should seek emergency medical assistance if any of the following symptoms occur:

- feeling like you may faint or pass out
- swelling of the face, lips, or tongue (angioedema)
- difficulty swallowing
- confusion
- abdominal pain
- signs of dehydration such as little or no urine output
- sudden weakness

Common but less serious side effects include:

- cough
- headache
- dizziness
- fatigue

Interactions

Many medications may cause serious interactions with ramipril. Individuals should tell their doctor and pharmacist about all prescription medications, over-the-counter medications, vitamins, herbs, and supplements that they are taking. It may be necessary to stop taking some medications or switch to different medications to reduce the chance of interactions with ramipril.

Drugs

Ramipril should not be used by individuals with diabetes who are taking aliskiren (Tekturna).

Ramipril should be used with caution in patients who are taking lithium, as lithium toxicity has been reported when these drugs are used concomitantly.

Food and other substances

Patients taking ramipril should not consume alcohol. Alcohol may increase or mimic potential side effects of ramipril such as dizziness or light-headedness.

Resources

BOOKS

Mann, Douglas, et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 10th ed. Philadelphia: Saunders, 2014.

PERIODICALS

Granger, C. B., et al. "Another Biomarker for Risk Assessment in Acute Myocardial Infarction?" *Journal of the American College of Cardiology* 64 (October 2014): 1708–10.

Kaufman, Michele B. "ACE Inhibitor-Related Angioedema: Are Your Patients at Risk?" *Pharmacy and Therapeutics* 38, no. 3 (2013): 170–72.

WEBSITES

Mayo Clinic staff. "Heart Failure." MayoClinic.org. <http://www.mayoclinic.com/health/heartfailure/DS00061> (accessed March 11, 2015).

U.S. National Library of Medicine. "Altace—Ramipril Capsule." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0fc34cd8-86e6-4034-73bd-4263a68ba046> (accessed January 26, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.

Heart Foundation, 80 William Street, Level 3, East Sydney NSW, 2011, Australia, +61 02 9219 2444, 300 36 27 87, <http://www.heartfoundation.org.au/>.

National Heart, Lung, and Blood Institute (NHLBI), PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbinfo@nhlbi.org, <http://www.nhlbi.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Laura Jean Cataldo, RN, EdD

REVIEWED BY GREGORY A. PRATT, RPH

Ranibizumab

Definition

Ranibizumab is an eye medication that inhibits the biologic activity of human vascular endothelial growth



Lucentis (ranibizumab), 10 mg/mL. (STOCKFOLIO®/Alamy)

factor A (VEGF-A). Used as a VEGF-A antagonist, this drug is designed for eye (intraocular) use only. It is used for the management of an eye condition known as “wet” age-related macular degeneration.

Purpose

Wet age-related macular degeneration occurs when blood vessels grow beneath the retina and cause a leakage of blood and fluid under the retinal membrane. Ranibizumab works to keep the formation of new blood vessels under the retina from occurring.

Patients with wet age-related macular degeneration, patients with diabetes and macular edema (swelling), and patients experiencing macular edema after retinal surgery may benefit from use of this drug.

Ranibizumab has also been recently approved by the U.S. Food and Drug Administration (FDA) to treat diabetic retinopathy in patients with diabetic macular edema.

Description

Ranibizumab is available as an ophthalmic injection. When used as directed, this drug may benefit the patient by maintaining or increasing visual acuity.

Some other medications for the treatment of wet age-related macular degeneration include:

- bevacizumab (Avastin)
- pegaptanib (Macugen)
- aflibercept (Eylea)

U.S. brand names

Ranibizumab is sold under the brand name Lucentis and is offered by prescription only.

Recommended dosage

Ranibizumab is administered as an ophthalmic injection. It is administered once a month, approximately every 28 days, only into the affected eye(s). The schedule may be modified to administration every three months after receiving the first four injections. Prior to injection, a numbing medication will be administered.

Dosing is 0.5 milligrams (mg) per eye for the treatment of wet age-related macular degeneration or swelling after retinal surgery. The dose is usually lowered to 0.3 mg (per eye) for diabetic patients with macular edema.

Geriatric

Many patients using ranibizumab are between 65 to 75 years of age. No notable differences in drug efficacy have been noted in this population.

Precautions

The following are some hazards associated with the use of ranibizumab. Patients should be monitored for the following serious events:

- retinal detachment
- endophthalmitis
- increased intraocular pressure
- stroke, heart attack, or death due to formation of blood clots

Ranibizumab may increase the risk of clot formation leading to stroke or possible death. It may also raise pressure within the eye (intraocular pressure).

Patients may experience blurred vision after administration of ranibizumab, so care should be taken to avoid driving or doing tasks requiring clear vision until the blurred vision subsides.

Patients receiving ranibizumab will need to be monitored closely to ensure there are no adverse effects of the drug, so it is important to continue eye exams on a regular, ongoing basis.

Pediatric

The safety and effectiveness of ranibizumab for use in the pediatric population have not been established.

Geriatric

Seniors should inform their healthcare provider if they have any other diseases or conditions, especially heart or vascular disease.

Pregnant or breastfeeding

Ranibizumab is considered a class C pregnancy drug, which means that there is not definitive evidence about whether the drug causes adverse effects in a fetus. Patients should tell their doctor if they are pregnant or plan to become pregnant.

It is not known whether or not this drug passes into breast milk. Women should tell their doctor if they are breastfeeding their baby.

Other conditions and allergies

Due to the risks of ranibizumab, patients with glaucoma or who have ever had a blood clot or stroke should use ranibizumab only after a discussion with their doctor.

Side effects

In some cases, allergic reactions to ranibizumab have occurred. Any patient who experiences symptoms of an allergic reaction, including swelling of the lips, throat, mouth or face; difficulty breathing; hives; or rash, should seek emergency medical attention immediately.

Patients should seek emergency medical assistance if any of the following symptoms occur:

- eye irritation or pain
- a sudden change in vision
- swelling around the eye
- bleeding or drainage from the eye
- seeing “floaters” or flashes of light in the visual field
- acute sensitivity to light
- speech difficulty
- sudden confusion or headache
- painful urination

Common but less serious side effects include:

- blurred vision

KEY TERMS

Diabetic retinopathy—A condition in which the tiny blood vessels to the retina, the tissues that sense light at the back of the eye, are damaged, leading to blurred vision, sudden blindness, or black spots, lines, or flashing lights in the field of vision.

Endophthalmitis—Inflammation inside the eye usually caused by an infection; associated with injections, surgery, or trauma to the eye.

Glaucoma—A group of disorders that cause pressure to build in the eye, which may result in vision loss.

Macular degeneration—A condition usually associated with age in which the area of the retina called the macula is impaired due to hardening of the arteries (arteriosclerosis). This condition interferes with vision.

Retina—The tissue that forms the inner surface of the back of the eyeballs; it receives the light that enters the eye and transmits it through the optic nerves to the brain to produce visual images.

Visual acuity—Pertaining to the sharpness or clearness of vision; usually assessed as part of an eye examination.

- dry eyes
- watery eyes

Interactions

Individuals should discuss the risks of potential drug interactions with their healthcare provider.

Drugs

Verteporfin (Visudyne) is often used during laser light therapy to enhance the eye’s sensitivity to light. Use of ranibizumab in conjunction with verteporfin has been known to cause inflammation to the eye.

Resources

BOOKS

Duker, Jay, S., et al. *Age-Related Macular Degeneration: Current Management*. Thorofare, NJ: SLACK, 2015.

Resources

PERIODICALS

Bakri, Sophie J., et al. “Pressure in Eyes Receiving Monthly Ranibizumab in 2 Pivotal Age-Related Macular Degeneration Clinical Trials.” *Ophthalmology* 121, no. 5 (2014): 1102–8.

Gibson, Jonathan Mark, et al. "A Safety Evaluation of Ranibizumab in the Treatment of Age-Related Macular Degeneration." *Expert Opinion on Drug Safety* 13, no. 9 (2014): 1259–70.

Resources

WEBSITES

U.S. National Library of Medicine. "Lucentis—Ranibizumab Injection, Solution." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=de4e66cc-ca05-4dc9-8262-e00e9b41c36d> (accessed January 26, 2015).

ORGANIZATIONS

Lighthouse International, 111 East 59th Street, New York, NY 10022, (800) 284-4422, info@lighthouse.org, <http://www.lighthouse.org/>.

National Eye Institute, 31 Center Drive MSC 2510, Bethesda, MD 20892-2510, (301) 496-5248, 2020@nei.nih.gov, <http://www.nei.nih.gov/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (800) INFO-FDA (463-6332), <http://www.fda.gov/>.

Laura Jean Cataldo, RN, EdD

REVIEWED BY GREGORY A. PRATT, RPh

Ranitidine

Definition

Ranitidine is a medication that is available in over-the-counter and prescription formulas to help relieve the heartburn and other symptoms associated with gastroesophageal reflux disease (GERD) and to treat ulcers. Ranitidine is in a class of drugs called histamine 2 blockers, or histamine 2 receptor antagonists, which decrease how much acid is produced in the stomach.

Purpose

People who have GERD have symptoms such as pain near the breast bone that burns, especially when they lie down or bend over. The burning is caused by acid created in the stomach to break down food. In GERD, some of the acid backs up into the esophagus, which is called reflux. The constant reflux of acid can eventually damage the thin lining of the esophagus and cause ulcers, or sores, in the lining. Ranitidine is used to treat heartburn, other GERD symptoms, and ulcers in the stomach and intestine.

Description

Ranitidine comes in several strengths and formulas, depending on the severity of symptoms, its intended use,



Ranitidine, 300 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

and the age of the person who uses the medication. Lower strength tablets usually are taken before meals to prevent heartburn or to treat mild GERD symptoms. Higher strength tablets help relieve heartburn that already is occurring. Ranitidine also comes in liquid formulas for young children. Another form of the medicine may be prescribed by doctors for intravenous, or injected, use in patients who cannot take medication by mouth.

U.S. brand names

Ranitidine is sold in the United States under the following brand names:

- Acid Reducer Maximum Strength
- Acid Reducer
- Ranitidine Acid Reducer
- Zantac
- Zantac 150 Maximum Strength
- Zantac 75
- Zantac in NaCl

Recommended dosage

Dosage for ranitidine varies, depending on the reason for its use and the size of the patient. Because it is sold over the counter, it is important that anyone using it follow the advice of a pharmacist, a doctor, and package inserts to ensure the drug is used as recommended.

To prevent heartburn, adults generally take a 75 mg tablet 30 to 60 minutes before eating food or drinking

beverages that typically cause heartburn. No more than two tablets, or 150 mg of ranitidine, should be taken in a 24-hour period when treating heartburn, and the medicine should not be taken for more than 14 days straight. To relieve symptoms of GERD, doctors usually recommend taking 150 mg twice a day. Treatment of a gastric, or stomach, ulcer with no symptoms involves taking 150 mg of ranitidine twice a day, with one of the doses at bedtime.

Doctors recommend a dose of 150 mg of ranitidine twice a day for an ulcer in the duodenum, the first section of the small intestine. Some patients take the full dose (300 mg) once a day after their nighttime meal or at bedtime. For more serious conditions, some patients need infusions of ranitidine, typically beginning with 1 mg per kilogram (kg, or 2.2 lb.) of body weight per hour, and increasing in increments of 0.5 mg per kg of patient body weight if necessary to relieve patient symptoms.

The dosage for children is based on the child's weight. For example, dosage for an ulcer in the duodenum is 4 to 8 mg per kg of the child's weight every 12 hours for a maximum of 300 mg per day. Doctors reduce the dose for maintenance of the ulcer. If a child receives the drug intravenously, the dose is 2 to 4 mg per kg of weight per day, split into doses every six to eight hours for a maximum of 200 mg per day.

To treat GERD in children one month old to 16 years old, doctors typically recommend 4 to 10 mg of ranitidine per kg of the child's weight each day, divided into two doses that are taken 12 hours apart. Children should take no more than 300 mg per day. If given the medication intravenously, children one month to 16 years old should receive 2 to 4 mg per kg of weight per day, divided into doses delivered every six to eight hours. Newborns can receive a liquid by mouth of 2 mg per kg of weight per day, divided into two doses delivered 12 hours apart, or intravenous (IV) ranitidine at an initial dose of 1.5 mg per kg of body weight, followed by 1.5 to 2 mg per kg of weight per day divided into doses 12 hours apart. Doctors also may choose to deliver the drug continuously through an IV at a very low amount.

Precautions

Some people are allergic to ranitidine, and it is important to tell the doctor about any known drug allergies, especially to histamine 2 blockers. People who have kidney disease or impaired kidney function should use special caution when taking this medication.

Pediatric

Gastroesophageal reflux is common in healthy infants and some older children, and it is important for doctors to distinguish normal episodes of reflux from the symptoms and

KEY TERMS

Gastroesophageal reflux disease—Abbreviated GERD, it is the passage of stomach acid back into the esophagus through the small muscle that normally allows food to travel down from the esophagus into the stomach. GERD can cause heartburn and lead to ulcers in the esophagus.

Intravenous—Within a vein, usually referring to how a drug is placed, or administered, through a needle or catheter into a vein and therefore into the blood system.

Ulcer—A sore or break in the skin or lining of an organ.

complications that make up GERD and require treatment. Some of the symptoms in infants that indicate GERD are refusing to eat, vomiting often, failing to gain weight or sleep well, and being irritable. In older children and teens, heartburn, frequent vomiting, asthma, bouts of pneumonia, and an ongoing cough or hoarse voice may be signs of GERD. It is important to thoroughly diagnose children so that they do not take ranitidine unless it is necessary to control GERD or prevent complications such as ulcers.

The safety and effectiveness of ranitidine in newborns have not been established. Studies have shown that care should be taken when prescribing ranitidine to newborns, especially to premature infants. The medication reduces stomach acid production, and can result in serious infections in the stomach because of these effects.

Geriatric

Ranitidine is generally as safe and effective in older adults as in the general adult population, but some older individuals may be more sensitive to the drug's effects. In particular, kidney function begins to decline somewhat with age, and may increase risk of serious side effects in some elderly patients who use ranitidine.

Pregnant or breastfeeding

Ranitidine is a pregnancy category B drug, and no well-controlled studies have been conducted in pregnant women. The medication should be used during pregnancy only if clearly needed. The drug has been found in breast milk, and women who choose to breastfeed should discuss use of ranitidine with their doctors.

Other conditions and allergies

Anyone with kidney or liver disease should inform their doctors about these conditions before taking ranitidine.

PATIENT PROFILE

A 58-year-old man who was overweight and had been diagnosed as prediabetic was also troubled by heartburn or acid indigestion. He complained of pain in his abdomen, which was sometimes a tight, constricting pain across the upper abdomen or chest and sometimes painful cramping in the lower abdomen, often preceding diarrhea. He had tried certain over-the-counter medications such as Tums or Pepto-Bismol, which provided temporary relief, but he sought his doctor's help to find a better way to improve his digestion and make him more comfortable. After a physical examination and laboratory tests, the doctor confirmed the prediabetes status and recommended implementing some dietary and lifestyle changes as well as medication for digestive issues.

The doctor prescribed ranitidine (Zantac), a histamine blocker that works by stopping the action of histamine at receptor sites on acid-secreting cells of the stomach. This action effectively slows down gastric acid secretion and reduces heartburn and abdominal pain in patients who produce excess stomach acid. The recommended starting dose was 150 mg taken twice a day, in the morning and at bedtime, and the doctor suggested following this regimen for four weeks and then reevaluating. Therapy could be extended to a total of eight weeks if sufficient progress had not been made in relieving gastrointestinal symptoms. The doctor also recommended consuming a low-fat, low-carbohydrate diet and limiting serving portions of all foods except fresh vegetables. Since the patient had also reported drinking "several beers" nightly after work, he was advised to reduce alcohol consumption to only one drink per night

to reduce calories and improve digestion. In addition, the doctor recommended engaging in regular exercise, especially brisk walking, which would help improve digestion, intestinal function, and weight control.

After two weeks of treatment, the patient reported that the severity of his heartburn was relieved both day and night but, though his diarrhea had been relieved, he was now constipated. He also reported waking up every day with a headache. The doctor advised that constipation and headache were likely temporary side effects and that he should try to complete the four-week treatment at the prescribed dosage. At his four-week follow-up visit, he reported complete relief of his heartburn and that he was no longer troubled by either diarrhea or constipation, but that his morning headaches were becoming more painful. He questioned whether or not he should stop the treatment. However, since both patient and doctor agreed that the ranitidine therapy had effectively relieved his digestive symptoms within the four-week treatment period, they hesitated to discontinue it. The doctor advised eliminating the second dose taken at bedtime and continuing with only the morning dose of 150 mg. This would cut the daily dosage in half. He was also advised to stay up at least two hours after his evening meal to allow complete digestion, and to sleep with two pillows to raise his upper body while sleeping. He was reminded as well to keep his serving portions of food small and to continue with regular exercise. The revised dosage schedule of ranitidine eliminated the morning headaches and, together with lifestyle measures, worked well to improve the patient's digestive health and help control weight.

Side effects

Side effects of ranitidine may include:

- stomach pain
- headache
- diarrhea or constipation
- nausea and vomiting

Interactions

It is important to tell the doctor about any medications, herbal preparations, or vitamin supplements taken before using ranitidine.

Drugs

When drugs interact with one another, it can affect how well one drug or another works, or increase side effects of a drug. Ranitidine can cause moderate or minor reactions with many drugs and more severe ones with a

drug used to treat human immunodeficiency virus and AIDS called atazanavir (Reyataz).

Resources

PERIODICALS

Lightdale, Jenifer R., and David A. Gremse. "Gastroesophageal Reflux: Management Guidance for the Pediatrician." *Pediatrics* vol. 131 (2013): e1684–95.

Terrin, Gianluca, et al. "Ranitidine Is Associated with Infections, Necrotizing Enterocolitis, and Fatal Outcome in Newborns." *Pediatrics* 129, no. 1 (2012): e40–5.

WEBSITES

Boehringer Ingelheim Pharmaceuticals. "Zantac." Zantacotc.com. <https://www.zantacotc.com/heartburn-relief.html> (accessed February 21, 2015).

Lexi-comp. "Ranitidine." Merckmanuals.com. <http://www.merckmanuals.com/professional/lexicomp/ranitidine.html> (accessed February 21, 2015).

MedlinePlus. "Ranitidine." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601106.html> (accessed February 21, 2015).

"Ranitidine." Drugs.com. <http://www.drugs.com/ranitidine.html> (accessed February 21, 2015).

"Zantac." Rxlist.com. <http://www.rxlist.com/zantac-drug.htm> (accessed February 21, 2015).

ORGANIZATIONS

American Gastroenterological Association, 4930 Del Ray Avenue, Bethesda, MD 20814, (301) 654-2055, Fax: (301) 654-5920, <http://www.gastro.org/>.

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, 1501 Bethlehem Pike, Flourtown, PA 19031, (215) 233-0808, naspghan@naspghan.org, <http://www.gikids.org/>.

Teresa G. Odle, BA, ELS

REVIEWED BY GREGORY A. PRATT, RPH

Razadyne see **Galantamine**

Rebif see **Interferon beta 1a**

Reclast see **Zoledronic acid**

Reglan see **Metoclopramide**

Relafen see **Nabumetone**

Remeron see **Mirtazapine**

Remicade see **Infliximab**

Requip see **Ropinirole**

Restoril see **Temazepam**

Retin-A see **Tretinoin (topical)**

Revatio see **Sildenafil**

Rhinocort see **Budesonide**

Rifadin see **Rifampin**

Rifampin

Definition

Rifampin is an antibiotic drug in a class of medications called antimycobacterials.

Purpose

Rifampin is frequently used in combination with two or three other drugs to treat tuberculosis (TB). Rifampin is also used to eliminate the bacteria *Neisseria meningitidis*, which is a cause of meningitis. Rifampin cannot be used to treat meningitis, but if people are carrying the



Rifampin, 300 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

bacteria in their nose or throat, rifampin can be used to eradicate it so that others are not infected.

Off-label use

Rifampin may be used off label to treat methicillin-resistant *Staphylococcus aureus* (MRSA) related abscesses (infected collections of pus) in the brain, covering of the brain and spinal cord, and lung cavity. It may also be used to treat severe itching from liver disease; bone infections; infections involving artificial joints, plates, screws, or other devices used to hold together bones or joints; and leprosy, and to prevent meningitis after exposure to a carrier.

Description

Rifampin is available in capsule and injectable forms. The capsules are maroon and scarlet in 150 or 300 milligram (mg) strengths, each printed with the dosage and the product name "RIFADIN." The contents of the capsules can be mixed into a liquid suspension to be taken by individuals (including children) who are unable to swallow capsules.

The solution for intravenous (IV) injection is dispensed in glass vials containing 600 mg of active drug.

U.S. brand names

Rifampin is sold under the brand names Rifadin and Rimactane. It is also manufactured as a generic by many different companies.

KEY TERMS

Anaphylaxis—A severe, systemic allergic reaction that can be potentially life-threatening.

Meningococcal—Disease (usually meningitis) caused by the bacteria *Neisseria meningitidis*.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Pregnancy category—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk, but no human studies; or adverse effects in animals, but not in well-controlled human studies. Category C: No adequate human or animal studies; or adverse fetal effects in animal studies, but no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk. Risks outweigh any benefits.

Resistance—A characteristic that can be developed by some organisms and allows them to escape the effects of certain antibiotics.

Secondary infection—An infection by a microbe that occurs because the body is weakened by a primary infection caused by a different kind of microbe; also called an opportunistic infection.

Tuberculosis—A severe, contagious bacterial infection of the lungs. Untreated, tuberculosis can also affect other organs of the body. The causative bacteria has grown resistant to many antibiotics, so a cocktail of two or three antibiotics over six months to two years is required to eradicate the infection.

Rifampin is often sold in a single tablet that combines both rifampin and isoniazid (another core drug for treating tuberculosis). This formulation is sold under the name Rifampicin or Rifamate. When combined with isoniazid and pyrazinamide, it is sold under the name Rifater.

Canadian brand names

Rifampin is sold as Rifadin and Rofact in Canada.

International brand names

In most countries overseas, rifampin is sold combined with isoniazid, or as a three-drug combination that includes rifampin, isoniazid, and pyrazinamide (Rifater) for treatment for tuberculosis. In these forms, it is on the World Health Organization's list of essential medications.

Recommended dosage

For TB, the dose is 10 mg per kilogram (kg) of body weight, administered once daily (orally or IV). The maximum dose is 600 mg per day. Rifampin alone is not sufficient to treat TB and is given with two to three other drugs over the course of six months to two years.

For meningococcal carriers, the dose is 600 mg taken twice a day for two days.

Other dosing formats may be followed for specific infections or circumstances.

Pediatric

For TB, the dose is 10–20 mg/kg/day (orally or IV). The maximum dose is 600 mg per day. Rifampin is given with two to three other drugs over the course of six months to two years.

For meningococcal carriers over one month of age, the dose is 10 mg/kg (maximum dose of 600 mg), twice a day for two days. For meningococcal carriers under one month of age, the dose is 5 mg/kg, taken twice a day for two days. Other dosing formats may be followed for specific infections or circumstances.

Precautions

The following precautions apply to all individuals:

- This drug should be taken for the entire length of the prescription. Failure to take a complete course of the medication can result in return of symptoms.
- Rifampin must be taken consistently; failure to do so (missing doses, stopping and starting the medication) results in a high risk of resistant infection, as well as the possibility of kidney damage.
- Rifampin should be taken either one hour prior or two hours after eating.
- Rifampin should be taken with a full glass of water.
- Rifampin can cause bodily fluids to turn a reddish-brown, including sweat, saliva, and tears.
- Contact lenses may be permanently stained by rifampin.
- Use over a long period of time can increase the risk of developing another fungal or bacterial infection (secondary infection).

Pregnant or breastfeeding

Rifampin is a pregnancy category C drug, meaning that research has suggested the possible risk of injury to a developing fetus, as well as bleeding during and after delivery. Women who are pregnant or breastfeeding should tell their doctor before taking rifampin. This drug can pass into breast milk. Use of the drug in pregnancy and breastfeeding will depend on a careful determination of the risks versus the benefits.

Other conditions and allergies

Individuals who are allergic to rifampin, rifabutin (Mycobutin), or rifapentine (Priftin) should not take the drug.

Individuals with a history of liver disease should tell their doctor prior to using this drug. Rifampin can cause liver damage and jaundice in susceptible individuals.

In patients with diabetes, rifampin may cause unpredictable swings in blood sugar.

Side effects

The most common adverse side effects of rifampin for all age groups include:

- upset stomach
- loose stools or diarrhea
- nausea and vomiting
- liver damage resulting in changes in liver function blood tests
- headache
- flushing
- rash
- decreased appetite
- digestive problems

These side effects should be brought to the doctor's attention if they do not go away within a few days.

A doctor should be notified immediately if any of these less common but more serious side effects occur.

- wheezing, difficulty breathing or swallowing (may indicate a severe allergic reaction and require immediate medical attention)
- severe skin rash, itching, or hives
- swelling
- yellowing of the skin
- vaginal itching or discharge (females)
- confusion, difficulty concentrating, changes in behavior
- weak muscles
- seizures
- abdominal pain with fever

- difficulty with balance and walking
- numbness, tingling, pain
- dizziness

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Rifampin interacts with a wide variety of medications, requiring the use of alternative medications or careful monitoring.

Some of the more major drugs with which rifampin has known interactions include:

- anticoagulant drugs (blood thinners)
- antifungal drugs
- barbiturates
- blood pressure medications (including beta blockers, calcium channel blockers, **enalapril**)
- antimicrobials (including antifungals, antivirals, antimalarials, **clarithromycin**, dapsone, **doxycycline**, chloramphenicol, fluoroquinolones, and sulfa drugs)
- immunosuppressant agents (including **cyclosporine**, **tacrolimus**, steroid agents)
- psychiatric medications (including **haloperidol** and tricyclic antidepressants)
- antiseizure medications; sedative and pain medications (including narcotics, **diazepam**, **methadone**)
- thyroid medications
- antiarrhythmics
- oral diabetic agents
- theophylline
- probenecid

Women taking **oral contraceptives** should ask their healthcare provider if they should use a second form of contraception while using rifampin, as this drug can interfere with the effectiveness of the birth control pill.

Antacids should not be taken for at least an hour after rifampin is administered.

Resources

BOOKS

Bloom, Allyson K., et al. *Hunter's Tropical Medicine and Emerging Infectious Disease*. Philadelphia: Saunders, 2013.

Cherry, J., et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Elsevier Saunders, 2014.

Drug Information Handbook. 23rd ed. Hudson, OH: Lexicomp Inc., 2014.

Mandell, G. L., et al. *Douglas and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. London: Churchill Livingstone, 2015.

Rang, H. P. *Rang & Dale's Pharmacology*. 7th ed. London: Churchill Livingstone, 2012.

WEBSITES

AHFS Consumer Medication Information. "Rifampin." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682403.html> (accessed March 12, 2015).

ORGANIZATIONS

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Rosalyn S. Carson-DeWitt, MD

REVIEWED BY GREGORY A. PRATT, RPh

Risedronate

Definition

Risedronate is a medication used to manage osteoporosis, a disease that weakens bones. The medication is in a class of drugs called bisphosphonates.

Purpose

The bones are living tissues that go through a growth cycle. Normally, new bone forms to replace older bone. As bone breaks down (resorption), new bone replaces it in a process called bone formation. As people age, and especially after menopause in women, the cycle of resorption and formation can become imbalanced, leading to osteoporosis and bone loss. Bisphosphonates such as risedronate are designed to help slow bone loss. People who have osteoporosis may take risedronate to prevent osteoporosis, delay its onset, or treat bone loss that has already begun and prevent fractures that are caused by weakened bones.



Risedronate actonel. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

Risedronate comes in tablet form to be taken by mouth. It may be taken daily or in delayed-release, or long-acting, form less often, usually once a week. The active ingredient in the medication is risedronate sodium. Although the medication helps to manage bone-related diseases and slow their progress or prevent problems such as fractures, it is not a cure for osteoporosis or other diseases. Most studies on bisphosphonates were first conducted in women, but later studies found that medications such as risedronate are important for controlling osteoporosis in older men.

U.S. brand names

In the United States, risedronate is sold under the brand names Actonel, Actonel with Calcium, and Atelvia.

Recommended dosage

Dosage depends on how often the tablet is taken. Postmenopausal women who have osteoporosis or want to prevent the disease generally take just one of the following options:

- 5 milligram (mg) tablet by mouth once a day
- 35 mg tablet once a week
- 75 mg tablet two days in a row, for a total of two tablets each month
- 150 mg tablet once a month

KEY TERMS

Bisphosphonates—A class of medications designed to strengthen bone by inhibiting or controlling bone removal.

Gastrointestinal—Refers to areas of the digestive system, especially the stomach and intestines.

Glucocorticoids—Medications made to closely resemble human hormones that affect mostly the body's metabolism.

Paget disease of the bone—A rare, chronic condition that causes some bones in the affected person to become soft.

Postmenopausal—The time after a woman has reached menopause, or gone a period of 12 months in a row without menstruating.

Men who need to increase bone mass, usually because of osteoporosis, should take one 35 mg tablet each week. If osteoporosis is caused by use of glucocorticoids, the recommended dose is a 5 mg tablet each day. People who have Paget disease of the bone usually take 30 mg once a day for two months and visit their doctor to see if the treatment has worked before taking risedronate again. The tablets should only be swallowed whole, never chewed or broken.

Precautions

Risedronate should be taken on an empty stomach, before having anything to eat or drink other than water and before taking any other medications or supplements. Risedronate tablets can cause upper gastrointestinal (GI) problems because the drug can irritate the thin lining of the GI tract. Doctors and pharmacists advise patients taking risedronate to avoid lying down for at least 30 minutes after taking the medicine to help prevent GI irritation.

Pediatric

Risedronate is not indicated for use in children. A study of its use in children with a rare disease called osteogenesis imperfecta that causes the bones to become fragile showed similar safety to use of the drug in adults, but many side effects such as vomiting, pain, and headache.

Geriatric

The use of risedronate in elderly patients is considered safe, but some older people may be more sensitive to the drug's effects.

Pregnant or breastfeeding

Risedronate is in pregnancy category C, meaning it only should be taken by a pregnant woman if the potential benefit outweighs any possible risk. The drug has not been tested in pregnant humans and fetuses, only in animals. Risedronate is released in breast milk and it is likely that a nursing mother should either discontinue use of the drug while nursing or choose not to nurse her infant while taking risedronate.

Other conditions and allergies

Anyone who is having radiation therapy should inform a doctor or pharmacist before taking risedronate. It is also important to talk to the doctor about the medication before having dental treatments. People who have severe kidney disease or impairment should not take risedronate.

Side effects

One of the most common side effects of risedronate is the irritation of the stomach and other parts of the GI system. The medication may cause:

- nausea
- gas or belching
- stomach pain
- diarrhea or constipation

Other symptoms of risedronate use include:

- headache
- mouth dryness
- weakness and dizziness
- frequent or painful urination

Serious side effects may be related to GI irritation or indicate a severe reaction to the drug. If a person experiences any of the side effects below after beginning to take risedronate, it is important to contact a doctor immediately:

- problems or pain when swallowing
- unusual or intense jaw pain
- new or worse heartburn
- itching, rash, or hives
- chest pain
- swelling of the facial and mouth area, or of the hands and feet
- difficulty breathing
- painful or swollen eyes or light sensitivity
- swelling of the gums and loosening of teeth

Taking risedronate or other bisphosphonates can increase risk of fracture of the thigh bone. Anyone who

feels pain in the hips, thighs, or groin area while taking risedronate should talk to a doctor. When on the medication, the thigh bone can break even without a traumatic injury.

Interactions

It is important to be aware of all other medications and their ingredients when taking risedronate. A pharmacist can help watch for possible interactions. Patients taking the drug should also inform their doctor of any herbs or supplements they are taking, including vitamins.

Drugs

Certain drugs can interact with risedronate and it is important to tell the doctor about any medications being taken before beginning the drug. One known interaction is with a drug called deferasirox, which is used to remove extra iron from people who have had blood transfusions. People who take risedronate should be aware of drug brand names to ensure that they do not take two medications with the same active ingredients.

Herbs and supplements

If a person takes vitamin D or calcium supplements, antacids, or iron supplements, these should be taken at a different time of day than risedronate. If taken at the same time, the supplements interfere with the drug's absorption and effectiveness.

Food and other substances

Eating or drinking anything before taking risedronate each morning can interfere with its usefulness. It is advised to avoid drinking mineral water or any water with supplements because these beverages might contain high concentrations of calcium. Once the tablet is taken, it is important to eat and drink plenty of foods high in calcium and vitamin D while on risedronate.

Resources

PERIODICALS

Brown, Jacques P., et al. "Bisphosphonates for Treatment of Osteoporosis." *Canadian Family Physician* 60, no. 4 (2014): 324–33.

Sim, Ie-Wen. "Treatment of Osteoporosis in Men with Bisphosphonates: Rationale and Latest Evidence." *Therapeutic Advancement in Musculoskeletal Disease* 5, no. 5 (2013): 259–67.

WEBSITES

Actavis Pharma, Inc. "Actonel." Actavis. Available from: <http://www.actonel.com/>

AHFS Consumer Medication Information. "Risedronate." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601247.html> (accessed March 12, 2015).

ORGANIZATIONS

National Osteoporosis Foundation, 1150 17th Street, Suite 850, Washington, DC 20036, (202) 223-2237, (800) 231-4422, info@nof.org, <http://nof.org/>.

NIH Osteoporosis and Related Bone Diseases National Resource Center, 2 AMS Circle, Bethesda, MD 20892-3676, (202) 223-0344, Fax: (202) 293-2356, (800) 624-2663, NIHBoneInfo@mail.nih.gov, <http://www.bones.nih.gov/>.

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Risperdal see **Risperidone**

Risperidone

Definition

Risperidone is classified as a second-generation antipsychotic drug, also known as an atypical antipsychotic drug.



Risperdal (risperidone), 3 mg. (© Cengage Learning®.)

KEY TERMS

Amenorrhea—Abnormal cessation of menstruation.

Bipolar disorder—A mood disorder marked by alternating episodes of extremely low mood (depression) and exuberant highs (mania). Also known as manic-depressive disorder.

Extrapyramidal symptoms—A group of side effects associated with antipsychotic medications and characterized by involuntary muscle movements, including contraction and tremor.

Schizophrenia—A severe mental disorder in which a person has difficulty distinguishing what is real from what is not real. It is often characterized by hallucinations, delusions, and withdrawal from people and social activities.

Tourette syndrome—An abnormal condition that causes uncontrollable facial grimaces and tics as well as arm and shoulder movements. Tourette syndrome is perhaps best known for uncontrollable vocal tics that include grunts, shouts, and use of obscene language (coprolalia).

Purpose

Risperidone is used for the management of symptoms of psychotic disorders such as schizophrenia and bipolar disorder (manic depression). It is also used to treat symptoms of irritability in children with autism and may be used in treating Tourette syndrome, an inherited nerve, motor, and vocal disorder.

Description

Risperidone is a second-generation antipsychotic drug in the chemical class of benzisoxazole. It is chemically different from the phenothiazine-based first-generation drugs. Differences in the mechanisms of the two types of drugs have led to the term “atypical” antipsychotics for newer drugs like risperidone. While the first-generation drugs primarily inhibit the actions of dopamine, a chemical in the brain that acts as a neurotransmitter, risperidone also acts against another neurotransmitter, serotonin. Maintaining the proper levels of both dopamine and serotonin are needed to establish and maintain mental well-being. Risperidone also acts against adrenergic and histamine receptors on cell surfaces.

Risperidone is metabolized in the liver and is rapidly distributed throughout the body. It is excreted primarily in urine.

One advantage of using risperidone rather than the first-generation drugs is its lower incidence of Parkinsonian-like symptoms. Patients who have shown little improvement with first-generation antipsychotic drugs may respond better to risperidone, which has been shown to improve the symptoms of schizophrenia and related quality of life.

Risperidone and other antipsychotic drugs are used for schizophrenia and other psychotic disorders with the goal of maintaining therapeutic efficacy and tolerability long-term so that treatment benefits can be maximized and side effects minimized so that patients will continue to take the drug. The effectiveness of risperidone in treating schizophrenia compared to that of first-generation antipsychotic drugs was evaluated in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Study. The investigators found that risperidone tended to be better tolerated than other atypical antipsychotics such as **quetiapine** and **ziprasidone**, and fewer patients discontinued the drug due to adverse effects. However, investigators also reported that the therapeutic effects and side effects of risperidone and other antipsychotic drugs varied considerably between individuals.

U.S. brand names

It is sold in the United States under the brand name Risperdal; the long-acting injectable form is Risperidal Consta.

Recommended dosage

Risperidone is available in 0.25, 0.5, 1, 2, 3, and 4 milligram (mg) tablets and as an oral solution containing 1 mg of the drug in each milliliter (mL) of solution. It is also available in a long-acting injectable formulation that achieves significant levels of the drug after a single injection. It is typically given as a 25 mg dose intramuscularly (injected into a muscle) every two weeks. For treating psychotic disorders in adults, the usual starting dose of risperidone is 1 mg twice daily. Dosage is increased gradually until a target range of 4 to 8 mg per day is reached. Some patients do just as well with a single daily dose (6 mg once a day, for example). There is little clinical evidence to indicate that increasing the daily dose beyond 8 mg offers additional benefit. Higher doses may contribute to additional side effects. Changes in dosage are recommended to be made only once per week.

Geriatric

In patients ages 60 and older, the starting dosage should not exceed 1 mg daily. Most patients should not take more than 3 mg daily, especially patients with low blood pressure or kidney disease.

Precautions

Risperidone has occasionally been associated with seizures. People with a past history of seizures should discuss with their doctors whether risperidone is the right antipsychotic drug for them to use.

Some patients may have trouble regulating body temperature while taking risperidone and could be at increased risk of developing malignant hyperthermia. Patients receiving this drug should be aware of this possibility and should avoid extremes in outdoor temperatures.

Patients may develop hyperglycemia (high blood sugar) while taking risperidone. People with schizophrenia are more likely to develop diabetes than those without schizophrenia, and taking risperidone increases this risk. Patients should alert their doctors immediately if they experience symptoms of diabetes including excessive thirst or hunger, frequent urination, blurry vision, or fatigue.

Risperidone has been associated with the risk of developing hyperprolactinemia, a blood disorder caused by heightened levels of the hormone prolactin. Symptoms include amenorrhea and lactation in women and breast development and erectile dysfunction in men.

Risperidone has significantly reduced the white blood cell count or specific types of white blood cells (leukopenia, neutropenia, agranulocytosis), which is associated with a reduced ability to fight infection. Patients with reduced white blood cells must be monitored while taking risperidone and, in some patients, the drug is discontinued until the white blood cell count is restored.

People taking risperidone may become sleepy and/or dizzy and should avoid operating machinery or vehicles of any kind until the drug's effects have been identified.

Geriatric

Risperidone has not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of psychosis or behavioral problems in elderly patients with dementia and may increase the risk of death in older adults with such conditions. In studies, the use of risperidone and other antipsychotic drugs significantly increased mortality in older patients with dementia compared to placebo. Most of the deaths were associated with heart failure or infections such as pneumonia. Overall, the main cause of death in patients of all ages receiving long-acting injectable risperidone is suicide.

Pregnant or breastfeeding

Women who are pregnant should not take risperidone and should alert their physicians if they become

pregnant while taking the drug. Babies born to mothers who took risperidone during pregnancy may develop extrapyramidal symptoms (EPS) and withdrawal symptoms, including agitation, trouble breathing, and difficulty feeding. Breastfeeding is not advised for women taking the drug.

Other conditions and allergies

Patients with a history of cardiovascular disease or low blood pressure should take risperidone only after discussing the risks and benefits with their physicians, and then with close physician monitoring. Risperidone may cause abnormal heart rhythms (arrhythmias) that may prove fatal.

Side effects

The most common and bothersome side effect associated with risperidone is decreased blood pressure when standing up (known as orthostatic hypotension). This can cause dizziness or fainting. A decrease in blood pressure usually occurs early in therapy while the proper dose is still being established. It is more common in older patients than in younger ones. Usually this side effect disappears entirely with time, but if it continues, the physician may decrease the dose. Meanwhile, people taking risperidone should be aware of this side effect and get up slowly if they have been sitting for an extended period of time.

The most common nervous system side effects of risperidone include insomnia, agitation, anxiety, and headache. Early in therapy, patients may experience an inability to think clearly or perform certain tasks that require mental alertness. High doses of risperidone can cause unwanted sleepiness in about 40% of patients.

Antipsychotic drugs, including risperidone, can cause side effects that are similar to the symptoms of Parkinson's disease, including muscle tremor, difficulty with voluntary movements, and poor muscle tone. They normally disappear if the drug is stopped. Drinking alcohol may increase certain side effects.

The most common gastrointestinal side effects include nausea, vomiting, constipation, and difficulty digesting food. Taking risperidone may result in weight gain.

Up to 10% of patients taking risperidone experience rhinitis (runny nose).

Interactions

Little is known about how risperidone interacts with other drugs except that drug-drug interactions may occur when certain drugs inhibit or interfere with the chemical

mechanism of risperidone, preventing it from being metabolized properly. Individuals should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs and supplements.

Drugs

Other drugs that lower blood pressure may possibly increase the incidence and severity of orthostatic hypotension when taken with risperidone.

The use of risperidone is not recommended when patients are already taking amifampridine, bepridil, cisapride, levomethadyl, mesoridazine, **metoclopramide**, pimozide, piperazine, terfenadine, or thioridazine.

Food and other substances

Using alcohol or tobacco may also cause abnormal interactions.

Resources

BOOKS

- Albers, Lawrence J., et al. *Handbook of Psychiatric Drugs*. Laguna Hills, CA: Current Clinical Strategies Publishing, 2010.
- American Society of Health-System Pharmacists. *AHFS Drug Information 2011*. Bethesda: American Society of Health-System Pharmacists, 2011.

Resources

PERIODICALS

- Foussias, G., and G. Remington. "Antipsychotics and Schizophrenia: From Efficacy and Effectiveness to Clinical Decision-Making." *Canadian Journal of Psychiatry* 55, no. 3 (2010): 117–25.
- Gentile, S. "Adverse Effects Associated with Second-Generation Antipsychotic Long-Acting Injection Treatment: A Comprehensive Systematic Review." *Pharmacotherapy* 33, no. 10 (2013): 1087–106.
- Kasper, S., et al. "Treatment of Depressive Symptoms in Patients with Schizophrenia: A Randomized, Open-Label, Parallel-Group, Flexible-Dose Subgroup Analysis of Patients Treated with Extended-Release Quetiapine Fumarate or Risperidone." *International Clinical Psychopharmacology* 30, no. 1 (2015): 14–22.
- Mirabzadeh, A., et al. "The Therapeutic Effectiveness of Risperidone on Negative Symptoms of Schizophrenia in Comparison to Haloperidol: A Randomized Clinical Trial." *Basic Clinical Neuroscience* 5, no. 3 (2014): 212–17.
- Naber, D., and M. Lambert. "The CATIE and CUtLASS Studies in Schizophrenia: Results and Implications for Clinicians." *CNS Drugs* 23, no. 8 (2009): 649–59.
- Naber, D., et al. "Subjective Well-Being in Schizophrenia: A Randomised Controlled Open-Label 12-Month Non-Inferiority Study Comparing Quetiapine XR with Risperidone

(RECOVER)." *European Neuropsychopharmacology* 23, no. 10 (2013): 1257–69.

Resources

WEBSITES

- AHFS Consumer Medication Information. "Risperidone." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a694015.html> (accessed March 12, 2015).

ORGANIZATIONS

- American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209, (703) 907-7300apa@psych.org, <http://www.psych.org/>.
- Mental Health America, 2000 N. Beauregard Street, 6th Floor, Alexandria, VA 22311, (703) 684-7722, (800) 969-6642, Fax: (703) 684-5968, <http://www1.nmha.org/>.
- National Alliance on Mental Illness (NAMI), 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.
- National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 8184, MSC 9663, Bethesda, MD 20892, (301) 443-4513, (866) 615-6464, Fax: (301) 443-4279, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Jack Raber, PharmD

Revised by L. Lee Culvert

REVIEWED BY GREGORY A. PRATT, RPH

Ritalin see **Methylphenidate**

Rituxan see **Rituximab**

Rituximab

Definition

Rituximab is a monoclonal antibody that selectively binds to CD20, a protein found on the surface of normal and malignant (cancerous) B cells. A monoclonal antibody is a sort of protein produced in a laboratory. Rituximab is used to reduce the numbers of circulating B cells, a type of immune system cell, in patients who have B-cell non-Hodgkin lymphoma (NHL).

Purpose

Rituximab is a type of biological therapy, also called immunotherapy. The monoclonal antibody is used to treat NHL, which is characterized by an overgrowth of B



Rituxan (rituximab), 100 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

cells, the cell involved in about 85% of NHL malignancies. Of all the B-cell cancers, more than 90% express a protein called CD20 on the cell surface. By binding the CD20 protein on the B cell, the antibody in rituximab targets it for removal. The developers of rituximab believe that the drug triggers two kinds of activity to attack the B cells in NHL. First, the antibody attaches to the CD20 protein receptor and programs it with a signal to die. Second, the monoclonal antibody can bring other immune cells into the circulation to help destroy the B cells.

Rituximab has been most effective against low-grade (indolent) or follicular B-cell NHL. Low-grade (slow progression) NHL often responds well to initial treatment but frequently relapses, making rituximab a welcome addition to treatment options. Additionally, rituximab has been used for a second course of treatments after relapse with some success. Since most patients with NHL are in the later stages of the disease by the time their cancer is diagnosed, rituximab treatment is primarily used in those stages of the disease.

Rituximab is also approved for use in patients with chronic lymphocytic leukemia (CLL), a slow-growing blood and bone marrow cancer. Clinical trials were being held testing the ability of this drug to work against several other types of cancers, including newly diagnosed acute lymphoblastic leukemia (ALL) and newly diagnosed mature B-cell ALL, treatment of NHL or B-cell ALL in younger patients, use of the drug for

mantle cell lymphoma, and several trials comparing the use of rituximab with other drugs and therapy approaches.

Description

Rituximab is produced in the laboratory using genetically engineered single clones of B cells. Like all antibodies, it is a Y-shaped molecule that can bind to one particular substance, the antigen for that monoclonal antibody. For rituximab that antigen is CD20, a protein found on the surface of B cells. Rituximab is a humanized antibody, meaning that the regions that bind CD20, located on the tips of the Y branches, are derived from mouse antibodies, but the rest of the antibody is human sequence. The presence of the human sequences helps to reduce the immune response by the patient against the antibody itself—a problem seen when complete mouse antibodies were used for cancer therapies. The human sequences also help to ensure that the various cell-destroying mechanisms of the human immune system are properly triggered by binding of the antibody.

Rituximab can be used alone or in combination with other chemotherapeutic drugs. Very good results have been seen when used in combination with the CHOP chemotherapy regimen, which consists of the drugs cyclophosphamide, doxorubicin, vincristine, and **prednisone**. When used in combination, dosages of the antibody given before beginning chemotherapy, alternating with the other drugs, and then after the chemotherapy have proven effective.

U.S. brand names

Rituximab is sold as Rituxan in the United States.

Origins

In 1997, Rituximab was the first unconjugated (not linked to a radioactive isotope or toxin) antibody approved for use by the U.S. Food and Drug Administration (FDA) to treat cancer. It was specifically approved for treatment of low-grade or follicular B-cell NHL. Administration of the antibody resulted in either complete or partial responses in a little less than half of those patients.

Recommended dosage

The recommended dosage for patients with low-grade or follicular NHL is 375 milligrams per square meter of body surface area (mg/m^2) infused intravenously. The infusion is given at weekly intervals for four total dosages. Acetaminophen and **diphenhydramine** hydrochloride are given 30–60 minutes before the infusion to help reduce side effects. If given as a

retreatment, the dosage is the same. Generally, a decrease in symptoms occurs at an average of 55 days after the last administration of the antibody.

Precautions

Serious (even fatal) infusion reactions, especially with the first infusion, have been known with this drug. There are a number of patient conditions that can make taking this drug more dangerous. Specifically, heart problems such as arrhythmias and high blood pressure, and the medications taken to treat those conditions, can be a problem with this treatment.

Side effects

Most side effects occur after or during the first infusion of the drug. Some common side effects include:

- dizziness
- feeling of swelling of tongue or throat
- fever and chills
- flushing of face
- headache
- itching
- nausea and vomiting
- runny nose
- shortness of breath
- skin rash
- unusual fatigue

Less common side effects include:

- black, tarry stools
- blood in urine or stools
- fever or chills with cough or hoarseness
- lower back or side pain, or painful or difficult urination
- pain at place of injection
- pinpoint red spots on skin
- red, itchy lining of eye
- swelling of feet or lower legs
- unusual bleeding or bruising
- unusual weakness

Although they are very rare, this drug does have potentially serious side effects, such as chest pain and irregular heartbeat, particularly in patients with heart conditions. It can also cause serious effects on the blood cells, such as low red blood cell count (anemia) and low white blood cell count (neutropenia). Additionally, this drug has caused low blood pressure (hypotension).

In patients with high tumor burden (a large number of circulating malignant B cells), this drug can cause a side effect called tumor lysis syndrome. Thought to be

KEY TERMS

Antibody—A protective protein made by the immune system in response to an antigen, also called an immunoglobulin.

B cell—Type of lymphocyte (white blood cell) that creates antibodies to fight infection; also referred to as a B-cell lymphocyte.

CD20—A protein found on the surface of normal and malignant B cells.

Follicular—Relating to one of the round cells in the ovary that contain an ovum.

Humanization—Fusing the constant and variable framework region of one or more human immunoglobulins with the binding region of an animal immunoglobulin, done to reduce human reaction against the fusion antibody.

Immunotherapy—Therapy that stimulates, enhances, or suppresses the body's immune response; includes products such as monoclonal antibodies, vaccines, and growth factors.

Monoclonal antibodies—Genetically engineered antibodies specific for one antigen.

Non-Hodgkin lymphoma—A cancer of the lymph system that causes the accumulation of large numbers of defective (cancerous) immune system cells.

Tumor lysis syndrome—Excess uric acid, potassium, and phosphate in the blood due to the rapid destruction of large numbers of cancer cells from radiation or chemotherapy.

due to the release of the lysed cells' contents into the bloodstream, it can cause a misbalance of urea, uric acid, phosphate, and calcium in the urine and blood. Patients at risk for this side effect must keep hydrated and can be given **allopurinol** (an antigout medication) before infusion.

Interactions

Patients should consult with their healthcare provider about the risks of interactions between rituximab and other drugs or supplements.

Drugs

Rituximab can interact with the chemotherapy drug cisplatin, resulting in kidney damage. Doctors will advise patients to stop taking blood pressure medicines on the

day of treatment because of rituximab's effect of lowering blood pressure. Likewise, because the drug can lower the number of platelets in the blood, patients should talk to doctors about any drugs or supplements they take related to blood clotting.

Resources

WEBSITES

AHFS Consumer Medication Information. "Rituximab Injection." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a607038.html> (accessed February 26, 2015).

American Cancer Society. "Rituximab." <http://www.cancer.org/treatment/treatmentsandsideeffects/guidetocancerdrugs/rituximab> (accessed February 26, 2015).

Genentech USA. "Rituxan (Rituximab)." <http://www.rituxan.com> (accessed February 26, 2015).

National Cancer Institute. "Rituximab." <http://www.cancer.gov/cancertopics/druginfo/rituximab> (accessed February 26, 2015).

ORGANIZATIONS

National Cancer Institute, 9609 Medical Center Drive, BG 9609 MSC 9760, Bethesda, MD 20892-9760, (800) 4-CANCER (422-6237), <http://www.cancer.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Teresa G. Odle

REVIEWED BY KEVIN GLAZA, RPh

Rivaroxaban

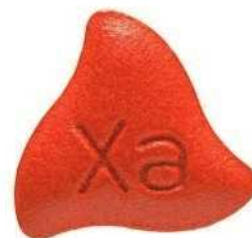
Definition

Rivaroxaban is a medication used for the prevention of thrombus formation (blood clots). This drug is classified as a factor Xa inhibitor (an anticoagulant). It blocks the activity of clotting factor Xa to prevent the formation of clots.

Purpose

Rivaroxaban works in preventing the formation of clots, thereby reducing the risk for stroke in patients with nonvalvular atrial fibrillation. It is not for use in patients who have active or uncontrolled bleeding.

This drug is also used to treat (and prevent) deep vein thrombosis (DVT) and pulmonary embolism (PE). Both of these conditions are a result of blood clot formation. Formation of a DVT may lead to a PE.



Xarelto (rivaroxaban), 20 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Rivaroxaban may also be prescribed for prevention (prophylaxis) of DVT in patients who are going to have hip or knee replacement surgery. Both operations pose a risk for clot formation, and rivaroxaban can help prevent this from occurring.

Description

Rivaroxaban is available as a tablet and is to be taken by mouth (orally).

Some other factor Xa inhibitors include:

- apixaban (Eliquis)
- edoxaban (Lixiana)
- fondaparinux (Arixtra)

U.S. brand names

Rivaroxaban is sold under the brand name Xarelto and is offered by prescription only.

Recommended dosage

Rivaroxaban comes in 10, 15, and 20 milligram (mg) tablets. Tablets may be taken one time or two times per day. The dosing regimen differs depending on the reason it is prescribed. The dose may be lowered for patients who are having an operation, and some patients may be instructed to stop taking this medication for a period of time prior to a surgical or dental procedure.

KEY TERMS

Anticoagulants—Drugs that are given to slow blood clot formation.

Atria—The two upper chambers (right and left atria) of the heart that receive blood from the body.

Atrial fibrillation—A common heart arrhythmia experienced by about 2 million Americans annually. In atrial fibrillation, the contractions of the atria are chaotic and uncoordinated. This leads to an irregular flow of blood and to the formation of blood clots that can leave the heart and travel to the brain, causing a stroke.

Deep vein thrombosis (DVT)—A blood clot (thrombus) in a deep vein that returns blood to the heart. DVT usually occurs in veins in the calf or thigh, and may be more prevalent after surgery, trauma, or prolonged periods of bed rest.

Emboli—A portion of a blood clot that migrates through the vascular system and may lodge in a major vessel of the lungs or heart, disrupting blood flow.

Embolism—Obstruction or closure of a vessel by a transported clot of foreign matter.

Pulmonary embolism—An obstruction of a blood vessel in the lungs, usually caused by a blood clot that blocks a coronary artery. Pulmonary embolism can be very serious and, in some cases, fatal.

Thromboemboli—Blood clots that develop in the circulation and lodge in capillary beds of tissues and organs.

Thrombus—A blood clot that may form in a blood vessel or in one of the cavities of the heart.

Thrombosis—The development of a blood clot inside a blood vessel.

Dosing recommendations for different purposes include:

- To reduce the risk of stroke in nonvalvular atrial fibrillation, the dose is 20 mg once a day. This medication should be taken with the evening meal.
- To treat DVT or PE, the dose is 15 mg two times a day for 21 days, then 20 mg once a day thereafter. It should be taken with food.
- To reduce the risk or recurrence of DVT or PE, the dose is 20 mg taken once a day. It should be taken with food.
- To help prevent DVT after a hip replacement, the dose is 10 mg once a day for 35 days.

- To help prevent DVT after a knee replacement, the dose is 10 mg once a day for 12 days.

This medication should be taken by mouth (orally). For individuals who are unable to swallow rivaroxaban as a whole tablet, it may be crushed and mixed with applesauce, then taken by mouth and followed with food.

Whether taken for stroke prevention, for reduction (or treatment) of DVT or PE, or following hip or knee surgery, patients taking rivaroxaban will be monitored closely for bleeding and to ensure that the drug is well tolerated.

Other conditions and allergies

Dose adjustments may be needed for patients who have poor kidney function (renal failure). For these patients, periodic blood work may be needed to assess renal function.

Precautions

Patients may experience easy bruising, and patients are also at risk for bleeding into organs, bleeding resulting in the need for transfusion, and major bleeding (hemorrhage) resulting in death. Patients should be monitored closely for bleeding occurrences and complications associated with bleeding. They should call their healthcare provider if they notice bleeding from the nose, mouth, vagina, or rectum.

Patients taking rivaroxaban should be monitored for changes in neurological status such as weakness, confusion, severe headache, slurred speech, diminished ability to move limbs, or trouble walking. These may be signs of bleeding in the brain (hemorrhagic stroke).

Patients who are taking rivaroxaban should not undergo lumbar puncture (spinal tap) or spinal anesthesia, because it may cause blood to clot around the spinal cord resulting in long-term or permanent paralysis.

Patients taking rivaroxaban should not discontinue use of the medication without first consulting with their doctor. Premature discontinuation of rivaroxaban increases the risk of thrombotic events.

Pediatric

The safety and effectiveness of rivaroxaban have not been established for children.

Geriatric

Patients in this population group should be monitored closely for concomitant medical problems and for any changes in their overall health. Special attention may be needed to ensure that education is given and properly

understood regarding dosing, daily drug regimen, and potential untoward effects of this medication.

Pregnant or breastfeeding

Rivaroxaban is considered a class C pregnancy drug, which means that there is not enough evidence to determine whether the drug causes adverse effects in a fetus. Patients should tell their doctor if they are pregnant or plan to become pregnant.

It is not known whether or not this drug passes into breast milk. Women should tell their doctor if they are breastfeeding their baby.

Other conditions and allergies

Rivaroxaban is not for use by patients who have an artificial heart valve.

Patients should not take rivaroxaban if they have a history of any of the following:

- recent lumbar puncture or spinal anesthesia
- surgery of the spine
- indwelling epidural (spinal) catheters
- genetic defects of the spine
- taking other medications prescribed to prevent or treat blood clot formation
- stomach ulcers or bleeding from the gastrointestinal tract
- prior stroke

Side effects

In some cases, allergic reactions to rivaroxaban have occurred. Any patient who experiences symptoms of an allergic reaction, including swelling of the lips, throat, mouth, or face; difficulty breathing; hives; or rash, should seek emergency medical attention immediately.

Patients should seek emergency medical assistance if any of the following symptoms occur:

- feeling like they may faint or pass out
- swelling of the face, lips, tongue, or throat
- difficulty swallowing
- difficulty breathing
- bloody or blood-tinged urine
- bloody stools

Interactions

Individuals should inform their healthcare provider of all drugs they are currently taking, including over-the-counter drugs and supplements, before starting treatment with rivaroxaban.

Drugs

Patients should not take rivaroxaban if they are taking nonsteroidal anti-inflammatory (NSAIDs) medications, as doing so may increase the risk of bleeding. Some common NSAIDs are:

- **ibuprofen** (Motrin)
- **naproxen** (Aleve)
- **celecoxib** (Celebrex)
- **aspirin** or aspirin-containing products such as Excedrin

The following medications should be used with caution if taken with rivaroxaban, as the combination may increase the risk of bleeding:

- **aspirin**
- **warfarin** (Coumadin)
- **heparin**
- **clopidogrel** (Plavix)

Resources

BOOKS

Mann, Douglas, et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 10th ed, Philadelphia: Saunders, 2014.

Resources

PERIODICALS

Colilla, S., et al. "Estimates of Current and Future Incidence and Prevalence of Atrial Fibrillation in the U.S. Adult Population." *American Journal of Cardiology* 112 (October 2013): 1142–47.

Patel, Manesh R., et al. "Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation." *New England Journal of Medicine* 365, no. 10 (2011): 883–91.

Resources

WEBSITES

American Heart Association. "Nonvalvular Atrial Fibrillation: 2014 Guidelines and Evidence-Based Practice." http://www.heart.org/HEARTORG/CPRAandECC/HealthcareProviders/Nonvalvular-Atrial-Fibrillation-2014-Guidelines-and-Evidence-Based-Practice_UCM_469963_Article.jsp (accessed March 11, 2015).

National Heart, Lung, and Blood Institute. "What Is Deep Vein Thrombosis?" <http://www.nhlbi.nih.gov/health/health-topics/topics/dvt/> (accessed March 11, 2015).

U.S. National Library of Medicine. "Xarelto—Rivaroxaban Tablet, Film Coated." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=10db92f9-2300-4a80-836b-673e1ae91610>.

ORGANIZATIONS

American College of Cardiology, Heart House, 2400 N Street NW, Washington, DC 20037, (202) 375-6000, (800) 253-

4636 x8603, Fax: (202) 375-7000, resource@acc.org,
http://www.acc.org/.

American Heart Association, 7272 Greenville Avenue, Dallas,
TX 75231, (800) 242-8721, http://www.heart.org/.

Heart Foundation, 80 William Street, Level 3, East Sydney
NSW, 2011, Australia, +61 02 9219 2444, 300 36 27 87,
http://www.heartfoundation.org.au/.

National Heart, Lung, and Blood Institute (NHLBI), PO Box
30105, Bethesda, MD 20824-0105, (301) 592-8573,
nhlbinfo@nhlbi.org, http://www.nhlbi.nih.gov/.

U.S. Food and Drug Administration, 10903 New Hampshire
Avenue, Silver Spring, MD 20993, (888) INFO-FDA
(463-6992), http://www.fda.gov/.

Laura Jean Cataldo, RN, EdD

REVIEWED BY GREGORY A. PRATT, RPh



Rivastigmine

Definition

Rivastigmine is a drug used to treat symptoms of Alzheimer's disease.

Purpose

Rivastigmine is used to treat symptoms of Alzheimer's disease in individuals with mild to moderate illness. It has also been used to treat dementia caused by other conditions such as Lewy body disease or following strokes. The drug may produce mild improvements in symptoms of thinking for a short period of time, but rivastigmine does not cure or stop the progression of the underlying diseases.

Description

In patients with Alzheimer's disease, some cells in specific regions of the brain die. Because of this cell death (apoptosis), these brain cells lose their ability to transmit nerve impulses. Brain cells normally transmit nerve impulses to one another by secreting various chemicals known as neurotransmitters.

Brain cells that make and secrete a neurotransmitter called acetylcholine are affected early in the course of Alzheimer's disease. Rivastigmine prevents the breakdown of acetylcholine in the brain, thus temporarily increasing its concentration. In doing so, rivastigmine may improve the thinking process by facilitating nerve impulse transmission within the brain.

Rivastigmine is available as capsules in four different strengths or as an oral solution for use by people who have difficulty swallowing. It is also

Rivastigmine tartrate, 4.5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

available in a transdermal patch that is applied to the skin. Unlike some other drugs used to treat Alzheimer's disease, rivastigmine is not broken down by the liver. As a result, it may be preferred in the treatment of people with Alzheimer's disease who also have liver disease.

U.S. brand names

In the United States, rivastigmine is sold as the brand name drug Exelon.

Origins

The U.S. Food and Drug Administration (FDA) approved rivastigmine in 2000.

Recommended dosage

The initial dosage of rivastigmine is 1.5 milligrams (mg) taken two times per day. If this dose is tolerated without difficulty, the dosage may be increased to 3 mg twice a day after at least two weeks at the lower dosage. Some people are unable to tolerate the side effects of nausea, vomiting, loss of appetite, and weight loss that may occur with higher dosages. If the drug does not cause significant adverse effects, the dose may be increased to 4.5 mg two times per day, followed by 6 mg two times per day. The dosage should be increased slowly at two-week intervals. If adverse effects occur and cannot be tolerated, the drug may be stopped for several doses. When the drug is started again, the same dosage or

KEY TERMS

Acetylcholine—A naturally occurring chemical in the body that transmits nerve impulses from cell to cell. Generally, it has opposite effects from dopamine and norepinephrine; it causes blood vessels to dilate, lowers blood pressure, and slows the heartbeat. Central nervous system well-being is dependent on a balance among acetylcholine, dopamine, serotonin, and norepinephrine.

Alzheimer's disease—A progressive, neurodegenerative disease characterized by loss of function and death of nerve cells in several areas of the brain, leading to loss of mental functions, including memory and learning. Alzheimer's disease is the most common cause of dementia.

Dementia—A group of symptoms (syndrome) associated with a progressive loss of memory and other intellectual functions that is serious enough to interfere with a person's ability to perform the tasks of daily life. Dementia impairs memory, alters personality, leads to deterioration in personal grooming, impairs reasoning ability, and causes disorientation.

Lewy body disease—A type of dementia that resembles Alzheimer's disease but progresses more rapidly. Common symptoms include fluctuations in confusion and recurring visual hallucinations. In this disease, abnormal brain cells are distributed throughout the brain.

Neurotransmitter—A chemical in the brain that transmits messages between neurons, or nerve cells.

the next lower dosage may be tried. The maximum daily dosage is 6 mg two times per day.

The patch is applied to dry skin on the back, upper arm, or chest. The patch is left on for 24 hours and then replaced with a new patch. Each new patch should be applied to a new area of skin; the same location should not be used until a two-week period has passed.

Precautions

Rivastigmine may slow heart rates, increase acid in the stomach, make urination difficult, cause breathing difficulties, and possibly contribute to seizures.

Individuals taking rivastigmine should be reassessed periodically to determine whether the drug is providing any benefits. If caregivers feel the drug is no longer beneficial, it may be stopped.

Other conditions and allergies

Due to its risks, rivastigmine should be used with close physician supervision and monitoring in people with certain heart conditions, tendencies to stomach ulcers, bladder obstruction, asthma or chronic obstructive pulmonary disease (COPD), and a history of seizure disorders.

Side effects

The most frequent side effects associated with rivastigmine involve stomach upset. Nausea, vomiting, anorexia, heartburn, and weakness occur in more than 5% of people. Dizziness and headaches also occur in more than 10% of people taking rivastigmine.

Other less common side effects include difficulty sleeping, confusion, depression, anxiety, sleepiness, hallucinations, tremors, fainting, aggression, constipation, gas, overwhelming fatigue, weight loss, increased sweating, and infections.

Interactions

Individuals should discuss with their healthcare provider the risk of potential interactions between rivastigmine and other drugs or supplements.

Drugs

Drugs such as dicyclomine may inhibit the effects of rivastigmine. Other drugs like bethanechol may possibly increase some of the side effects of rivastigmine. Rivastigmine may interact with some of the drugs used to relax muscles during surgery. The interaction increases the effects of both drugs.

Resources

BOOKS

Tekin, Sibel, and Roger Lane. "Rivastigmine in the Treatment of Dementia Associated with Parkinson's Disease: A Randomized, Double-Blind, Placebo-Controlled Study." In *Progress in Neurotherapeutics and Neuropsychopharmacology*, edited by Jeffrey L. Cummings. New York: Cambridge University Press, 2006.

PERIODICALS

- Grossberg, G. T. "Evaluating High-Dose Rivastigmine Patch in Severe Alzheimer's Disease: Analyses with Concomitant Memantine Usage as a Factor." *Current Alzheimer Research* 12, no. 1 (2015): 53–60.
- Kim, Y. K., et al. "Effects of a Rivastigmine Patch on Self-Care Activities in Patients with Alzheimer's Disease plus Cerebrovascular Disease." *Dementia and Geriatric Cognitive Disorders Extra* 4, no. 3 (2014): 395–401.
- Sadowsky, C. H., et al. "Rivastigmine from Capsules to Patch: Therapeutic Advances in the Management of Alzheimer's

Disease and Parkinson's Disease Dementia." *Primary Care Companion for CNS Disorders* 16, no. 5 (September 4, 2014).

WEBSITES

- AHFS Consumer Medication Information. "Rivastigmine." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a602009.html> (accessed February 26, 2015).
- Alzheimer's Association. "Current Alzheimer's Treatments." http://www.alz.org/research/science/alzheimers_disease_treatments.asp (accessed February 26, 2015).
- Micromedex. "Rivastigmine (Transdermal Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/rivastigmine-transdermal-route/description/drg-20071170> (accessed February 26, 2015).

ORGANIZATIONS

- Alzheimer's Association, 225 N. Michigan Avenue, Floor 17, Chicago, IL 60601-7633, (312) 335-8700, (800) 272-3900, Fax: (866) 699-1246, TTY: (866) 403-3073info@alz.org, <http://www.alz.org/>.
- Alzheimer's Foundation of America, 322 Eighth Avenue, 7th Floor, New York, NY 10001, (646) 638-1542, (866) 232-8484, Fax: (646) 638-1546, <http://www.alzfdn.org/>.
- Alzheimer's Society, Devon House, 58 St Katharine's Way, London E1W 1LB, England, +44 0300 222 11 22, Enquiries@alzheimers.org.uk, <http://www.alzheimers.org.uk/>.

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Rizatriptan

Definition

Rizatriptan is an oral medication used to treat the symptoms of migraine headaches. Rizatriptan is classified as an anti-migraine agent in the drug family known as selective serotonin receptor agonists (SSRAs) or triptans.

Purpose

Rizatriptan is used to treat symptoms of acute migraines in adults and children aged six to seventeen. Migraines are severe, throbbing headaches that may be accompanied by nausea and sensitivity to light and sound. Rizatriptan is used for migraines with and without auras—visual symptoms such as flashing lights and wavy lines that precede or accompany some migraines. Rizatriptan can only treat a headache that has already started—it cannot prevent migraines or reduce their frequency. Although rizatriptan may be used for other



Rizatriptan benzoate ODT, 10 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

purposes, it is only used for headaches that have been unequivocally diagnosed as migraines. It cannot be used to treat cluster headaches.

Description

Migraine headaches are believed to be caused by the widening (dilating) of cranial blood vessels that puts pressure on the brain. Rizatriptan benzoate binds to specific receptors for the neurotransmitter serotonin (5-hydroxytryptamine or 5-HT). These receptors, called 5-HT_{1B/1D} receptors, are located on blood vessels in the brain and sensory nerves leading to the brain. Rizatriptan is known as a selective 5-HT_{1B/1D} receptor "agonist" because when it binds with high affinity to these receptor subtypes, it exerts the same effects as serotonin binding to the receptors, acting as a powerful vasoconstrictor that narrows the widened blood vessels around the brain. This reduces pressure on the brain and blocks the transmission of pain signals and the release of inflammatory neuropeptides that cause pain, nausea, sensitivity to light and sound, and other migraine symptoms. Rizatriptan can be taken at the first sign of a migraine or in the midst of a migraine attack.

U.S. brand names

Rizatriptan benzoate is marketed in the United States under the brand names Maxalt tablets and Maxalt-MLT (orally disintegrating tablets).

KEY TERMS

5-Hydroxytryptamine_{1B/1D} (5-HT_{1B/1D})—Serotonin receptors in blood vessels in the brain that bind rizatriptan.

Agonist—A drug, such as rizatriptan, that binds to a receptor and mimics the effects of the endogenous receptor-binding substance.

Aura—Visual and other sensory disturbances that can precede the onset of a migraine headache.

Cluster headache—Severe pain in one eye or temple.

Maxalt—Rizatriptan tablets.

Maxalt-MLT—Rizatriptan orally disintegrating tablets.

Migraine—A common primary headache characterized by debilitating neurological symptoms, especially severe throbbing pain on one or both sides of the head, lasting for several hours or more.

Monoamine oxidase A (MAO-A) inhibitors—A class of antidepressants that can interact with rizatriptan.

Monoamine oxidase inhibitors (MAOIs)—A class of antidepressants that can interact with rizatriptan.

Neurotransmitter—A chemical that carries nerve impulses from one nerve cell to another across a synapse or from a nerve cell to a muscle cell.

Receptor—A molecule, such as a protein, inside or on the surface of a cell, that binds a specific substance.

Selective serotonin receptor agonist (SSRA)—A drug, such as rizatriptan, that binds to specific serotonin receptors, mimicking the effects of serotonin binding.

Selective serotonin reuptake inhibitors (SSRIs)—A class of antidepressants that increase levels of serotonin in the brain by preventing its reuptake by nerve-cell endings.

Serotonin—5-Hydroxytryptamine; a neurotransmitter in the brain and blood; low levels are associated with various disorders including migraines and depression.

Serotonin-norepinephrine reuptake inhibitors (SNRIs)—A class of antidepressants that increase the levels of the neurotransmitters serotonin and norepinephrine by preventing their reuptake.

Serotonin syndrome—A potentially life-threatening reaction to excess serotonin that can result from drugs that increase serotonin or its effects.

Sumatriptans—Various formulations of first-generation triptans.

Triptans—A class of drugs that bind to serotonin receptors and mimic the action of serotonin; believed to treat migraine headaches by constricting cranial blood vessels, inhibiting inflammatory neuropeptides, and blocking the transmission of pain signals.

International brand names

In Canada and most other countries, rizatriptan benzoate is marketed under the brand name Maxalt. It is also marketed under the brand names:

- Latariz, Rizatriptan Actavis, Rizatriptan CF, Rizatriptan Glenmark, Rizatriptan Mylan, Rizatriptan PCH, Rizatriptan ratiopharm, Rizatriptan Sandoz, Rizatriptan Sigillata, and Triptosig in the Netherlands.
- Maxalt lingual in Germany and Switzerland.
- Maxalt Melt in Denmark.
- Maxalt-Rapidisc in Turkey.
- Maxalt RPD in Bulgaria, Canada, Chile, Costa Rica, El Salvador, Guatemala, Japan, Panama, and Poland.
- Maxalt Smelt in Iceland.
- Maxaltlyo in France.
- Migoff in Taiwan.
- Ouliting, Xin Qu, and Shanqing in China.

- Rizact in India.
- Rizaliv and Trizadol in Italy.
- Rizalt in Israel.
- Rizamig and Rizat in Bangladesh.
- Rizatan in India, Taiwan, and the Netherlands.
- Rizatriptan in Slovenia.

Origins

Maxalt and Maxalt-MLT were initially approved by the U.S. Food and Drug Administration (FDA) in 1998. Rizatriptan benzoate is a second-generation triptan, succeeding the first-generation sumatriptans. Second-generation triptans tend to be more effective because they are longer lasting. This is particularly important for migraines that can persist for several days. Various generic oral and orally disintegrating rizatriptan benzoate tablets have been approved by the FDA since 2012. In 2014, the FDA declined to approve

an oral thin-film formulation called VersaFilm. Rizatriptan is available only by prescription in the United States, Canada, the United Kingdom, Australia, Finland, the Netherlands, Croatia, Spain, New Zealand, Italy, and Israel. Both orally disintegrating and swallowed forms of rizatriptan are available as 5 mg and 10 mg tablets.

Recommended dosage

The recommended adult dosage of rizatriptan is one 5 or 10 mg tablet, usually at the first sign of a migraine. If symptoms improve after the first dose, but the headache does not completely disappear or returns, additional doses may be taken at intervals of at least two hours, for a maximum of 30 mg in 24 hours. However, if symptoms do not improve with the first dose, a second dose should not be taken without consulting the doctor. Rizatriptan tablets are swallowed whole with a full glass of water. Orally disintegrating tablets must be kept in their blister packs until use. The package is opened, and the foil is peeled back with dry hands. Pushing the tablet through the foil may damage it. The tablet is placed on the tongue, dissolved without chewing, and swallowed with saliva.

Pediatric

Only orally disintegrating tablets are approved for use in children ages six to seventeen. A single 5 mg dose should be used for children weighing less than 88 lb. (40 kg). A single 10 mg dose may be taken by children weighing 88 lb. or more.

Geriatric

Dosing in elderly patients should begin at the low end because of the greater likelihood of decreased liver, kidney, and/or cardiac functioning; other diseases; and other drug therapies.

Other conditions and allergies

The rizatriptan dose must be adjusted if it is coadministered with **propranolol**.

Precautions

Rizatriptan should be avoided or prescribed with caution for:

- men over 40 and women who are over 55 or menopausal
- patients with heart disease risk factors such as smoking, obesity, diabetes, or high cholesterol
- patients with a family history of early heart disease or stroke

Other precautions include:

- The first dose of rizatriptan may be given in a medical setting to monitor for serious side effects.
- Rizatriptan should only be used for confirmed migraine headaches. It should not be used for common tension headaches, cluster headaches, headaches that cause movement loss on one side of the body, basilar or hemiplegic migraines, or any headache that is different from the patient's usual migraines.
- Headache medications should not be taken for more than ten days per month or for more than four headaches per month. Rizatriptan should not be taken in larger or smaller doses than prescribed or used more often or for longer than recommended. Overuse of migraine medications can worsen headaches or increase their frequency.
- Rizatriptan must not be taken within 24 hours of taking another migraine medication, including another SSRA or an ergot-type medication.
- Rizatriptan must not be taken within 14 days of a monoamine oxidase inhibitor (MAOI) or a monoamine oxidase A (MAO-A) inhibitor.
- Rizatriptan can cause drowsiness. Patients should not drive or operate machinery until they know how rizatriptan affects them.
- Patients should have their blood pressure checked regularly while using rizatriptan.
- Heart-function tests may be needed if rizatriptan is used long term.
- Overdose can cause high blood pressure, with symptoms including severe headache, blurred vision, buzzing in the ears, anxiety, confusion, chest pain, shortness of breath, irregular heartbeat, or seizures.

Pediatric

The safety and effectiveness of rizatriptan has been established for children aged six to seventeen, but not for children under age six. Adverse reactions in children are expected to be similar to those in adults. In an acute clinical trial, the incidence of adverse reactions was similar in pediatric patients receiving rizatriptan or a placebo.

Geriatric

No differences in responses to rizatriptan have been identified between older and younger patients. Geriatric patients with cardiovascular risk factors should have a cardiovascular evaluation before taking rizatriptan.

Pregnant or breastfeeding

Rizatriptan is in the FDA pregnancy category C, meaning that it is not known whether the drug poses

harm to the fetus, but animal studies indicate that it might. It should be avoided or prescribed with caution during pregnancy and women should use effective birth control while taking rizatriptan. Rizatriptan is excreted in rat milk at very high levels. It is not known whether it passes into human breast milk or poses harm to the baby. The risks and benefits of rizatriptan during pregnancy or breastfeeding should be discussed with the doctor.

Other conditions and allergies

The doctor and pharmacist should be informed of allergies to any medications or to any of the ingredients in rizatriptan tablets or orally disintegrating tablets. Rizatriptan should not be taken by anyone who is allergic to rizatriptan or has coronary heart disease, angina, circulatory problems, poor blood supply to the heart, severe or uncontrolled high blood pressure, ischemic bowel disease, or a history of heart disease, heart attack, stroke, or transient ischemic attack. The doctor should be informed if the patient has:

- liver or kidney disease
- high blood pressure
- a heart rhythm disorder
- any risk factors for coronary heart disease
- phenylketonuria, since rizatriptan orally disintegrating tablets contain aspartame, which is converted to phenylalanine

Side effects

The most common side effects of rizatriptan, occurring in more than 5% of adults, are:

- drowsiness
- weakness/fatigue
- sensations of pain or pressure
- dizziness

Less serious side effects may include:

- mild non-migraine headache
- dry mouth
- mild nausea
- pressure or heavy feeling in any part of the body
- warmth, redness, or mild tingling under the skin

The doctor should be contacted if any of the following symptoms are severe or persistent:

- drowsiness
- dizziness
- fatigue
- upset stomach
- vomiting

- diarrhea
- muscle pain or cramps
- tremors
- flushing
- dry mouth

Serious side effects that require immediately calling the doctor or emergency medical attention are:

- signs of an allergic reaction—hives, difficulty breathing, or swelling of the face, lips, tongue, or throat
- tightness, pain, pressure, or heaviness in the chest, throat, neck, or jaw
- rapid, pounding, or irregular heartbeat
- shortness of breath
- cold sweat
- light-headedness
- weakness or numbness of an arm or leg or on one side of the body
- sudden or severe stomach pain
- bloody diarrhea
- numbness or tingling and paleness or blue color to the fingers and toes
- pain, burning, or tingling in the hands or feet
- swelling of the eyes, hands, feet, ankles, or lower legs
- rash
- itching
- chest pain or heaviness, pain spreading to the arm or shoulder, nausea, sweating, or general ill-feeling
- sudden severe headache, confusion, or problems with vision, speech, or balance
- agitation, hallucinations, fever, fast heart rate, overactive reflexes, nausea, vomiting, diarrhea, loss of coordination, or fainting in patients taking an antidepressant

Interactions

It is very important to inform the doctor and pharmacist of any and all prescription and nonprescription medicines, herbs, vitamins, and dietary supplements being used by the patient.

Drugs

Drugs that can interact with rizatriptan include:

- propranolol (Inderal, InnoPran)
- selective serotonin reuptake inhibitors (SSRIs)—such as **fluoxetine** (Prozac, Rapiflux, Sarafem, Selfemra, Symbyax), **citalopram** (Celexa), **fluvoxamine** (Luvox), **sertraline** (Zoloft), **escitalopram** (Lexapro), **paroxetine** (Paxil, Pexeva), or vilazodone (Viibryd)—

and serotonin-norepinephrine reuptake inhibitors (SNRIs)—such as desvenlafaxine (Pristiq), **duloxetine** (Cymbalta), sibutramine (Meridia), or **venlafaxine** (Effexor)—all of which can increase the risk of potentially fatal serotonin syndrome

- other antidepressants, such as **trazodone** (Desyrel, Oleptro), **amitriptyline** (Elavil), amoxapine (Asendin), clomipramine (Anafranil), **desipramine** (Norpramin), **doxepin** (Adapin, Sinequan), **imipramine** (Tofranil), **nortriptyline** (Aventyl, Pamelor), protriptyline (Vivacril), and trimipramine (Surmontil)
- other migraine medicines taken within 24 hours of rizatriptan, such as **almotriptan** (Axert), eletriptan (Relpax), frovatriptan (Frova), naratriptan (Amerge), **sumatriptan** (Imitrex, Treximet), or **zolmitriptan** (Zomig) or ergot-containing drugs, such as ergotamine (Ergomar, Cafergot, Migergot), dihydroergotamine (D. H.E. 45, Migranal), methylergonovine (Methergine), bromocriptine (Parlodel), cabergoline, ergoloid mesylates (Hydergine), ergonovine (Ergotrate), methysergide (Sansert), or pergolide (Permax)
- MAOIs or MAO-A inhibitors, such as furazolidone (Furoxone), isocarboxazid (Marplan), phenelzine (Nardil), rasagiline (Azilect), selegiline (Eldepryl, Emsam, Zelapar), or tranylcypromine (Parnate) taken within the past 14 days
- acetaminophen (Tylenol)
- **aspirin** and nonsteroidal anti-inflammatory medications (NSAIDs), such as **ibuprofen** (Advil, Motrin) and naproxen (Aleve, Naprosyn)

Resources

BOOKS

Smith, Howard S., et al. *Essential Pain Pharmacology: The Prescriber's Guide*. New York: Cambridge University, 2012.

PERIODICALS

Pringsheim, Tamara, et al. "Triptans for Symptomatic Treatment of Migraine Headache." *British Medical Journal* 348, no. 7953 (April 12, 2014): 35.

WEBSITES

American Society of Health-System Pharmacists, Inc. "Rizatriptan." MedlinePlus. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601109.html> (accessed November 25, 2014).

Merck Sharp & Dohme Corp. "Prescribing Information." Merck. Available from: https://www.merck.com/product/usa/pi_circulars/m/maxalt/maxalt_pi.pdf (accessed November 25, 2014).

Rizatriptan. Drugs.com. Available from: <http://www.drugs.com/mtm/rizatriptan.html> (accessed November 25, 2014).

Triptans: What You Should Know. "Consumer Reports." Available from: <http://www.consumerreports.org/health/>

resources/pdf/best-buy-drugs/BBD_Triptans_Summary.pdf (accessed November 21, 2014).

ORGANIZATIONS

American Headache Society, 19 Mantua Road, Mount Royal, NJ 08061, 856423-0043, Fax: 856423-0082, ahshq@talley.com, <http://www.americanheadachesociety.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY KEVIN GLAZA, RPh

Robaxin see **Methocarbamol**

Rocaltrol see **Calcitriol**

Ropinirole

Definition

Ropinirole HCL is a medicine used to treat Parkinson's disease, a chronic and progressive movement disorder. The drug is in a class of medications called dopamine agonists, meaning that it replaces natural dopamine in the body. HCL stands for hydrochloride, which is a salt used to help improve how the body absorbs and breaks down the ropinirole.

Purpose

People who have Parkinson's disease have progressively worse symptoms such as tremors, or slight shakiness, while the person is at rest. They also have rigid limbs, slow movements, and problems with balance and walking, in addition to pain, fatigue, and other symptoms. Most of the symptoms are caused by a problem with neurons, or nerve cells, in the brain that die and lead to reduced amounts of dopamine. Ropinirole HCL acts in place of natural dopamine to relieve some of these symptoms.

Ropinirole HCL also is prescribed to some people who have a condition known as restless legs syndrome (also called Willis-Ekbom disease) that causes them to have discomfort in their legs, especially when sitting or lying down. The discomfort is accompanied by an urge to move the legs.

Description

Ropinirole HCL is available by prescription as a coated tablet with extended-release, or long-lasting, action. The tablets come in varying dosage amounts,



Ropinirole, 1 mg. (© Cengage Learning®.)

from 0.25 mg through 5 mg. Among the class of dopamine agonists, or replacements for dopamine, it is one of the most common treatments for restless legs syndrome and one of several approved medications for treating Parkinson's disease symptoms. Although ropinirole HCL can manage symptoms of Parkinson's disease and restless legs syndrome, it does not cure either of the diseases.

U.S. brand names

In the United States, ropinirole HCL is sold as Requip and Requip XL.

Recommended dosage

Doctors usually start patients on ropinirole at the lowest recommended dose to see how well the medicine controls symptoms and how well the patient tolerates the drug's side effects. Increasing dose is titrated, or increased gradually over many weeks in small amounts (1.5 mg a day) as the doctor observes the drug's effects. The starting dose for managing Parkinson's disease symptoms is usually 0.25 mg three times a day. It is not recommended that patients exceed a total of 24 mg of ropinirole HCL a day. If a patient stops taking the drug, this also should be done gradually, not suddenly.

The starting dose for restless legs syndrome is 0.25 mg once a day, taken within one to three hours of bedtime. Dose can be increased every few days in increments of 0.5 mg a day, but should not exceed 4 mg a day of ropinirole HCL.

Precautions

Patients taking ropinirole HCL have reported episodes of falling asleep while participating in daily activities, including driving. This has resulted in accidents. Anyone who must drive a vehicle, operate machinery at work, or perform any potentially dangerous activity should report problems with wakefulness to their doctors. Some patients take ropinirole and a drug called levodopa at the same time. Taking these drugs together can worsen a side effect known as dyskinesias, or jerky motions. Decreasing the amount of levodopa usually can lessen the movements.

Some people have reported fainting episodes while on ropinirole, along with hallucinations, problems with impulse control, and other psychological symptoms. The drug also has been known to cause lung complications in some patients.

Pediatric

The drug has not been studied for safety or effectiveness in children.

Geriatric

Some patients taking the drug have hallucinations, and the risk of this side effect is higher in older patients. Although the elderly may not clear the drug through their bodies as well, doctors adjust dose based on effectiveness and side effects, including for older patients.

Pregnant or breastfeeding

Ropinirole is a pregnancy category C drug, meaning that it has only been tested in animals. Women who are pregnant should only take the medication if the potential benefits outweigh possible risks. Ropinirole can affect or halt lactation in nursing mothers, and the drug can be excreted in breast milk. A nursing mother must work with her doctors to decide whether it is more beneficial to stop taking ropinirole while nursing or to continue the drug and choose not to breastfeed her infant.

Other conditions and allergies

Smoking can decrease how effective ropinirole is in managing symptoms, and people who smoke should discuss this with their doctors if taking ropinirole.

KEY TERMS

Dopamine—A neurotransmitter in the brain that influences many of the brain's functions, including movement, areas of thinking, pleasure, and control of hormones.

Lactation—Secretion of milk from the breasts; the act of breastfeeding.

Neurotransmitter—A chemical in the brain that can affect the activity of neurons, or nerve cells.

Side effects

Some of the most common side effects from use of ropinirole include:

- dizziness or lightheadedness, especially when rising from a seated or sleeping position
- confusion or problems with memory
- sleepiness
- nausea, vomiting, and stomach pain
- uncontrollable shaking
- heartburn and gas
- weakness and fatigue
- anxiety
- dry mouth

Some side effects of ropinirole can be severe and should be reported to a doctor immediately. These include:

- hallucinations
- fainting
- rapid or irregular heartbeat
- chest pain
- problems breathing or swallowing
- changes in vision and double vision
- excessive daytime sleepiness

Interactions

Ropinirole can interact with some other drugs and substances. Anyone taking the drug should inform the doctor and pharmacist of other medications they are taking. The doctor also should know about all herbs, supplements, and vitamins a person is taking.

Drugs

Taking ropinirole at the same time as estrogens, a type of female hormone, might affect the dose of ropinirole required.

Food and other substances

Because of the sleepiness caused by ropinirole HCL, it is recommended to use caution when drinking alcohol while taking the drug. The drug can be taken with or without food. Taking ropinirole HCL with food can help reduce nausea associated with the medicine.

Resources

PERIODICALS

Patel, Tejal, et al. "Parkinson's Disease Guidelines for Pharmacists." *Canadian Pharmacy Journal* vol. 147 (2014): 161–170.

Singer, Carlos. "Managing the Patient with Newly Diagnosed Parkinson Disease." *Cleveland Clinic Journal of Medicine* vol. 79, supply 2 (2012): 83–87.

St. Louis, Erik K. "New Evidence for Reduced Leg Oxygen Levels in Restless Legs Syndrome." *Neurology* vol. 82 (2014): 185–7.

WEBSITES

American Society of Health-System Pharmacists. "Ropinirole." MedlinePlus. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a698013.html>

Drugs.com. "Ropinirole." Drugs.com. Available from: <http://www.drugs.com/cdi/ropinirole.html>

GlaxoSmithKline. "Requip." U.S. Food and Drug Administration. http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020658s020s021b1.pdf

RXList. "Requip." RXList. <http://www.rxlist.com/requip-drug.htm>

ORGANIZATIONS

The Michael J. Fox Foundation for Parkinson's Research, Grand Central Station, PO Box 4777, New York, NY 10163-4777, (800) 708-7644, <https://www.michaeljfox.org/>.

Restless Legs Syndrome Foundation, 3006 Bee Caves Road, Suite D206, Austin, TX 78746, (512) 366-9109, Fax: (512) 366-9189, info@rls.org, <http://www.rls.org/>.

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REVIEWED BY GREGORY A. PRATT, RPh

Rosuvastatin

Definition

Rosuvastatin is a member of the class of statins, used to reduce high blood cholesterol levels and lower the risk of cardiovascular disease. Statins are also known as HMG-CoA reductase inhibitors because they inhibit the action of an enzyme called HMG-CoA reductase, which plays an important role in the liver's production of cholesterol.



Crestor (rosuvastatin), 5 mg. (© Cengage Learning®.)

Purpose

Rosuvastatin is used to lower the level of cholesterol and triglycerides in the blood in patients for whom exercise and dietary modifications are insufficient to lower their risk of heart disease. It is reported to lower low-density lipoprotein (LDL or “bad”) cholesterol levels to the greatest extent of all currently marketed statins. Rosuvastatin is also used to prevent or slow the progression of atherosclerosis and to lower the risk of stroke or heart attack in patients without present signs of heart disease but who have the following risk factors:

- age above 50 years in men, 60 years in women
- elevated high-sensitivity C-reactive protein level (2 mg/L)
- at least one other factor, including high blood pressure, smoking, or family history of heart disease

Rosuvastatin is used in children over the age of 10 to treat a condition known as familial heterozygous hypercholesterolemia, a genetic disorder in which people have one abnormal copy of the *LDLR* gene on chromosome 19, which encodes a protein that removes LDL cholesterol from the blood. These patients typically develop premature heart disease by age 30 or 40.

Off-label use

Rosuvastatin is used off label as an orphan drug for the treatment of pediatric homozygous familial hypercholesterolemia, a genetic disorder in which the patient has two copies of a defective *LDLR* gene.

Description

Rosuvastatin is formulated as 5 mg, 10 mg, 20 mg, and 40 mg tablets; the 5 mg tablets are yellow in color and round in shape, while the three larger sizes are peach-colored. The 10 mg and 20 mg tablets are round in shape and the 40 mg tablets are oval.

U.S. brand names

Rosuvastatin is distributed by AstraZeneca Pharmaceuticals in the United States under the trade name Crestor. Crestor is the fourth-highest selling drug in the United States, accounting for over five billion dollars in sales in 2013.

International brand names

Rosuvastatin is sold in India by Zydus CND under the trade name Zyrova.

Origins

Rosuvastatin was developed in Japan by Shionogi, a well-known Japanese pharmaceutical firm. It was approved for use in the United States by the FDA in August 2003. No generic formulations are available as of 2015 because the drugs patent will not expire until 2016.

Recommended dosage

The recommended dosages for rosuvastatin in adults vary according to the condition being treated:

- Hypertriglyceridemia, hyperlipidemia, dyslipidemia, slowing the progression of atherosclerosis, or familial dysbetalipoproteinemia: initial dose of 10–20 mg by mouth once daily; dosage may be adjusted but should not exceed 40 mg per day.
- Homozygous familial hypercholesterolemia: initial dose of 20 mg by mouth once per day; may be adjusted but should not exceed 40 mg per day.
- Primary prevention of cardiovascular disease in patients without clinical evidence of heart disease: 10 to 20 mg by mouth once per day, with a dosage range of 5 to 40 mg per day.

Pediatric

Heterozygous familial hypercholesterolemia for children between 10 and 17 years of age: 5 to 20 mg

by mouth per day; dosage may be adjusted every 4 weeks; dosage not to exceed 20 mg per day.

Other conditions and allergies

The dosage of rosuvastatin may require adjustment in the following groups of adult patients:

- Patients taking other lipid-lowering medications: the dose of rosuvastatin should be reduced if the patient is also taking niacin or **fenofibrate**, because of the risk of muscle damage.
- Patients taking **cyclosporine**: dose of rosuvastatin should not exceed 5 mg per day.
- Patients taking **gemfibrozil**: avoid giving rosuvastatin if at all possible; otherwise, give no more than 10 mg per day.
- Patients taking ritonavir, lopinavir/ritonavir, or atazanavir/ritonavir: the dose of rosuvastatin should not exceed 10 mg per day.
- Patients with severe kidney impairment: dose should be started at 5 mg per day and should not exceed 10 mg per day.
- Patients of Asian descent: initial therapy should be no more than 5 mg per day. The FDA issued an advisory in 2005 that persons of Asian descent appear to process rosuvastatin differently and should be started on the lowest possible dose to lower the risk of muscle damage.

Precautions

Patients should observe the following precautions before taking rosuvastatin:

- Inform their doctor of any known allergies to foods, dyes, or other medications.
- Inform their doctor if they have a history of alcohol abuse, excessive amounts of exercise, or a history of muscle problems.
- Inform their doctor if they are undergoing dialysis.
- Inform their doctor if they have received an organ transplant, have recently undergone major surgery, or have recently had a serious injury.

Pediatric

Rosuvastatin is not recommended for use in children younger than 10 years.

Pregnant or breastfeeding

Rosuvastatin is a pregnancy Category X drug, which indicates that it is not to be used by pregnant women because the risk of harm to the fetus outweighs any

KEY TERMS

Atherosclerosis—Thickening and hardening of the walls of an artery as the result of accumulations of white blood cells, cholesterol, and triglycerides (fats).

C-reactive protein (CRP)—A ring-shaped protein found in blood plasma whose levels rise in response to inflammation. High basal levels of CRP are thought to indicate increased risk of type 2 diabetes, cardiovascular disease, and high blood pressure.

Familial dysbetalipoproteinemia—A genetic disorder characterized by high triglyceride levels, high LDL cholesterol levels, low HDL cholesterol levels, and the early onset of atherosclerosis.

Familial hypercholesterolemia (FH)—A genetic disorder characterized by high levels of LDL cholesterol in the blood and cardiovascular disease early in life. The heterozygous form is more common and can be treated with statins; the homozygous form is very rare (about one case in every million live births) and may respond only to liver transplantation.

HMG-CoA reductase—An enzyme that affects the production of cholesterol in the liver. Rosuvastatin and other statins lower blood cholesterol levels by inhibiting the activity of this enzyme.

Orphan drug—A medication that has been developed to treat a rare disease, defined in the United States as a disease or disorder affecting fewer than 200,000 people.

Rhabdomyolysis—A condition in which damaged skeletal muscle undergoes rapid breakdown. It is a rare but potentially serious effect of taking statins.

possible benefit of the drug. Rosuvastatin is also contraindicated for use by nursing mothers.

Other conditions and allergies

Rosuvastatin is contraindicated in patients with active liver disease and should be used cautiously in patients with alcoholic liver disease.

Rosuvastatin should be used with caution in patients with diabetes, poorly controlled seizure disorders, hypothyroidism, severe endocrine disorders, or severe electrolyte disturbances.

Patients scheduled for major surgery or who have a medical emergency may need to stop taking rosuvastatin for a short period of time.

Side effects

The most common side effects of rosuvastatin include:

- body aches or mild muscle pain
- headache
- dry or sore throat, cough
- swollen glands in the neck
- hoarseness or voice changes
- nausea
- constipation
- weakness

Less common side effects include:

- acid indigestion or belching
- a bloated or full feeling
- pain in the bladder
- prickling, stinging, or pins-and-needles sensations
- anxiety
- fruity breath odor
- loss of appetite
- insomnia
- unusual bleeding or bruising
- difficulty concentrating

The following side effects may indicate a serious condition and should be reported to the doctor at once:

- signs of a severe allergic reaction (hives; itching; sudden and unexplained swelling of the lips, mouth, or throat; difficulty breathing)
- jaundice, dark-colored urine, pain in the upper abdomen, or other signs of a liver disorder
- unexplained changes in urine output
- severe upper abdominal pain accompanied by nausea and vomiting, which may indicate pancreatitis
- severe muscle pain or tenderness accompanied by fever, which may indicate rhabdomyolysis (sudden breakdown of muscle tissue)
- memory loss
- increased blood sugar levels, particularly in diabetic patients

Interactions

Drugs

Rosuvastatin interacts with the following medications:

- antacids (decrease the absorption of rosuvastatin)
- other statin medications (**lovastatin**, **pravastatin**, **simvastatin**, **atorvastatin**, etc.)
- **colchicine** (gout medication)
- birth control pills
- **ketoconazole** (antifungal drug)
- cyclosporine
- fibrates
- niacin
- antiretroviral medications (indinavir, atazanavir, delavirdine, ritonavir, nelfinavir, etc.)
- **spironolactone**
- **warfarin**

Food and other substances

Patients taking rosuvastatin should not drink alcoholic beverages while taking the drug because of increased risk of liver damage. Alcohol can also raise the patient's triglyceride levels.

Patients taking rosuvastatin should not eat red yeast rice, a dietary supplement that contains a compound nearly identical to lovastatin, another statin medication.

Resources

BOOKS

LaGrúa, Benedetta, et al. *Statins: Pharmacology, Clinical Implications, and Adverse Effects*. New York: Nova Biomedical/Nova Science Publishers, 2012.

Travers, Eric R., et al. *Statins: Medical Uses, Mechanisms of Action, and Clinical Outcomes*. Hauppauge, NY: Nova Science Publishers, 2014.

PERIODICALS

Adams, S. P., et al. "Lipid-Lowering Efficacy of Rosuvastatin." *Cochrane Database of Systematic Reviews* 11 (November 21, 2014): CD010254.

Alonso-Zaldivar, Ricardo. "FDA Advisory Targets Asian Patients." *Los Angeles Times*. March 3, 2005.

Hu, M., et al. "Current Perspectives on Rosuvastatin." *Integrated Blood Pressure Control* 6 (April 18, 2013): 15–25.

Park, Z.H., et al. "Statin-associated Incident Diabetes: A Literature Review." *The Consultant Pharmacist* 29 (May 2014): 317–334.

Toth, P.P. "An Update on the Risks and Benefits of Rosuvastatin Therapy." *Postgraduate Medicine*. 126 (March 2014): 7–17.

WEBSITES

AHFS DI Monograph. "Rosuvastatin." Available from: <http://www.drugs.com/mtm/rosuvastatin.html> (accessed January 3, 2015).

Medscape Reference. "Rosuvastatin (Rx)." Available from: <http://reference.medscape.com/drug/crestor-rosuvastatin-342467> (accessed January 3, 2015).

Micromedex. "Rosuvastatin (Oral Route)." Mayo Clinic. Available from: <http://www.mayoclinic.org/drugs-supplements/rosuvastatin-oral-route/description/drg-20065889> (accessed January 3, 2015).

ORGANIZATIONS

American College of Cardiology (ACC), Heart House, 2400 N Street NW, Washington, DC 20037, (202) 375-6000, ext. 5603, Fax: (202) 375-7000, (800) 253-4636, ext. 5603, resource@acc.org, <http://www.cardiosource.org/>.

American Heart Association (AHA), 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://connect.ashp.org/contactus>, <http://www.ashp.org/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/AboutFDA/ContactFDA/default.htm>, <http://www.fda.gov/default.htm>.

Rebecca J. Frey, PhD

REVIEWED BY KEVIN GLAZA, RPH

Roxicodone see **Oxycodone**

Rozerem see **Ramelteon**

S

Salmeterol

Definition

Salmeterol xinafoate is a medicine that is inhaled to help prevent and manage bronchospasms, or episodes of serious breathing problems and symptoms in people who have asthma and chronic obstructive pulmonary disease (COPD). It is in a class of drugs called long-acting beta-agonists.

Purpose

Children and adults who have asthma have problems breathing and symptoms such as wheezing, coughing, or a tight feeling in the chest. These symptoms are related to tightening of the airways, or bronchi. Salmeterol xinafoate and other long-acting beta-agonists help relax and open the airways, which makes breathing easier. It is used in inhalers to prevent bronchospasms, or severe breathing episodes, in people who have asthma that is not controlled well with their current medications. Salmeterol xinafoate also is used to prevent severe episodes in people who have COPD.

Description

Salmeterol xinafoate is sold by prescription only. The medicine comes in the form of a dry powder that is loaded into a disk-shaped inhaler. The inhaler is specially designed to be used at regular times each day to prevent breathing problems. This type of asthma medication is not designed for use during an asthma attack. Instead, it is meant to help prevent sudden attacks and lessen ongoing symptoms. People who take salmeterol xinafoate should use a short-acting beta-agonist such as **albuterol** only as needed during sudden attacks of asthma.

U.S. brand names

In the United States, salmeterol xinafoate is sold under the brand name Serevent.

Recommended dosage

The inhaler that contains salmeterol xinafoate delivers the drug in metered doses, and includes a counter to let patients know when the inhaler is close to empty. The usual recommended dose that is delivered for adults and children age four and older for asthma control is in inhalation twice a day, spaced 12 hours apart. Each inhalation delivers 50 mcg of salmeterol xinafoate. Adults using salmeterol xinafoate for COPD symptom control also take a 50 mcg dose twice a day at 12-hour intervals. Some adults and children may take salmeterol xinafoate to prevent asthma attacks caused by exercise. They should use the inhaler 30 minutes before the scheduled activity. However, salmeterol xinafoate should never be inhaled more than once within a 12-hour period.

It is important that anyone using a disk inhaler for salmeterol xinafoate space doses at regular 12-hour intervals and try not to miss a dose. It is also important to use the inhaler as directed by the doctor, pharmacist, and package insert so that the medicine works most safely and effectively.

Precautions

Studies have shown that people who use salmeterol have experienced more severe asthma episodes, even resulting in hospitalization or death, than people who did not use the medication. Once a person's asthma is under control, doctors should begin to gradually reduce their dose of salmeterol xinafoate until they no longer need the medicine.

Salmeterol xinafoate should never be used while a patient is having a worsening or life-threatening episode of asthma or COPD. Use of salmeterol xinafoate can result in a condition called paradoxical bronchospasm, which is a potentially life-threatening tightening of the airways. It is important to stop using salmeterol xinafoate if asthma symptoms worsen.

Some people are allergic to salmeterol xinafoate and have immediate reactions, including a rash or hives, low blood pressure, anaphylaxis, and other symptoms.



Serevent Diskus (salmeterol xinafoate). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Anaphylaxis is a serious allergic reaction requiring immediate medical attention. Some patients with severe milk protein allergies may also have a reaction to salmeterol xinafoate. Patients who suspect they may have this allergy should alert the prescribing physician.

Pediatric

Studies have shown that use of salmeterol xinafoate and other long-term beta-agonists can increase the risk of hospitalization from asthma episodes in children and adolescents. Other data have shown that there is no need to adjust dosage for children age four years and older. It is not known whether salmeterol xinafoate is effective or safe in children younger than age four.

Pregnant or breastfeeding

Salmeterol xinafoate is a pregnancy category C medication. It has not been tested adequately in pregnant women. Women who are pregnant or in labor should only use salmeterol xinafoate if the potential benefits to the mother outweigh possible harm to her unborn child.

It is possible that salmeterol xinafoate is passed from mother to infant through breast milk. Nursing mothers should use caution and discuss use of the drug if they plan to breastfeed their child.

Other conditions and allergies

People who have diseases of the liver should be closely monitored while using salmeterol xinafoate.

Caution also should be used in patients who have certain cardiovascular diseases.

Side effects

Salmeterol xinafoate can cause several side effects, including:

- headache
- dizziness
- nervousness
- uncontrollable shaking in a part of the body
- cough and runny or congested nose
- ear pain
- sore or irritated throat
- nausea and heartburn
- dry mouth or sores in the mouth
- problems sleeping

Some side effects of salmeterol xinafoate use can be severe and should be reported to a doctor immediately. These include:

- symptoms of bronchospasm such as wheezing, tight chest, and coughing soon after taking salmeterol xinafoate
- rapid or pounding heartbeat
- rash or hives
- swelling of the throat, tongue, lips, face, eyes, or lower limbs
- chest pain
- choking or problems swallowing
- high-pitched sounds when breathing or loud breathing

Pediatric

Children who use salmeterol xinafoate can have worsening asthma symptoms after taking the drug. Parents should immediately call the doctor or seek medical attention.

Interactions

Drugs can interact with each other or with other substances, affecting how well a drug works or worsening side effects. Patients should tell the doctor about any medications, herbal remedies, or supplements they are using before taking salmeterol xinafoate.

Drugs

Some drugs must be used with caution while a person is taking salmeterol xinafoate. Among these are:

KEY TERMS

Anaphylaxis—A severe and potentially life-threatening allergic reaction that can occur instantly when a person is exposed to a medicine, food, or other allergen. Also called anaphylactic shock or anaphylactic reaction.

Bronchospasm—Sudden tightening of the muscles around the airways that leads to difficulty breathing.

Chronic obstructive pulmonary disease—A group of ongoing and progressive lung diseases such as emphysema and chronic bronchitis.

Long-acting beta-agonist—A medication that helps relax muscles around airways to open the air passages and improve breathing. Long-acting beta-agonists usually last about 12 hours and are used to prevent symptoms, not to relieve them immediately.

- monoamine oxidase inhibitors, such as selegiline (Emsam) and phenelzine (Nardil), which are used to treat depression
- tricyclic antidepressants such as **amitriptyline** and nortriptyline (Pamelor)
- certain drugs used to treat HIV and AIDS, such as ritonavir (Norvir) and atazanavir (Reyataz)
- beta-blockers, such as **metoprolol** (Lopressor, Toprol-XL) and propranolol (Inderal and InnoPran)

Resources

PERIODICALS

- Hatipoglu, Umur, et al. "Chronic Obstructive Pulmonary Disease: An Update for the Primary Physician." *Cleveland Clinic Journal of Medicine* vol. 81, no. 6 (2014): 373–83.
- Xia, Ying, et al. "Safety of Long-acting Beta Agonists and Inhaled Corticosteroids in Children and Adolescents with Asthma." *Therapeutic Advances in Drug Safety* vol. 4, no. 6 (2013): 254–63.

WEBSITES

- American Society of Health-System Pharmacists. "Salmeterol Oral Inhalation." MedlinePlus. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a695001.html>
- Drugs.com. "Salmeterol." Drugs.com. Available from: <http://www.drugs.com/cdi/salmeterol.html>
- GlaxoSmithKline. "Medication Guide: Serevent Diskus." U.S. Food and Drug Administration. Available from: <http://www.fda.gov/downloads/Drugs/DrugSafety/ucm089125.pdf>

RXList. "Serevent Diskus." RXList. Available from: <http://www.rxlist.com/serevent-diskus-drug.htm>

ORGANIZATIONS

- American Academy of Allergy, Asthma & Immunology, 555 East Wells, Suite 1100, Milwaukee, WI 53202-3823, (414) 272-6071, <http://www.aaaai.org/home.aspx/>.
- American Lung Association, 55 West Wacker Drive, Chicago, IL 60601, (202) 452-1805, (800) 586-4872, <http://www.lung.org/>.

Teresa G. Odle, BA, ELS

REVIEWED BY GREGORY A. PRATT, RPh

Salmeterol/fluticasone see **Fluticasone/salmeterol**

Sandostatin see **Octreotide**

Savella see **Milnacipran**

Septra see **Sulfamethoxazole/trimethoprim**

Serevent see **Salmeterol**

Seroquel see **Quetiapine**

Sertraline

Definition

Sertraline is an antidepressant that belongs to the class of drugs called selective serotonin reuptake inhibitors (SSRIs).

Purpose

Sertraline is approved by the U.S. Food and Drug Administration (FDA) for use in adults in treating major depressive disorder, obsessive-compulsive disorder (OCD), panic disorder, post-traumatic stress disorder (PTSD), premenstrual dysphoric disorder (PMDD), and social anxiety disorder. Sertraline is not approved in persons younger than the age of 24 unless used in the treatment of OCD.

Description

Serotonin is a brain chemical that carries nerve impulses from one nerve cell to another. Researchers think that depression and certain other mental disorders may be caused, in part, because there is not enough serotonin being released and transmitted in the brain. Like the other SSRI antidepressants **fluvoxamine** (Luvox), **fluoxetine** (Prozac), and paroxetine (Paxil), sertraline increases the level of brain serotonin (also



Zoloft (sertraline), 25 mg. (© Cengage Learning®.)

known as 5-HT). Increased serotonin levels in the brain may be beneficial in patients with obsessive-compulsive disorder, alcoholism, certain types of headaches, post-traumatic stress disorder (PTSD), premenstrual tension and mood swings, and panic disorder.

The benefits of sertraline develop slowly over a period of up to four weeks. Patients should be aware of this and continue to take the drug as directed, even if they feel no immediate improvement.

Sertraline is available in 25, 50, and 100 milligram (mg) tablets, or as a 20 mg per milliliter (mL) solution.

U.S. brand names

In the United States, sertraline is sold under the brand name Zoloft.

Recommended dosage

The recommended dosage of sertraline depends on the disorder being treated. The initial recommended dosage for depression and obsessive-compulsive disorder is 50 mg daily. This may be increased at intervals of at least one week to the maximum recommended dosage of 200 mg daily. For the treatment of panic disorder and post-traumatic stress disorder, the initial dose is 25 mg once daily. This dosage is increased to 50 mg daily after one week. If there is no therapeutic response, the dosage

may be increased to the maximum of 200 mg daily at intervals of at least one week.

Pediatric

For the treatment of obsessive-compulsive disorder in the pediatric population, treatment should be initiated at a dose of 25 mg per day in children 6 to 12 years old and 50 mg per day in children 13 to 17 years. Doses may be increased at one-week intervals to a total daily dose of 200 mg.

Geriatric

Dosages may need to be reduced in patients over the age of 65.

Other condition and allergies

Individuals with impaired liver function may require dosage adjustments.

Precautions

Children and adults up to age 24 are at an increased risk of developing suicidal thoughts and behaviors when taking sertraline or any other antidepressant drug. Patients of all ages should be monitored for signs of worsening depression or changes in behavior. Sertraline may precipitate a shift to mania in patients with bipolar disorder.

Pregnant or breastfeeding

Sertraline has been associated with adverse fetal effects when used early in pregnancy. Women taking sertraline should discuss the risks with their healthcare provider.

Other conditions and allergies

The drug should be used cautiously and with close physician supervision by people with a prior history of seizures, people who are at an increased risk of bleeding, and those for whom weight loss is undesirable. The risk of bleeding may increase when taking sertraline with medication that thins the blood, including **aspirin**.

Side effects

More than 5% of patients experience insomnia, dizziness, and headache. About 14% of men report delayed ejaculation while 6% report decreased sex drive while taking this drug. In order to reduce these sexual side effects, patients can wait for drug tolerance to develop (this may take up to 12 weeks), reduce the dose, have drug holidays (where the weekend dose is either decreased or skipped), or discuss with their physician using a different antidepressant.

KEY TERMS

Major depressive disorder—A clinical psychiatric diagnosis of chronic depressed mood that interferes with normal life activities.

Monoamine oxidase inhibitors (MAOIs)—A group of antidepressant drugs that decrease the activity of monoamine oxidase, a neurotransmitter found in the brain that affects mood.

Obsessive-compulsive disorder (OCD)—A disorder in which affected individuals have an obsession (such as a fear of contamination, or thoughts they do not like to have and cannot control) and feel compelled to perform certain acts to neutralize the obsession (such as repeated hand washing).

Selective serotonin reuptake inhibitors (SSRIs)—A class of antidepressants that works by blocking the reabsorption of serotonin in brain cells, raising the level of the chemical in the brain.

Serotonin—5-Hydroxytryptamine; a substance that occurs throughout the body with numerous effects, including neurotransmission. Low serotonin levels are associated with mood disorders, particularly depression and obsessive-compulsive disorder.

Serotonin syndrome—A potentially life-threatening drug reaction involving an excess of the neurotransmitter serotonin, usually occurring when too many medications that increase serotonin are taken together.

More than 10% of patients report nausea and diarrhea while taking sertraline. Other possible side effects include agitation, anxiety, rash, constipation, vomiting, tremors, or visual difficulty. Although most side effects eventually subside, it may take up to four weeks for people to adjust to the drug.

Interactions

Patients should ask their healthcare provider about all potential drug interactions.

Drugs

A group of serious side effects, referred to collectively as serotonin syndrome, have resulted from the combination of antidepressants such as sertraline and members of another class of antidepressants known as monoamine oxidase inhibitors (MAOIs). Serotonin syndrome usually consists of at least three of the following symptoms: diarrhea, fever, sweatiness, mood

or behavior changes, overactive reflexes, fast heart rate, restlessness, shivering, or shaking. Because of this, sertraline should never be taken in combination with monoamine oxidase inhibitors. Patient taking any MAOIs—for example, Nardil (phenelzine sulfate) or Parnate (tranylcypromine sulfate)—should stop the MAOI and wait at least 14 days before starting sertraline or any other antidepressant. The same holds true when discontinuing sertraline and starting an MAOI. Also, people should not take sertraline oral concentrate while using disulfiram (Antabuse). Sertraline should never be taken by people who are taking any other SSRI antidepressants.

The risk of seizures is increased in patients using **tramadol** and sertraline. **Erythromycin**, an antibiotic, may inhibit the breakdown of sertraline in the liver and cause increased central nervous system effects such as drowsiness and decreased mental alertness. Other antidepressants should not be taken by people using sertraline except in rare cases where prescribed by a physician. If a combination of antidepressants is considered beneficial, a low dose of tricyclic antidepressants (10–25 mg daily) should be used.

Herbs and supplements

Sertraline interacts with St. John's wort, an herbal remedy for depression.

Food and other substances

Sertraline should not be taken with grapefruit juice as the combination may increase sertraline levels in the body.

Resources

BOOKS

Stern, T. A., et al. *Massachusetts General Hospital Comprehensive Clinical Psychiatry*. 2nd ed. Philadelphia: Elsevier, 2015.

PERIODICALS

- Bérard, A., J. P. Zhao, and O. Sheehy. "Sertraline Use during Pregnancy and the Risk of Major Malformations." *American Journal of Obstetrics & Gynecology* (January 28, 2015): e-pub ahead of print. <http://dx.doi.org/10.1016/j.ajog.2015.01.034> (accessed February 26, 2015).
- Khazaie, H., et al. "Antidepressant-Induced Sexual Dysfunction during Treatment with Fluoxetine, Sertraline, and Trazodone; A Randomized Controlled Trial." *General Hospital Psychiatry* 37, no. 1 (2015): 40–45.

WEBSITES

AHFS Consumer Medication Information. "Sertraline." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a697048.html> (accessed February 26, 2015).

National Alliance on Mental Illness. "Sertraline (Zoloft)." [http://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Sertraline-\(Zoloft\)](http://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Sertraline-(Zoloft)) (accessed February 26, 2015).

National Institute of Mental Health. "Introduction: Mental Health Medications." <http://www.nimh.nih.gov/health/publications/mental-health-medications/index.shtml> (accessed February 26, 2015).

ORGANIZATIONS

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.

National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.

National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

Ajna Hamidovic, PharmD

REVIEWED BY KEVIN GLAZA, RPh

Sildenafil

Definition

Sildenafil citrate increases circulation in the lungs and penis.

Purpose

Sildenafil is used to treat arterial hypertension in the lungs and erectile dysfunction (ED) in men. Though it has not been clinically tested for this purpose, a significant number of men take Viagra in hopes of improving their sexual performance.

Description

By increasing blood flow to the penis during sexual stimulation, men with erectile dysfunction who take sildenafil are able to achieve stronger erections and/or maintain them longer. Erectile dysfunction can be caused by a host of emotional and psychological conditions, metabolic diseases, injuries to blood vessels and/or nerves supplying the penis, and side effects of many medications.

For pulmonary arterial hypertension, sildenafil relaxes the blood vessels in the lung, increasing blood flow and improving exercise tolerance. For this purpose, it is taken more frequently and regularly.



Viagra (sildenafil), 50 mg. (© Cengage Learning®.)

U.S. brand names

Sildenafil is available under the brand names Viagra (for erectile dysfunction) and Revatio (pulmonary arterial hypertension). Viagra is available in 25, 50, and 100 milligram (mg) tablets, and Revatio is available in a 20 mg tablet or as a liquid suspension.

Origins

Sildenafil citrate was originally developed in 1991 to improve circulation to the heart and treat angina, or chest pain. It is not used for that purpose.

Recommended dosage

The recommended starting dose of Viagra for treating erectile dysfunction is 50 mg taken 30–60 minutes prior to sexual activity. If needed, the dose may be decreased to 25 mg or increased to 100 mg. It should not be taken for this purpose more often than once every 24 hours.

For treating pulmonary hypertension, 20 mg of Revatio is taken three times daily.

Geriatric

For men over 85, the recommended dose is 25 mg taken 30–60 minutes prior to sexual activity.

KEY TERMS

Erectile dysfunction (ED)—The consistent inability to achieve or maintain a penile erection.

Pulmonary arterial hypertension—High blood pressure in the veins and arteries of the lungs.

Precautions

Sexual activity can stress the heart. A combination of high blood pressure and/or underlying heart or vascular disease plus Viagra and sexual activity may produce irregular heartbeat, heart attack, stroke, and/or sudden death. Men who experience shortness of breath, dizziness, or chest pain during sexual activity should not take Viagra and should consult a doctor.

Men with deformed penises or who have experienced prolonged or painful erections should discuss these problems with a doctor before taking Viagra.

Men who have recently been ill and/or lost body fluids through vomiting, diarrhea, or sweating are more likely to experience side effects when taking Viagra.

Pediatric

Revatio may sometimes be used in children, but it is not approved by the FDA for this use.

Other conditions and allergies

Men who have stomach, liver, or kidney disease; myeloma; leukemia; or other blood disorders should discuss with a doctor whether or not it is safe to take Viagra.

Men who have circulation problems involving their eyes or vision, or family members with inherited vision problems like retinitis pigmentosa, should discuss these problems with an eye specialist before taking Viagra.

Side effects

Men who experience these symptoms should consult their physician. Side effects may be reduced or eliminated by adjusting the dose of Viagra.

The most common side effects of Viagra are mild headache, flushing of the face, upset stomach, and nasal congestion.

Other side effects of Viagra can be more serious. These include:

- heartburn
- chest pain

- shortness of breath
- nosebleed
- numbness, burning, or tingling in the arms, hands, feet, or legs
- muscle aches
- vision problems, including sudden loss of vision, sensitivity to light, blurred vision, and a blue or green color tinge to vision
- ringing in the ears or sudden decrease or loss of hearing
- itching and burning during urination
- diarrhea
- dizziness or fainting
- rash

Interactions

Many prescription and nonprescription medications, herbs, and nutritional supplements can alter the effects and toxicity of sildenafil. Before taking the drug, men should consult with a healthcare provider and discuss the possible interactions between medications they take and sildenafil.

Drugs

Men who use nitrate medications to treat chest pain, like **isosorbide** or nitroglycerine in any form, should not take sildenafil. These drugs can act together to produce dangerous decreases in blood pressure.

Resources

WEBSITES

- Lexi-Comp. "Sildenafil." Merck Manual Professional Edition. <http://www.merckmanuals.com/professional/lexicomp/sildenafil.html> (accessed February 27, 2015).
- Micromedex. "Sildenafil (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/sildenafil-oral-route/description/drg-20066989> (accessed February 27, 2015).
- UK National Health Service. "Sildenafil Citrate (Sildenafil 20mg Tablets)." <http://www.nhs.uk/medicine-guides/pages/medicineoverview.aspx?condition=High%20blood%20pressure&medicine=sildenafil%20citrate> (accessed February 27, 2015).
- U.S. Food and Drug Administration. "FDA Drug Safety Communication: FDA Clarifies Warning about Pediatric Use of Revatio (Sildenafil) for Pulmonary Arterial Hypertension." <http://www.fda.gov/Drugs/DrugSafety/ucm390876.htm> (accessed February 27, 2015).

ORGANIZATIONS

- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>

James Waun, MD, RPh

REVIEWED BY JAMES WAUN, MD, RPh

Simvastatin

Definition

Simvastatin is a statin drug prescribed to help lower cholesterol.

Purpose

Simvastatin is a statin drug. Statins are drugs that help lower the “bad” (LDL) cholesterol in the body while raising the amount of “good” (HDL) cholesterol. Simvastatin helps reduce cholesterol by blocking an enzyme in the liver called HMG-CoA reductase. This enzyme is needed for the body to create cholesterol and by blocking it, simvastatin reduces the body’s ability to produce cholesterol. This then reduces the amount of cholesterol circulating in the blood. Simvastatin also helps the body reabsorb cholesterol that has already hardened into plaque on the walls of arteries. This can help improve blood flow throughout the body and reduce the risk of heart attack and stroke.

Description

Statin drugs like simvastatin have been widely studied in clinical research trials, and have been overwhelmingly found to be effective at reducing LDL cholesterol levels. They have also been found to significantly reduce the risk of death from cardiac events. Most of the participants in these studies have been men,



Simvastatin, 40 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

as men are more likely to develop cardiovascular disease than women and tend to develop it earlier. However, reviews of women participants in these studies have found that statins are also effective at lowering LDL cholesterol in women and in reducing the risk that they will die from complications of cardiovascular disease.

Simvastatin is available as an oral tablet in 5, 10, 20, 40, and 80 milligram (mg) strengths. The 5 mg tablet is a yellow shield-shaped tablet with MSD 726 imprinted on one side and Zocor imprinted on the other. The 10 mg tablet is a tan oval with MSD 735 imprinted on one side and the other side blank. The 20 mg tablet is also a tan oval and has MSD 740 imprinted on one side. The 40 mg tablet is a red oval with MSD 749 imprinted on one side. The 80 mg tablet is a red capsule-shaped tablet with 543 imprinted on one side and 80 imprinted on the other. The appearance of generic versions of simvastatin vary greatly depending on the manufacturer and strength, but are often white, tan, or red tablets in oval or capsule shapes.

U.S. brand names

Simvastatin is sold by Merck and Company, Inc. under the brand name Zocor. Simvastatin in combination with **sitagliptin** is marketed as Juvisync; simvastatin in combination with ezetimibe is sold as Vytorin; simvastatin in combination with niacin is sold under the brand name Simcor.

International brand names

Simvastatin is manufactured by many different international manufacturers in many strengths and combinations. An extensive list of international brand names for simvastatin is available at <http://www.drugs.com/international/simvastatin.html>. Individuals should not purchase drugs from foreign countries unless they have consulted with their physician.

Origins

Simvastatin was approved by the U.S. Food and Drug Administration (FDA) on July 10, 1998. In June 2006, simvastatin was also approved by the FDA for sale as a generic drug.

Recommended dosage

For most individuals, the initial dosage of simvastatin is between 10 and 20 mg daily and can be adjusted up or down over time, although it should not exceed 40 mg per day for most patients. Individuals at serious risk of coronary heart disease may be started with a dose as high as 40 mg daily. Simvastatin is usually taken once per day in the evening.

KEY TERMS

Cholesterol—A waxy substance made by the liver and also acquired through diet. High levels in the blood may increase the risk of cardiovascular disease.

Cirrhosis—A chronic degenerative disease of the liver, in which normal cells are replaced by fibrous tissue and normal liver function is disrupted. If left untreated, cirrhosis leads to liver failure.

Diabetes—A disease in which insufficient insulin is made by the body (type 1 diabetes) to metabolize sugars or the cells of the body do not respond adequately to insulin circulating in the blood (type 2 diabetes).

LDL cholesterol—Low-density lipoprotein (LDL) cholesterol is the primary cholesterol molecule. High levels of LDL increase the risk of coronary heart disease. LDL is nicknamed “bad cholesterol.”

Plaque—Fatty material that is deposited on the inside of the arterial wall.

Stroke—Irreversible damage to the brain caused by insufficient blood flow to the brain as a result of a blocked artery. Damage can include loss of speech or vision, paralysis, cognitive impairment, and death.

Dosing of simvastatin should be done carefully and may need to be reduced in patients taking certain other medications. When simvastatin is taken with lomitapide, the dose of simvastatin should be reduced by half. When simvastatin is taken with **diltiazem**, the dose should not exceed 10 mg daily. When it is taken with amiodarone, the dose should not exceed 20 mg daily.

Pediatric

Simvastatin is generally not prescribed for children under the age of 10. For children ages 10 to 17, dosage depends on the weight of the child. Dosing is typically started at 10 mg daily and can be increased every four weeks if needed. For children in this age group total dose should not exceed 40 mg daily.

Geriatric

Dosing in the elderly should generally be conservative as this group may be at increased risk for serious side effects. Smaller doses can be used at first, and increased after four weeks if the individual is tolerating it well and cholesterol levels have not improved sufficiently.

Other conditions and allergies

Individuals with certain risk factors such as serious kidney (renal) disease are usually started with a dose of 5 mg daily.

Precautions

Simvastatin can cause liver damage and exacerbate existing liver problems. Simvastatin may cause increased blood sugar levels, which may be dangerous in individuals with diabetes. Individuals with kidney disease should be very cautious about taking simvastatin. Heavy alcohol use in combination with simvastatin can lead to serious liver problems. However, recent evidence suggests that statins may be safe for use in patients with cirrhosis.

Pediatric

Simvastatin has not been established to be safe for children under 10 years of age, although there also does not exist specific evidence that it harms children in this age group. Children age 10 to 17 should be monitored carefully for side effects. There is little data on the long-term effects of simvastatin in children and it should generally be prescribed only in situations in which the benefits are clear, and in which lifestyle and diet changes are not sufficiently effective in reducing cholesterol levels.

Geriatric

Elderly individuals may be at an increased risk for side effects from simvastatin, especially side effects related to muscle soreness and weakness. There is also some evidence that simvastatin and other statins may increase the risk of liver problems in elderly patients and may lead to memory issues. The Society for Post-Acute and Long-Term Care Medicine recommended that healthcare providers consider carefully before prescribing statins to anyone over the age of 70 due to the potential for serious side effects in individuals in this age group and the lack of evidence that this class of drugs helps individuals in this age group.

Pregnant or breastfeeding

Simvastatin is a pregnancy class X drug. This means that there is strong evidence that the drug harms the fetus during development if it is taken by pregnant women. Simvastatin should not be taken during pregnancy because the risks to the fetus outweigh any potential benefits, and there are safer alternatives. No evidence exists about the risks of taking simvastatin while breastfeeding, but it is strongly recommended against because of the potential risks to the baby.

PATIENT PROFILE

A 60-year-old woman was found to have markedly increased levels of cholesterol in her blood. She had visited her doctor because of concern about her increased weight after menopause and her inability to lose it. The doctor first ordered a series of blood tests to evaluate her overall health status and to make sure she did not have diabetes or another chronic condition. Although her blood sugar (blood glucose) was slightly higher than normal, it did not indicate prediabetes. However, her blood lipids, including total cholesterol, high-density and low-density cholesterol, and triglycerides were almost all higher than normal. Her blood pressure was also higher than normal and, given her high cholesterol, could indicate narrowing of the blood vessels due to accumulated plaque (atherosclerosis). Her doctor prescribed a statin drug, simvastatin (Zocor), which could help to reduce cholesterol levels and also blood pressure.

The starting dose of simvastatin was a 10 mg tablet taken once a day in the evening. The patient returned to the doctor's office after four weeks of treatment, and laboratory tests revealed that total cholesterol and low-density lipoprotein (LDL) cholesterol were reduced, but not significantly. Continued treatment would be needed, and her doctor increased her dosage of simvastatin to 40 mg per day to try and achieve more significant cholesterol reduction. The doctor also recommended that the patient modify her diet, eating a low-fat, low-sugar diet of mainly vegetables and whole grains with small portions of lean meat and white fish. Regular

physical exercise was also advised, which could include non-weight-bearing exercise such as swimming, walking, or yoga. These measures would supplement the action of simvastatin in lowering cholesterol and also would likely help with weight loss.

Soon after taking the increased dose of simvastatin, the patient reported having pain in her legs, arms, and shoulders. She described that her arms and legs felt sore and weak, and the pain was relatively consistent. When her doctor ordered more blood tests, it was discovered that the patient had a mild increase in a blood chemical called creatine kinase, which was a side effect of simvastatin known to contribute to muscle symptoms in some patients. However, the doctor advised that this could be temporary and that the patient should continue with simvastatin for another few weeks, at which time the creatine kinase would be measured again. In the meantime, he suggested taking acetaminophen to relieve the muscle pain. The subsequent blood test for creatine kinase showed no additional increase and the doctor concluded that it was a mild, transient reaction to simvastatin and was not associated with the patient's symptoms. After three months of treatment with the higher dose of simvastatin (40 mg per day), accompanied by dietary changes and exercise, the patient's cholesterol was approaching normal levels, she had lost eight pounds, and she no longer complained of muscle pain, soreness, or weakness. Nevertheless, the doctor ordered regular laboratory tests to monitor both cholesterol levels and creatine kinase during her course of simvastatin.

Other conditions and allergies

Simvastatin should not be prescribed for individuals who have acute liver disease.

Side effects

In very rare cases, allergic reaction to simvastatin may occur. Individuals who experience rash or hives; swelling of the throat, face, neck, or mouth; severe dizziness; or difficulty breathing should seek emergency medical attention immediately.

Individuals who experience any of the following side effects should stop taking simvastatin and promptly call their healthcare provider:

- faintness
- fast heartbeat
- irregular heartbeat or palpitations
- dizziness
- blurred vision

- blood in urine or very dark urine
- difficulty breathing
- difficulty moving the limbs or body
- persistent vomiting
- yellowing skin or eyes
- severe stomach pain or abdominal cramping

Common but less serious side effects include:

- nausea
- constipation
- fatigue
- indigestion
- diarrhea
- muscle soreness
- muscle weakness

Interactions

Individuals should tell their doctor and pharmacist about all medications, including prescription medications, over-the-counter medications, herbs, supplements, and vitamins, that they are taking. The doctor or pharmacist can check a complete and up-to-date list of known interactions to ensure that the patient takes simvastatin as safely as possible.

Drugs

Simvastatin should not be taken with a class of drugs known as CYP3A4 inhibitors (e.g., nefazodone, telaprevir, **ketoconazole**) or with HIV protease inhibitors. It should also not be taken with **cyclosporine**, danazol, or **gemfibrozil**. Simvastatin may also cause serious interactions with certain antibiotics, including **erythromycin**, heart medications, blood thinners such as **warfarin**, medications used to treat hepatitis C, and medications used to treat HIV and AIDS.

Other drugs may interact with simvastatin.

Food and other substances

Patients who are taking simvastatin should not consume grapefruit juice, raw grapefruit, or grapefruit products. Grapefruit juice may increase the amount of simvastatin that the body absorbs, leading to a serious or fatal overdose or serious side effects. Some sources also recommend that patients taking simvastatin avoid cranberry juice. Individuals taking simvastatin should also avoid red yeast rice and related products because such products contain another substance similar to simvastatin, increasing the risk of serious side effects and overdose.

Resources

BOOKS

- Lesslie, Robert D. *60 Ways to Lower Your Cholesterol*. Eugene, OR: Harvest House, 2015.
- Roberts, Barbara H. *The Truth about Statins: Risks and Alternatives to Cholesterol-Lowering Drugs*. New York: Gallery Books, 2012.

Resources

PERIODICALS

- Kellick, Kenneth, A., et al. "A Clinician's Guide to Statin Drug-Drug Interactions." *Journal of Clinical Lipidology*. 8, no. 3 (2014): S30–S46.
- Pisani, Mara, et al. "Is Simvastatin Harmful in Children? A Case Report." *International Journal of Pharmacological Research*. 4, no. 3 (2014): 148–52.
- Zarek, Judith, et al. "The Fetal Safety of Statins: A Systematic Review and Meta-Analysis." *Journal of Obstetrics and Gynecology Canada* 36, no. 5 (2014): 506–9.

Resources

WEBSITES

- American Heart Association. "Good vs. Bad Cholesterols." Available from: http://www.heart.org/HEARTORG/Conditions/Cholesterol/AboutCholesterol/Good-vs-Bad-Cholesterol_UCM_305561_Article.jsp (accessed January 14, 2015).
- MedlinePlus. "Simvastatin." Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a692030.html> (accessed January 14, 2015).
- Micromedex. "Simvastatin (Oral Route)." Available from: <http://www.mayoclinic.org/drugs-supplements/simvastatin-oral-route/description/drg-20069006> (accessed January 14, 2015).
- U.S. Food and Drug Administration. "Simvastatin Information." Available from: <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm203669.htm> (accessed January 14, 2015).

ORGANIZATIONS

- American College of Cardiology, Heart House, 2400 N Street, NW, Washington, DC 20037, (202) 375-6000 ext. 5603, (800) 253-4636 ext. 5603, Fax: (202) 375-7000, resource@acc.org, <http://www.acc.org/>.
- American Heart Association National Center, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.
- National Heart Lung and Blood Institute Health Information Center, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, Fax: (301) 592-8563, nhlbiinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Tish Davidson, AM

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Sinemet see **Carbidopa/levodopa**

Sinequan see **Doxepin**

Singulair see **Montelukast**

Sitagliptin

Definition

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor used for the management of type 2 diabetes. It works to lower the blood sugar (glucose) and does so by increasing the amount of insulin released by the body and decreasing the amount of sugar made by the body.



Januvia (sitagliptin), 25 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Patients who have had trouble controlling their blood sugar levels by diet and exercise alone may benefit from the addition of this medication to their diabetes regimen.

Purpose

Sitagliptin is used for patients with type 2 diabetes, also known as non-insulin-dependent diabetes. Type 2 diabetes is a condition in which the body's cells become insulin resistant and do not properly utilize the insulin being synthesized and secreted by the pancreas. In the beginning stages, the pancreas increases insulin production in response to the increased demand. However, as the disease progresses, the pancreas loses the ability to secrete sufficient insulin in response to meals.

Type 2 diabetes may proceed for long periods of time with no symptoms. When diabetes is present, symptoms include the following:

- increased thirst, especially for sweet beverages
- increased urination
- increased appetite
- fatigue
- blurred vision
- frequent or slow-healing infections (including urinary tract, vaginal, skin)
- dry, itchy skin
- tingling or numbness in hands or feet
- erectile dysfunction in men

Sitagliptin is not for use by patients with type 1 diabetes or who have a history of high blood ketone levels (diabetic ketoacidosis).

Description

Sitagliptin is available as a tablet and is to be taken by mouth (orally). It may be used alone or in conjunction with other medications in the management of type 2 diabetes. Along with the use of sitagliptin, general diabetes treatment may include regular doctor visits for an evaluation of general health and neurological function; regular blood tests to evaluate overall blood glucose control; regular evaluation of blood pressure, cholesterol, and triglyceride levels; annual eye examinations; dental examinations and cleanings every six months; daily foot inspections; and current immunizations. Diabetes education is critical to the treatment plan. Changes or modification in diet and exercise also usually accompany use of this medication.

Medications that contain sitagliptin in combination with an additional medication include Janumet (contains sitagliptin and **metformin**) and Juvisyne (contains sitagliptin and **simvastatin**).

U.S. brand names

Sitagliptin is sold under the brand name Januvia. It is offered by prescription only.

Recommended dosage

Sitagliptin comes in 25, 50, and 100 milligram (mg) tablets. This medication is taken once daily and may be taken with or without food. It is recommended that this medication be taken at the same time each day.

Sitagliptin tablets should be taken whole and not crushed, broken, or chewed. Breaking down the pill can result in an inconsistent or unpredictable amount of the medication entering the bloodstream at one time.

Geriatric

Dosing should be done conservatively in seniors as they may be more sensitive to the effects of this medication. Seniors should be monitored closely and given the lowest effective dosage.

Other conditions and allergies

Dose adjustments may be made for patients who have liver (hepatic) or kidney (renal) problems. The dose will generally be lower for patients in these groups. All patients taking sitagliptin should be monitored closely and the dosage should be re-evaluated regularly.

KEY TERMS

Diabetes mellitus—Disease characterized by the inability of the body to produce or respond properly to insulin, required by the body to convert glucose to energy.

Glucose—The type of sugar found in the blood.

Hypoglycemia—Abnormally low levels of blood glucose.

Ketoacidosis—Condition that results in untreated diabetes from the body's attempt to burn fat for fuel when carbohydrates cannot be utilized. Ketones, the byproduct of fat metabolism, enter the bloodstream and make the blood more acidic than the body's tissues.

Precautions

Patients should be aware that sitagliptin helps control type 2 diabetes by controlling high blood sugar. It does not, however, cure type 2 diabetes. Patients should check their blood sugar regularly, as prescribed by their doctor.

Development of a fever or infection may affect blood sugar, necessitating a dose change of sitagliptin. Patients should tell their doctor if they are feeling ill or have been prescribed medication for an infection, as they may also need to make a temporary change in their daily sitagliptin regimen.

Sitagliptin may cause a change in kidney function, increasing serum creatinine levels, so special caution should be taken for use in patients who have poor kidney function.

Pediatric

Sitagliptin is not used for treatment in children.

Geriatric

Seniors are at an increased risk of side effects from sitagliptin and should be monitored closely. Seniors may take a number of other medications that may interact with sitagliptin, so the use of all medications and supplements should be discussed with a healthcare provider.

Pregnant or breastfeeding

Sitagliptin is considered a class B pregnancy drug, which means that although no adequate and well-controlled studies have been performed in pregnant women, animal studies have not shown evidence of fetal

risk. Patients should tell their doctor if they are pregnant or plan to become pregnant.

It is not known whether or not this drug passes into breast milk. Women should tell their doctor if they are breastfeeding their baby.

Other conditions and allergies

Sitagliptin should be used with caution in patients who have a history of pancreas or gallbladder problems, alcoholism, or high triglyceride levels.

Side effects

In some cases, allergic reactions to sitagliptin have occurred. Any patient who experiences symptoms of an allergic reaction, including swelling of the lips, throat, mouth or face; difficulty breathing; hives; or rash, should seek emergency medical attention immediately.

Sitagliptin may cause mild to serious side effects, which include:

- sore throat
- nasal congestion
- upper respiratory infection
- diarrhea
- headache

Sitagliptin may cause severe inflammation to the pancreas, which may be life-threatening.

Patients should seek emergency medical assistance if any of the following symptoms occur:

- ongoing abdominal pain
- ongoing back pain
- nausea and vomiting
- loss of appetite due to abdominal pain or nausea and vomiting
- signs of dehydration such as little or no urine output

Interactions

Some medications may cause serious interactions with sitagliptin. The patient should tell his or her doctor and pharmacist about all prescription medications, over-the-counter medications, vitamins, herbs, and supplements that he or she is taking. It may be necessary to stop taking some medications or switch to different medications to reduce the chance of interactions with sitagliptin.

Drugs

Sitagliptin should be used with caution in patients who are taking **digoxin**, as digoxin toxicity has been reported when these drugs are used concomitantly.

Sitagliptin should be used with caution in patients who are taking insulin or a sulfonylurea medication, as there is a higher incidence of hypoglycemia when these drugs are used concomitantly.

Use of steroids may alter blood sugar, necessitating a dose change of sitagliptin. Patients taking steroids should be sure to discuss potential changes in their daily sitagliptin regimen.

Food and other substances

Patients taking sitagliptin should not consume alcohol as alcohol may alter blood glucose levels in patients with type 2 diabetes.

Resources

BOOKS

- Bryer-Ash, Michael. *100 Questions & Answers about Diabetes*. Sudbury, MA: Jones & Bartlett, 2010.
- Kasper, Dennis, et al. *Harrison's Principles of Internal Medicine*. 19th ed. New York: McGraw-Hill Professional, 2015.

PERIODICALS

- Engel, Samuel S., et al. "Safety and Tolerability of Sitagliptin in Type 2 Diabetes: Pooled Analysis of 25 Clinical Studies." *Diabetes Therapy* 4, no. 1 (2013): 119–45.
- Eurich, D. T., et al. "Comparative Safety and Effectiveness of Sitagliptin in Patients with Type 2 Diabetes: Retrospective Population-Based Cohort Study." *BMJ* 346 (April 25, 2013) <http://dx.doi.org/10.1136/bmj.f2267> (accessed March 11, 2015).

WEBSITES

- American Diabetes Association. "Oral Medications: What Are My Options?" <http://www.diabetes.org/living-with-diabetes/treatment-and-care/medication/oral-medications/what-are-my-options.html> (accessed March 11, 2015).
- MedlinePlus. "Diabetes." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/diabetes.html> (accessed March 11, 2015).
- U.S. National Library of Medicine. "Januvia–Sitagliptin Phosphate Tablet, Film Coated." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f85a48d0-0407-4c50-b0fa-7673a160bf01> (accessed March 11, 2015).

ORGANIZATIONS

- American Diabetes Association, 1701 North Beauregard Street, Alexandria, VA 22311, (800) DIABETES (342-2383), <http://www.diabetes.org/>.
- National Diabetes Information Clearinghouse, 1 Information Way, Bethesda, MD 20892-3560, (800) 860-8747, <http://diabetes.niddk.nih.gov/>.

Laura Jean Cataldo, RN, EdD
REVIEWED BY GREGORY A. PRATT, RPH

Sitagliptin/metformin

Definition

Sitagliptin/metformin is a medication used for the management of type 2 diabetes. It is a combination of the drugs **sitagliptin** and **metformin**. Sitagliptin (a dipeptidyl peptidase-4 [DPP-4] inhibitor) works to lower the blood sugar (glucose) by increasing the amount of insulin released by the body and decreasing the amount of sugar made by the body. Metformin (an oral antihyperglycemic agent) works by lowering sugar production in the liver and lowering the absorption of sugar by the intestines.

Purpose

Type 2 diabetes, also known as non-insulin-dependent diabetes, is a condition in which the body's cells become insulin resistant and do not properly utilize the insulin being synthesized and secreted by the pancreas. In the beginning stages, the pancreas increases insulin production in response to the increased demand. However, as the disease progresses, the pancreas loses the ability to secrete sufficient insulin in response to meals.

Type 2 diabetes may proceed for long periods of time with no symptoms. When diabetes is present, symptoms include:

- increased thirst, especially for sweet beverages
- increased urination



Janumet (sitagliptin/metformin), 50 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Diabetes mellitus—Disease characterized by the inability of the body to produce or respond properly to insulin, required by the body to convert glucose to energy.

Glucose—The type of sugar found in the blood.

Hyperglycemia—Abnormally high levels of blood glucose.

Hypoglycemia—Abnormally low levels of blood glucose.

Ketoacidosis—Condition that results in untreated diabetes from the body's attempt to burn fat for fuel when carbohydrates cannot be utilized. Ketones, the byproduct of fat metabolism, enter the bloodstream and make the blood more acidic than the body's tissues.

Lactic acidosis—Condition that results when lactic acids builds up in the bloodstream faster than it can be removed. Occurs when oxygen levels in the body drop causing a decrease in tissue oxygenation and a buildup of lactate in the blood.

- increased appetite
- fatigue
- blurred vision
- frequent or slow-healing infections (including urinary tract, vaginal, skin)
- dry, itchy skin
- tingling or numbness in hands or feet
- erectile dysfunction in men

Patients who have had trouble controlling their blood sugar levels by diet and exercise alone may benefit from the addition of this medication to their diabetes regimen. It is not for use by patients with type 1 diabetes or who have a history of high blood ketone levels (diabetic ketoacidosis).

Description

Sitagliptin/metformin is available as a tablet and is to be taken by mouth (orally). It may be used alone or in conjunction with other medications in the management of type 2 diabetes. Along with the use of medication, general diabetes treatment may include regular doctor visits for an evaluation of general health and neurological function; regular blood tests to evaluate overall blood glucose control; regular evaluation of blood pressure, cholesterol, and triglyceride levels; annual eye

examinations; dental examinations and cleanings every six months; daily foot inspections; and current immunizations. Diabetes education is critical to the treatment plan. Changes or modifications in diet and exercise usually accompany use of this medication.

U.S. brand names

Sitagliptin/metformin is sold under the brand name Janumet. It is offered by prescription only.

Recommended dosage

Sitagliptin/metformin comes in immediate-release and extended-release tablets containing sitagliptin (dose range of 50–100 milligrams [mg]) and metformin (dose range of 500–1,000 mg) per tablet. Patients who were already taking metformin alone will begin sitagliptin/metformin with doses adjusted accordingly. This medication is taken one or two times daily and should be taken with food. It is recommended that this medication be taken at the same time each day.

Sitagliptin/metformin tablets should be taken whole and not crushed, broken, or chewed. Breaking down the pill can result in an inconsistent or unpredictable amount of the medication entering the bloodstream at one time.

All patients taking sitagliptin/metformin should be monitored closely and the dosage should be re-evaluated regularly.

Geriatric

Dosing should be done conservatively in seniors as they may be more sensitive to the effects of this medication. Seniors should be monitored closely and given the lowest effective dosage.

Other conditions and allergies

Dose adjustments may be made for patients who have liver (hepatic) or kidney (renal) problems. The dose will generally be lower for patients in these groups.

Precautions

Patients should be aware that sitagliptin/metformin helps control type 2 diabetes by controlling high blood sugar. It does not, however, cure type 2 diabetes. Patients should check their blood sugar regularly, as prescribed by their doctor.

Sitagliptin/metformin may cause a change in kidney function, increasing serum creatinine levels. It can cause severe inflammation in the pancreas, which can be life-threatening. The drug may also cause lactic acidosis due to metformin accumulation. Lactic acidosis can be

serious or life-threatening. In the event of lactic acidosis, the patient should be hospitalized and the medication should be stopped immediately. Patients taking sitagliptin/metformin should have blood tests performed regularly to evaluate kidney and liver function.

Patients taking sitagliptin/metformin who are undergoing certain x-rays or a computed tomography (CT) scan will need to stop taking this medication temporarily before and after the scan. Patients should be sure to tell the radiology technician that they are taking this medication prior to their procedure.

Pediatric

Sitagliptin/metformin is not used for treatment in children.

Geriatric

Seniors are at an increased risk of side effects from sitagliptin and should be monitored closely.

Pregnant or breastfeeding

Sitagliptin/metformin is considered a class B pregnancy drug, which means that although no adequate and well-controlled studies have been performed in pregnant women, animal studies have not shown evidence of fetal risk. Patients should tell their doctor if they are pregnant or plan to become pregnant.

It is not known whether or not this drug passes into breast milk. Women should tell their doctor if they are breastfeeding.

Other conditions and allergies

Due to an increased risk of lactic acidosis, sitagliptin/metformin is contraindicated in patients with the following conditions:

- kidney dysfunction
- liver dysfunction
- unstable or acute congestive heart failure (CHF)
- acute myocardial infarction (heart attack)
- severe dehydration
- severe anemia

Sitagliptin/metformin should be used with caution in patients who have a history of pancreatitis, pancreas or gallbladder problems, alcoholism, or high triglyceride levels.

Side effects

In some cases, allergic reactions to sitagliptin/metformin have occurred. Any patient who experiences symptoms of an allergic reaction, including swelling of

the lips, throat, mouth or face; difficulty breathing; hives; or rash, should seek emergency medical attention immediately.

Sitagliptin/metformin may cause mild to serious side effects, including:

- sore throat
- nasal congestion
- upper respiratory infection
- nausea, vomiting, diarrhea
- headache
- leg or ankle swelling (edema)
- gas and bloating
- decrease in vitamin B₁₂ absorption leading to anemia

Vitamin B₁₂ supplementation may be necessary for some patients taking sitagliptin/metformin. Blood tests should be done to evaluate the patient for anemia or other blood disorders.

Patients should seek emergency medical assistance if any of the following symptoms occur:

- ongoing abdominal pain
- ongoing back pain
- nausea and vomiting
- loss of appetite due to abdominal pain or nausea and vomiting
- signs of dehydration such as little or no urine output
- shortness of breath
- dizziness
- muscle pain
- numbness or weakness in the arms or legs

Interactions

Patients should tell their doctor and pharmacist about all prescription medications, over-the-counter medications, vitamins, herbs, and supplements they are taking. It may be necessary to stop taking some medications or switch to different medications to reduce the chance of interactions with sitagliptin/metformin.

Drugs

Some medications may cause potentially serious interactions with sitagliptin/metformin. Some of these medications include:

- **topiramate** (Topamax)
- **morphine**
- procainamide (Pronestyl)
- vancomycin
- cimetidine (Tagamet)

- **furosemide** (Lasix)
- **nifedipine** (Adalat, Procardia)
- **NSAIDs** (such as Aleve, Celebrex, Indocin, Motrin)

Sitagliptin/metformin should be used with caution in patients who are taking **digoxin**, as digoxin toxicity has been reported when these drugs are used concomitantly.

Sitagliptin/metformin should be used with caution in patients who are taking insulin or a sulfonylurea medication, as there is a higher incidence of hypoglycemia when these drugs are used concomitantly.

Food and other substances

Individuals taking sitagliptin/metformin should not use alcohol.

Resources

BOOKS

- Bryer-Ash, Michael. *100 Questions & Answers about Diabetes*. Sudbury, MA: Jones & Bartlett, 2010.
- Kasper, Dennis, et al. *Harrison's Principles of Internal Medicine*. 19th ed. New York: McGraw-Hill Professional, 2015.

PERIODICALS

- Engel, Samuel S., et al. "Safety and Tolerability of Sitagliptin/Metformin in Type 2 Diabetes: Pooled Analysis of 25 Clinical Studies." *Diabetes Therapy* 4, no. 1 (2013): 119–145.
- Onge, Erin L., et al. "Sitagliptin/Metformin (Janumet) as Combination Therapy in the Treatment of Type-2 Diabetes Mellitus." *Pharmacy and Therapeutics* 37, no. 12 (2012): 699.
- Reasner, C., et al. "The Effect of Initial Therapy with the Fixed-Dose Combination of Sitagliptin and Metformin Compared with Metformin Monotherapy in Patients with Type 2 Diabetes Mellitus." *Diabetes, Obesity and Metabolism* 13, no. 7 (2011): 644–52.

WEBSITES

- American Diabetes Association. "Oral Medications: What Are My Options?" <http://www.diabetes.org/living-with-diabetes/treatment-and-care/medication/oral-medications/what-are-my-options.html> (accessed March 11, 2015).
- MedlinePlus. "Diabetes." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/diabetes.html> (accessed March 11, 2015).
- U.S. National Library of Medicine. "JANUMET—Sitagliptin Phosphate and Metformin Hydrochloride Tablet, Film Coated." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d19c7ed0-ad5c-426e-b2df-722508f97d67> (accessed January 26, 2015).

ORGANIZATIONS

- American Diabetes Association, 1701 North Beauregard Street, Alexandria, VA 22311, (800) DIABETES (342-2383), <http://www.diabetes.org/>.

National Diabetes Information Clearinghouse, 1 Information Way, Bethesda, MD 20892-3560, (800) 860-8747, <http://diabetes.niddk.nih.gov/>.

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REVIEWED BY GREGORY A. PRATT, RPh

Skelaxin see **Metaxalone**

Sofosbuvir

Definition

Sofosbuvir is an oral antiviral drug that is used in combination with other antiviral drugs to cure chronic infection with the hepatitis C virus (HCV). Sofosbuvir is in a class of direct-acting antiviral medications called nucleotide polymerase inhibitors.

Purpose

Sofosbuvir is a breakthrough drug—a single once-daily pill with relatively mild side effects—that appears to cure more than 90% of infections with common HCV strains in as little as eight to twelve weeks. HCV, discovered in 1989, can cause liver damage and cirrhosis and is a leading cause of liver cancer. The virus is believed to infect at least 150 million people worldwide—almost five times the number of people infected with HIV. Although HCV kills more Americans than HIV/AIDS, about half of the



Bottle of Solvaldi (sofosbuvir), 400 mg. (Tribune Content Agency LLC/Alamy)

3–4 million infected Americans are unaware of their infections. Until the introduction of sofosbuvir and other new drugs, the only treatment for HCV was 48 weeks of precise dosing with the broad-spectrum antiviral ribavirin along with weekly injections of interferon. These drugs have severe side effects that are tolerated by less than half of HCV patients, and they frequently fail to cure the infection.

Sofosbuvir is never used alone; it is always used in combination with other antiviral agents, such as ledipasvir, simeprevir, or ribavirin and sometimes peginterferon alfa. It is used with ribavirin for patients with HCV and liver cancer who are awaiting a liver transplant and to decrease the risk of re-infection following the transplant. In a clinical trial combining sofosbuvir and ledipasvir, 99% of patients were cleared of HCV after 12 weeks. The success rate was over 95% in patients with the difficult-to-treat HCV type 1 genotype. Virtually 100% of patients with cirrhosis, for whom previous treatments had failed, were virus-free after 24 weeks of treatment. Success rates in patients co-infected with HCV and HIV are comparable to those in patients without HIV previously. HCV infections in HIV-infected patients were very hard to treat. Although sofosbuvir is only approved by the U.S. Food and Drug Administration (FDA) for treating HCV genotypes 1–4, it appears to be effective against all HCV genotypes. Furthermore, sofosbuvir:

- has few adverse effects
- is effective in patients with or without previous treatment
- is safe and effective for seriously at-risk patients, including those with HIV co-infection, advanced liver disease, and liver cancer
- has only minimal interactions with other drugs
- has no meal restrictions

Description

Sofosbuvir is a “prodrug” that is rapidly converted in the body to a molecule called GS-331007, which accounts for more than 90% of the active circulating drug. GS-331007 is efficiently taken up by liver cells, where cellular enzymes convert it to an analog of uridine triphosphate, a normal component of RNA (the HCV genetic material). When the analog is incorporated into the HCV RNA in place of the normal nucleotide, it prevents the viral polymerase enzyme from continuing to copy the RNA, thereby preventing the virus from replicating (copying itself). Because the drug does not inhibit host DNA or RNA polymerases, side effects are minimized. Furthermore, it is very difficult for the virus to develop resistance to sofosbuvir.

The sofosbuvir treatment regimen depends on:

- the HCV genotype
- the subtype, such as type 1a or 1b
- previous treatments
- the stage of liver disease, such as cirrhosis
- other medical issues

Recommended treatment regimens for patients with chronic HCV mono-infection or HCV/HIV-1 co-infection include:

- genotypes 1 or 4: sofosbuvir plus peginterferon-alfa plus ribavirin for 12 weeks
- genotype 1 in interferon-ineligible patients: sofosbuvir plus ribavirin for 24 weeks
- genotype 2: sofosbuvir plus ribavirin for 12 weeks
- genotype 3: sofosbuvir plus ribavirin for 24 weeks
- patients without cirrhosis: simeprevir and sofosbuvir for 12 weeks
- patients with cirrhosis: simeprevir and sofosbuvir for 24 weeks
- chronic HCV mono-infection in patients with hepatocellular carcinoma awaiting liver transplantation: sofosbuvir plus ribavirin for up to 48 weeks or until the transplantation, whichever occurs first, for preventing post-transplant re-infection

The guidelines of the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America further recommend sofosbuvir plus peginterferon plus ribavirin for genotypes 1, 4, 5, and 6 and sofosbuvir plus simeprevir with or without ribavirin for genotypes 1, 4, 5, and 6 in interferon-ineligible patients.

U.S. brand names

Sofosbuvir is sold under the brand name Sovaldi.

Origins

Sofosbuvir was first approved by the FDA in December 2013 as a component of HCV combination therapy. Sofosbuvir plus ribavirin was the first FDA-approved all-oral therapy for HCV. In October 2014, the FDA approved a single pill combining sofosbuvir and ledipasvir (Harvoni) for chronic HCV genotype 1: the first approved regimen with neither interferon nor ribavirin. In November 2014, the FDA approved simeprevir in combination with sofosbuvir for chronic HCV genotype 1.

The introduction of sofosbuvir was accompanied by controversy because its initial price was set at \$80,000–\$90,000 for 12 weeks (about \$1,000 per pill) in addition

KEY TERMS

Cirrhosis—Liver damage and destruction, usually caused by hepatitis infection or chronic alcohol abuse.

Genotype—The genetic composition of an organism; there are different genotypes of the hepatitis C virus that may require different treatments.

GS-331007—The circulating metabolite of sofosbuvir that is taken up by liver cells and converted to the active drug.

Harvoni—The brand name of the sofosbuvir/ledipasvir combination tablet.

Hepatitis C virus (HCV)—A single-stranded RNA virus that causes liver disease.

Ledipasvir—A drug used in combination with sofosbuvir to treat hepatitis C.

Nucleotide polymerase inhibitor—A drug, such as sofosbuvir, that is similar (an analog) to a component of RNA or DNA and inhibits the polymerase enzyme that synthesizes the genetic material.

Peginterferon alfa—Pegylated interferon; an antiviral drug used in combination with sofosbuvir for treating hepatitis C.

Ribavirin—An antiviral drug used in combination with sofosbuvir for treating hepatitis C.

Simeprevir—An antiviral drug used in combination with sofosbuvir for treating hepatitis C.

Sovaldi—The brand name for sofosbuvir.

to the costs of the other required medication(s). Thus, 24 weeks of treatment with sofosbuvir plus ribavirin for an interferon-ineligible patient would cost \$168,000. Sofosbuvir prices in Europe are also high, but lower than in the United States. Although drugs similar to sofosbuvir are in development, these are expected to be priced similarly high. Some private U.S. insurers are covering sofosbuvir, but others may limit coverage to only the sickest patients. Gilead Sciences, the California-based manufacturer of Sovaldi, offers an assistance program for eligible patients. With approximately 90% of HCV infections in low- or middle-income countries, sofosbuvir will be made available in such countries at far lower cost. In 2014, Gilead was planning to license several Indian companies to manufacture sofosbuvir at prices of about \$2,000 for six months of treatment. Similar arrangements are expected for other low- and middle-income countries.

Sofosbuvir is supplied as a 400 mg tablet. Harvoni is supplied as a single tablet of 400 mg sofosbuvir and 90 mg ledipasvir.

Recommended dosage

The recommended dosage of sofosbuvir is 400 mg once a day, regardless of the drug combination used, HCV genotype, or prior treatment. It is taken with or without food at about the same time every day. A missed dose should be taken on the same day; otherwise, the missed dose should be skipped and the regular dosing schedule resumed. The entire sofosbuvir course must be taken, even if symptoms disappear. Sofosbuvir should be stored at room temperature, away from excess heat and moisture (not in the bathroom).

Geriatric

No dose adjustment is necessary for geriatric patients.

Other conditions and allergies

No dose adjustment is required for mild-to-moderate kidney impairment or mild, moderate, or severe liver impairment.

Precautions

Sofosbuvir may not prevent the transmission of HCV. HCV is most often spread by sharing needles or syringes to inject drugs, needle pricks in healthcare settings, or birth to an infected mother. Less often, it can be spread through sexual contact or sharing items that have come in contact with infected blood. Before widespread screening began in 1992, HCV was commonly spread through blood transfusions and organ transplants.

Pediatric

The safety and effectiveness of sofosbuvir have not been established for children under age 18.

Geriatric

The response rates to sofosbuvir are similar in patients over age 65 and younger patients in all treatment groups.

Pregnant or breastfeeding

Sofosbuvir is in the FDA pregnancy category B, meaning there is no data on its usage by pregnant women, although no effects on fetal development have been observed in animal studies. However, sofosbuvir with ribavirin or peginterferon alfa/ribavirin is in

pregnancy category X, meaning that ribavirin may cause birth defects and fetal death, and interferons may cause abortion. Women taking these combination drugs and female partners of male patients must have a negative pregnancy test prior to the start of therapy, use at least two forms of effective contraception during treatment and for six months following treatment, and have monthly pregnancy tests during and after treatment. Hormonal contraceptives, including birth control pills, patches, implants, rings, and injections, may not work effectively in women taking these medications.

It is not known if sofosbuvir or its metabolites are present in human breast milk. GS-331007 was the primary drug in milk of lactating rats and had no effect on the nursing pups. However, because of potential harm to nursing infants from ribavirin, women must decide whether to breastfeed or be treated with ribavirin-containing regimens.

Other conditions and allergies

The doctor and pharmacist should be informed of allergies to sofosbuvir, any ingredients in sofosbuvir tablets, or any other medications. The doctor should be informed if the patient has or has ever had:

- a liver transplant
- HIV
- kidney disease
- liver disease other than HCV

Side effects

Sofosbuvir and simeprevir without ribavirin are generally well-tolerated. The most common side effects with sofosbuvir in combination with ribavirin are headache and fatigue, occurring in at least 20% of patients. The most common side effects of sofosbuvir with peginterferon alfa and ribavirin are fatigue, headache, nausea, insomnia, and anemia (low red blood cells).

The doctor should be notified if any of the following symptoms are severe or persistent:

- nausea
- diarrhea
- headache
- muscle pain
- difficulty falling asleep or staying asleep
- loss of appetite
- irritability
- itching
- rash

The following side effects require notifying the doctor immediately:

- pale skin
- dizziness
- shortness of breath
- tiredness
- weakness
- sore throat, fever, chills, and other signs of infection
- depression
- changes in mood or behavior
- thoughts of harming or killing oneself

Interactions

It is important that the doctor and pharmacist be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

The following medications should not be used with sofosbuvir because they can significantly lower sofosbuvir levels or may require significant monitoring for side effects:

- the anticonvulsants **carbamazepine**, oxcarbazepine, phenobarbital, and **phenytoin**
- the antimycobacterials rifabutin, **rifampin**, and rifapentine
- the HIV protease inhibitor tipranavir-ritonavir

Herbs and supplements

The herbal supplement St. John's wart (*Hypericum perforatum*) should not be used while taking sofosbuvir, since it may significantly lower the levels of sofosbuvir and GS-331007.

Resources

PERIODICALS

- Healy, Melissa. "Drugs Provide Cure for Hepatitis C, Trials Show; Medications Are Hailed as a Triumph, but Are Pricey." *Los Angeles Times* (April 12, 2014): A1.
- Hoofnagle, Jay H., et al. "Therapy for Hepatitis C: The Costs of Success." *New England Journal of Medicine* 370, no. 16 (April 17, 2014): 1552–3.
- Kowdley, Kris V., et al. "Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis." *New England Journal of Medicine* 370, no. 20 (May 15, 2014): 1879–88.
- Liang, T. Jake, et al. "Therapy of Hepatitis C: Back to the Future." *New England Journal of Medicine* 370, no. 21 (May 22, 2014): 2043–7.

"Only Just the Beginning of the End of Hepatitis C." *Lancet*. 383, no. 9914 (January 25, 2014): 281.

Senior, Melanie. "Sovaldi Makes Blockbuster History, Ignites Drug Pricing Unrest." *Nature Biotechnology*. 32, no. 6 (June 2014): 501–2.

Shiffman, Mitchell L. "My Treatment Approach to Chronic Hepatitis C Virus." *Mayo Clinic Proceedings*. 89, no. 7 (July 2014): 934–42.

Slomski, Anita. "New Drugs Achieve High Cure Rates for Untreated HCV." *Journal of the American Medical Association*. 311, no. 20 (May 28, 2014): 2056.

OTHER

Franciscus, Alan. "Genotype 1: Sovaldi (Sofosbuvir) & Olysio (Simeprevir)." HCSP Fact Sheet. June 2014. http://www.hcvadvocate.org/hepatitis/factsheets_pdf/GT1_Sov_Oly.pdf (accessed December 6, 2014).

WEBSITES

American Association for the Study of Liver Diseases/Infectious Diseases Society of America. "Recommendations for Testing, Managing, and Treating Hepatitis C." <http://www.hcvguidelines.org> (accessed December 8, 2014).

American Society of Health-System Pharmacists, Inc. "Sofosbuvir." MedlinePlus. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a614014.html> (accessed December 6, 2014).

Division of Viral Hepatitis and National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. "Know More Hepatitis." Centers for Disease Control and Prevention. <http://www.cdc.gov/knowmorehepatitis> (accessed December 8, 2014).

Hepatitis C Online. "Sofosbuvir (Sovaldi)." <http://www.hepatitisc.uw.edu/page/treatment/drugs/sofosbuvir-drug> (accessed December 6, 2014).

Sovaldi.com. <http://www.sovaldi.com/> (accessed December 8, 2014).

U.S. Department of Veterans Affairs. "Viral Hepatitis Treatment: Entire Lesson." Available from: <http://www.hepatitis.va.gov/patient/hcv/treat/single-page.asp> (accessed December 6, 2014).

ORGANIZATIONS

American Association for the Study of Liver Diseases, 1001 North Fairfax Street, Suite 400, Alexandria, VA 22314, (703) 299-9766, Fax: (703) 299-9622, aasld@aasld.org, <http://www.aasld.org>.

U.S. Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30329, (800) CDC-INFO (232-4636), cdcinfo@cdc.gov, <http://www.cdc.gov>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

World Health Organization, Avenue Appia 20, 1211 Geneva, 27, 791 21 11, Fax: 791 31 11, info@who.int, <http://www.who.int/en>.

Margaret Alic, PhD

REVIEWED BY KEVIN GLAZA, RPH

Solifenacin

Definition

Solifenacin succinate is a medication used to treat bladder problems caused by an over-active bladder. It is available only by prescription and is in a class of drugs called anticholinergics or antimuscarinics.

Purpose

A person with an over-active bladder has the urge to urinate more often than normal and may experience problems with uncontrollable leakage of urine. Drugs such as solifenacin succinate help relax the muscles of the bladder and ease the symptoms of an over-active bladder.

Description

Solifenacin succinate is a prescription medicine that comes in tablet form. It is taken by mouth.

U.S. brand names

In the United States, solifenacin succinate is sold under the brand name VESicare.

Recommended dosage

Patients usually are started on 5 mg dosages of solifenacin succinate once a day for urinary frequency or incontinence, and may be increased to 10 mg if necessary.



Vesicare (solifenacin succinate), 10 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Anticholinergic—A class of drugs that affect nerve impulses from parasympathetic nerves, which control involuntary movements such as organ function.

Antimuscarinic—Drugs that block certain nerve receptors to relax smooth muscles in the body.

Urinary incontinence—The loss of bladder control, usually with symptoms that vary from minor leaking to wetting that cannot be controlled.

Precautions

Some patients who have taken solifenacin succinate have reported angioedema, or swelling just under the skin, around the face, lips, or larynx. Rarely, a patient reports a severe allergic reaction called anaphylactic shock. Patients who have an obstruction of the bladder should use this medication with caution because it can cause the bladder to retain urine.

Pediatric

Solifenacin succinate has not been tested in children for safety or effectiveness.

Pregnant or breastfeeding

Solifenacin succinate is a pregnancy category C drug. It has only been tested in animals, not in people. Women who are pregnant should only use the medicine if the potential benefits outweigh possible harm to their unborn child. It is not known whether solifenacin succinate can be passed from a nursing mother to her infant. Women who want to breastfeed should stop using solifenacin succinate before breastfeeding or choose not to breastfeed if they decide to take the drug.

Other conditions and allergies

Individuals with liver or kidney problems should use caution when taking solifenacin succinate. Caution is also advised for people who have certain types of glaucoma.

Side effects

Solifenacin succinate causes several side effects, including:

- dry mouth and eyes
- stomach pain
- upset stomach, vomiting, and constipation

- heartburn
- blurry vision
- extreme fatigue

Some side effects of solifenacin succinate can be severe and should be reported to a healthcare provider immediately. These include:

- painful or frequent urination
- severe stomach pain
- constipation lasting more than three days
- back pain
- urine that turns bloody or cloudy
- problems breathing or swallowing
- swelling of the face and mouth area or of the hands and lower limbs

Interactions

Certain drugs and other substances can cause interactions with solifenacin succinate that either decrease one drug's effectiveness or increase unwanted side effects. It is important to tell the treating physician about all drugs, herbal remedies, and supplements being taken before using solifenacin succinate.

Drugs

Some drugs used to treat antifungal infections such as ketoconazole (Bizoral) or **carbamazepine** (Tegretol) can cause increased concentrations of solifenacin succinate.

Resources

PERIODICALS

Robinson, Dudley, et al. "Antimuscarinic Drugs to Treat Overactive Bladder." *British Medical Journal* vol. 344 (2012): e2130.

Wood, Lauren N., et al. "Urinary Incontinence in Women." *British Medical Journal* vol. 349 (2014): g4531.

WEBSITES

American Society of Health-System Pharmacists. "Solifenacin." MedlinePlus. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a605019.html>

Astellas Pharma Technologies, Inc. "VESIcare (Solifenacin Succinate) Tablets." Astrella US.com. <http://www.vesicare.com>

Drugs.com. "Solifenacin." Drugs.com. <http://www.drugs.com/cdi/solifenacin.html>

RXList. "VESIcare." RXList.com. <http://www.rxlist.com/vesicare-drug.htm>

ORGANIZATIONS

American Geriatrics Society, 40 Fulton Street, 18th Floor, New York, NY 10038, (212) 308-1414, Fax: (212) 832-8646, info.amger@americangeriatrics.org, <http://www.americangeriatrics.org/>

Urology Care Foundation, 1000 Corporate Boulevard, Linthicum, MD 21090, (410) 689-3700, Fax: (410) 689-3998, (800) 828-7866, info@urologycarefoundation.org, <http://www.urologyhealth.org/>.

Teresa G. Odle, BA, ELS

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Soma see **Carisoprodol**

Sotalol

Definition

Sotalol is an antiarrhythmic drug (a medication to treat heart rhythm disorders). It is classified as a nonselective beta-blocker. Sotalol works by preventing (blocking) stimulation of beta adrenergic receptors in the sympathetic nervous system. Both the heart and lungs contain beta-1 and beta-2 receptors; however, the heart contains mostly beta-1 receptors, whereas the lungs contain mostly beta-2 receptors. Beta-blockers are a type of drug that block stimulation of these receptors, resulting in a slower heart rate, reduced blood pressure, and a decrease in the heart's demand for oxygen.



Sotalol, 80 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Sotalol is used for the management of ventricular cardiac arrhythmias such as ventricular tachycardia and ventricular fibrillation. It may be used to treat life-threatening cardiac arrhythmias and as such will be given in a hospital setting. In such cases, patients will be placed on continuous cardiac monitoring devices. Later, when patients transition to its use as an ongoing therapy, patients may be evaluated for treatment response by Holter monitoring or other non-hospital monitoring methods.

Another form of sotalol called sotalol AF is indicated for the management of atrial flutter and atrial fibrillation. Sotalol is not approved for management of atrial arrhythmias.

Description

Sotalol is available as a tablet or syrup to be taken by mouth (orally) and also as a solution to be administered into the vein (intravenously). It may be used alone or in combination with other medications for the management of ventricular arrhythmias.

Care should be taken to ensure that sotalol is not confused with sotalol AF. Sotalol is used to treat arrhythmias arising from the ventricles (lower chambers of the heart), such as ventricular tachycardia and ventricular fibrillation, whereas sotalol AF is used to treat arrhythmias arising from the atria (upper chambers of the heart), such as atrial flutter and atrial fibrillation. These are the same drug, but sotalol AF contains specific written information for patients with atrial fibrillation. When picking up their prescription, patients should always check to make sure they received the correct medication as prescribed.

U.S. brand names

Sotalol is sold under the brand names Betapace and Sorine and is offered by prescription only.

Sotalol AF is sold under the brand name Betapace AF and is offered by prescription only.

Recommended dosage

Adults

Ventricular arrhythmias (Sotalol)

The initial oral dose of sotalol for treatment of ventricular arrhythmias in adults is 80 milligrams (mg) taken two times a day. Later, a gradual increase (about three days between dose adjustments) toward a maintenance dose of 120–160 mg taken twice a day may be prescribed. Patients may be prescribed (depending on

KEY TERMS

Arrhythmia—An abnormal or irregular heart rhythm.

Atrial fibrillation—A common heart arrhythmia experienced by about two million Americans annually. In atrial fibrillation, the contractions of the atria are chaotic and uncoordinated. This leads to an irregular flow of blood and to the formation of blood clots that can leave the heart and travel to the brain, causing a stroke.

Atrium (plural, atria)—The two upper chambers (right and left atria) of the heart that receive blood from the body.

Bronchospasm—Tightening (contraction) of muscles of the respiratory tract causing narrowing of the airway and possible obstruction.

Congestive heart failure (CHF)—Also called heart failure; a condition in which a damaged or overworked heart cannot pump enough blood to meet the oxygen and nutrient needs of the body. People with heart failure may find it hard to exercise due to the insufficient blood flow, but many people live a long time with this condition.

Heart attack—Also called myocardial infarction, myocardial means heart muscle and infarction means death of tissue from lack of oxygen.

Holter monitor—Portable heart monitor device worn by a patient over an extended period of time (usually a 24-48 hour period) in order to monitor and track cardiac rhythm. The device is held in a pouch worn at the neck or waist.

QT interval—Measurement of time between the beginning of the Q wave and the end of the T wave in the cardiac electrical cycle. Represents electrical depolarization and repolarization of the ventricles. Measurements may be determined through cardiac rhythm strips and 12 lead electrocardiograms. QT

interval varies depending on heart rate, age, and gender, but normal measurement is usually around 0.40 second (400 milliseconds). Long QT interval may be caused by certain drugs or electrolyte imbalances (acquired) or it may be an inherited condition (congenital). QT interval greater than or equal to 0.50 second (500 milliseconds) is considered dangerous. Prolonged QT interval is a determinant for potential ventricular arrhythmias and is a risk factor for sudden cardiac death.

Torsades de Pointes—French term meaning “twisting of the spikes,” a type of ventricular tachycardia with definitive characteristic peaks seen on an electrocardiogram. Considered an unstable heart arrhythmia often leading to ventricular fibrillation. Associated with prolonged QT interval.

Ventricle—A lower pumping chamber of the heart. There are two ventricles, right and left. The right ventricle pumps oxygen-poor blood to the lungs to be re-oxygenated. The left ventricle pumps oxygen-rich blood to the body.

Ventricular fibrillation—Irregular chaotic heartbeat resulting in no effective cardiac contractions and no cardiac output. A life-threatening medical emergency necessitating immediate defibrillation by medical personnel in a hospital setting or by use of an automated external defibrillator (AED) by non-clinicians outside of a hospital setting.

Ventricular tachycardia—Irregular chaotic heartbeat where the ventricles are quivering rather than beating and circulating blood in a normal fashion. May lead to ventricular fibrillation. Considered a life-threatening medical emergency necessitating cardiac drugs and defibrillation by trained medical personnel.

creatinine levels) up to 320 mg daily taken over two or three divided doses. It is recommended that patients take this medication at the same time every day. Patients will be monitored during the dosing phase to assess their heart rate, QT interval, side effects, and other cardiac concerns.

Sotalol for adults may also be administered intravenously (IV) if a patient's baseline QT interval and creatinine level are within clinically acceptable parameters. Administration (usually 75 mg initially) must be slow (over a five-hour period) and should not exceed more than 300 mg once or twice a day. Patients receiving

sotalol intravenously should do so only in a hospital setting that can provide cardiac resuscitation if needed. Patients should be placed on continuous cardiac monitoring throughout the entire use (including dose adjustment) of this medication. The adjustment (titration) should always be guided by clinical response to the medication.

All patients taking sotalol will be monitored closely over an extended period to ensure the drug is well tolerated before progressing to a higher maintenance dosage. QT intervals should remain less than 0.50 second

(500 milliseconds). Patients will be evaluated for the lowest effective dose meeting the resultant desired clinical effect.

Atrial arrhythmias (Sotalol AF)

The initial oral dose of sotalol AF for treatment of atrial arrhythmias in adults is 80 mg taken two times a day. This can be increased (depending on creatinine levels) over a period of days to a total dose of up to 160 mg taken twice daily as a maintenance dose. Continuous monitoring and assessment of QT interval measurements will be determining factors toward meeting the lowest effective dose with the desired clinical effect.

Sotalol AF administered intravenously (IV) for atrial arrhythmias in adults is usually dosed at 112.5 mg one or two times daily with a gradual increase of up to 150 mg one or two times daily as a maintenance dose. As with oral administration, continuous monitoring and assessment of QT interval measurements will be determining factors toward meeting the lowest effective dose with the desired clinical effect.

Pediatric

Administration of sotalol and sotalol AF in the pediatric population has been approved for infants and children, but the safety and efficacy for use in neonatal patients have not been established. Dosing is determined by the body surface area (BSA), age, and body weight (kilograms) of the infant or child. Doses may range from 2 mg/kg/day, given in divided doses every eight hours up to a maximum of 10 mg/kg/day (titrated) to reach the desired clinical effect. Like adults, children will be closely monitored to evaluate the heart rate and QT interval, with a slow and steady dose increase until an acceptable clinical response has been reached.

Geriatric

Dosing should be done conservatively in seniors. As the body ages, it becomes less efficient at eliminating drugs, which can lead to increased risk of side effects and an increased risk of overdose. Seniors should be monitored closely and given the lowest effective dosage.

Other conditions and allergies

Sotalol is excreted primarily in the urine; therefore, patients with a history of poor kidney function (renal impairment) may need to have dosing modifications in order to avoid excessive accumulation of the medication. Serum creatinine levels will be evaluated before dose determination. Patients with renal impairment will likely receive a lowered dose of sotalol or have an increase in the interval between doses of this medication.

Precautions

Patients receiving sotalol initially and during incremental dosing should be monitored for a prolonged or widening QT interval and for the onset of new or worsened sustained ventricular tachycardia.

This medication causes lightheadedness so it is advised that patients who are taking it move from a lying to a standing position slowly so as to avoid becoming dizzy or falling.

Sotalol tablets should be taken whole, and not crushed, broken, or chewed. Breaking down the pill can result in an inconsistent or unpredictable amount of the medication entering the bloodstream at one time.

Pediatric

Infants and children who are administered sotalol must be monitored closely for side effects associated with dosing changes. Heart rate and QT intervals must be assessed regularly, evaluating for the lowest effective dose meeting the resultant desired clinical effect.

Geriatric

Seniors are at an increased risk of side effects from sotalol and should be monitored closely. Seniors may take a number of other medications that may interact poorly with sotalol, so the use of all medications and supplements should be discussed with their doctor.

Pregnant or breastfeeding

Sotalol is considered a class B pregnancy drug, which means that although no adequate and well-controlled studies have been performed in pregnant women, animal studies have not shown evidence of fetal risk. Patients should tell their doctor if they are pregnant or plan to become pregnant.

It is not known whether or not this drug passes into breast milk. Patients should tell their doctor if they are breastfeeding their baby.

Other conditions and allergies

Sotalol should not be used in patients with the following conditions:

- bradycardia (slow heartbeat)
- long QT syndrome
- atrioventricular (AV) block (unless a functioning pacemaker is present)
- heart failure
- previous evidence of hypersensitivity to sotalol
- uncontrolled congestive heart failure
- asthma

Sotalol should be used with caution in patients who have a history of the following:

- diabetes
- asthma, emphysema, or other respiratory problems
- congestive heart failure
- recent heart attack (myocardial infarction)
- kidney problems
- thyroid disorder
- low potassium or low magnesium (blood electrolytes)

Patients with low potassium or low magnesium levels should have these conditions corrected prior to administration of sotalol because they cause an increase in the potential for a QT interval prolongation leading to Torsades de Pointes. Other conditions that may pose the same risk are bradycardia and recent heart attack.

Because beta blockers also act on beta receptors in the lungs, they are used with caution in patients who have respiratory conditions. Patients with chronic bronchitis, emphysema, or asthma should receive the lowest effective dose of sotalol to minimize the risk of bronchospasm.

Side effects

In some cases, allergic reactions to sotalol have occurred. Any patient who experiences symptoms of an allergic reaction, including swelling of the lips, throat, mouth, or face; difficulty breathing; hives; or rash, should seek emergency medical attention immediately.

Other serious side effects may occur with use of this medication. Patients should seek emergency medical assistance if any of the following symptoms occur:

- feeling faint
- swelling of the face, lips, or tongue (angioedema)
- shortness of breath
- palpitations (feeling of the heart pounding in the chest)
- chest pain
- sweating or feeling clammy
- rapid heartbeat
- slow heartbeat
- swelling or rapid weight gain
- dizziness
- sudden weakness

Accidental or intentional overdose of sotalol may result in a medical emergency. Symptoms of an overdose generally include heightened, more severe forms of the potential side effects of this medication. Patients should seek prompt medical assistance if they believe they may have taken a higher dose of sotalol than prescribed.

Common side effects that generally resolve while taking sotalol include:

- mild nausea
- stomach acidity or indigestion
- fatigue
- mild headache

Interactions

Many medications may interact with sotalol. The patient should tell his or her doctor and pharmacist about all prescription medications, over-the-counter medications, vitamins, herbs, and supplements that he or she is taking. It may be necessary to stop taking some medications or switch to different medications to reduce the chance of serious interactions with sotalol.

Drugs

Some medications for various conditions may cause potentially serious interactions with sotalol, including:

- antibiotics
- antidepressants
- antimalaria medications
- antipsychotic medications
- heart medications
- blood pressure medications
- breathing medications
- oral diabetes medications
- diuretics
- insulin
- migraine medications
- nausea medications
- pain (narcotic) medications

Antacids should not be taken within two hours of taking sotalol, as antacids compete with the absorption of this medication. Patients who take antacids within two hours of taking sotalol may not receive the correct dose as prescribed.

Resources

BOOKS

Mann, Douglas, et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 10th ed. Philadelphia: Saunders, 2014.

PERIODICALS

Kandasamy, Ashok, et al. "Sotalol: A Rescue Drug in the Face of Life-Threatening Refractory Ventricular Tachycardia." *Annals of Cardiac Anaesthesia* 17, no. 2 (2014): 170.

Zhang, Yan, et al. "Intravenous Sotalol for Incessant Tachyarrhythmias in Children." *Heart* 98, suppl. 2 (2012): E260.

WEBSITES

Texas Heart Institute. "Arrhythmias." <http://www.texasheartinstitute.org/HIC/Topics/Cond/Arrhythmia.cfm> (accessed March 11, 2015).

U.S. National Library of Medicine. "Betapace—Sotalol Hydrochloride Tablet." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c4caf469-f684-4f6d-98e8-b6a2fff1de98> (accessed January 29, 2015).

ORGANIZATIONS

American College of Cardiology, Heart House, 2400 N Street NW, Washington, DC 20037, (202) 375-6000, (800) 253-4636 x8603, Fax: (202) 375-7000, resource@acc.org, <http://www.acc.org/>.

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.

Heart Foundation, 80 William Street, Level 3, East Sydney NSW, 2011, Australia +61 02 9219 2444, 300 36 27 87, <http://www.heartfoundation.org.au/>.

National Heart, Lung, and Blood Institute (NHLBI), PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573 nhlbinfo@nhlbi.org, <http://www.nhlbi.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Laura Jean Cataldo, RN, EdD

REVIEWED BY GREGORY A. PRATT, RPh

Sovaldi see **Sofosbuvir**

Spiriva see **Tiotropium**

Spironolactone

Definition

Spironolactone (an aldosterone antagonist) is a potassium-sparing diuretic. It helps the body diurese (get rid of extra fluid) but leaves more potassium in the blood than some (non-sparing) diuretics.

Purpose

Spironolactone is used to treat the following medical conditions:

- primary hyperaldosteronism (and establishing the diagnosis of hyperaldosteronism)
- essential hypertension
- hypokalemia
- heart failure



Spironolactone, 50 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

- cirrhosis of the liver
- nephrotic syndrome
- aldosterone-producing adrenal adenomas
- hirsutism (excessive hair growth in women with polycystic ovary disease)

Spironolactone is used to manage the fluid retention (edema) or low potassium (hypokalemia) that may accompany heart failure, essential hypertension, cirrhosis of the liver, and nephrotic syndrome.

Individuals with hyperaldosteronism have higher than normal aldosterone levels in their body. Aldosterone is a hormone made by the adrenal glands that helps balance the level of water and electrolytes in the body. When too much aldosterone is secreted the balance of sodium and potassium is affected. Spironolactone helps rectify this imbalance.

Description

Spironolactone works in concert to balance and affect the absorption and excretion of both sodium and potassium. By preventing high levels of sodium from being absorbed into the body, it helps prevent potassium from becoming too low. The result is diuresis, with sodium and water being excreted in the urine while at the same time prohibiting too much potassium from being excreted during the process.

U.S. brand names

Spironolactone is sold under the brand name Aldactone. It is offered by prescription only.

KEY TERMS

Addison's disease—Also known as primary adrenal insufficiency, a disease of adrenocortical under-activity.

Adrenal glands—Located just above the kidneys, glands responsible for the production of hormones that help regulate essential functions in the body.

Cirrhosis—A condition that affects the liver, involving long-term inflammation and scarring, which can lead to problems with liver function.

Diurese—Reduction of fluid; usually pertains to reduction of fluid and swelling due to an increase in urine output.

Diuretic—Type of medication that increases the body's output of urine.

Edema—Swelling in the body's tissues caused by excess fluids.

Electrolytes—Positively and negatively charged molecules, called ions, that are found within the body's cells and extracellular fluids, including blood plasma. A test for electrolytes typically includes the measurement of sodium, potassium, chloride, calcium, magnesium, bicarbonate, and phosphorus.

Heart failure—A condition in which a damaged or overworked heart cannot pump enough blood to meet the oxygen and nutrient needs of the body.

Hirsutism—Male-pattern hair growth (excess hair on face, chest, and back) in women.

Hyperkalemia—An abnormally high concentration of potassium in the blood. The usual reference range for potassium is 3.6-5.0 mmol/L (or mEq/L).

Hypernatremia—An abnormally high concentration of sodium in the blood. The usual reference range for sodium is 135 to 145 mmol/L (or mEq/L).

Hypokalemia—An abnormally low concentration of potassium in the blood. The usual reference range for potassium is 3.6-5.0 mmol/L (or mEq/L).

Hyponatremia—An abnormally low concentration of sodium in the blood. The usual reference range for sodium is 135 to 145 mmol/L (or mEq/L).

Recommended dosage

Spirolactone comes in 25, 50, and 100 milligram (mg) tablets to be taken by mouth (orally). Tablets may be prescribed to be taken one time or two times per day. An oral liquid is also available for use in children.

The dosing regimen differs depending on the reason it is prescribed:

- The adult dose for the treatment of edema in heart failure, liver cirrhosis, or nephrotic syndrome is 25–200 mg per day, which may be taken in one or two divided doses.
- The adult dose for the treatment of essential hypertension is 25–200 mg per day, which may be taken in one or two divided doses.
- The adult dose for the treatment of hypokalemia is 25–200 mg per day, which may be taken in one or two divided doses.
- The adult dose for the diagnosis of primary hyperaldosteronism is up to 400 mg per days for 4–28 days, depending on which diagnostic test is used. After a diagnosis of primary hyperaldosteronism has been established, a dose of 100–400 mg per day may be prescribed. Patients will need to be monitored for untoward symptoms such as hypokalemia, weakness, hypertension, and sodium retention.
- The adult dose for the treatment of hirsutism is 50–200 mg per day, which may be taken in one or two divided doses.

Some patients taking spironolactone for conditions of the adrenal gland may need blood pressure medication as well to treat associated hypertension (high blood pressure).

Dose adjustments may be made dependent on sodium and potassium electrolyte levels. A maintenance dose may be prescribed after titration (adjustment) of the drug is made to good effect. Periodic blood work may be needed to check renal (kidney) and liver function and to assess overall electrolyte balance in the body.

The dose may be lowered for patients who are having an operation, and some patients may be instructed to stop taking this medication for a period of time prior to a surgical or dental procedure.

Pediatric

Spirolactone may be used for treatment of hypertension or primary hyperaldosteronism in children. The dose in neonates as a diuretic is 1 to 2 mg per kilogram of body weight (kg, or 2.2 lb.) per day, given in one to two divided doses. The dose for children is 1–3 mg/kg/day in one to two divided doses, not to exceed 100 mg/day.

The dose in neonates for the treatment of primary hyperaldosteronism is up to a maximum of 7 mg/kg/day. The dose for children is 9 mg/kg/day up to a maximum of 400 mg daily.

Geriatric

Dosing should be done conservatively in seniors. As the body ages, it becomes less efficient at eliminating

drugs, which can lead to increased risk of side effects and an increased risk of overdose. Seniors should be monitored closely and given the lowest effective dosage.

Other conditions and allergies

The dose of spironolactone for a patient with adrenal adenoma or carcinoma will be at the lowest effective dose while the person is awaiting surgery.

Precautions

Patients receiving spironolactone will need to have blood drawn on a regular basis to check sodium and potassium levels and the overall electrolyte balance in the body.

Spironolactone should not be used for edema that is associated with pregnancy.

Spironolactone for adult use should be taken whole, and not crushed, broken, or chewed. Breaking down the pill can result in an inconsistent or unpredictable amount of the medication entering the bloodstream at one time.

Patients taking spironolactone should not discontinue use of the medication without first consulting with their doctor. Premature discontinuation of spironolactone may cause adverse effects.

Patients should seek medical treatment if they experience symptoms of the following conditions, which may occur while taking spironolactone:

- High potassium (hyperkalemia)—symptoms include muscle weakness, a slow or weak pulse, and tingling in limbs.
- Low sodium—symptoms include feeling faint, dry mouth, thirst, confusion, imbalance, shallow or halted breathing, slurred speech, and severe weakness.
- Internal bleeding—symptoms include bright or dark blood noted with coughing, bright or dark blood noted when vomiting, and bright or dark blood noted in stools.
- Electrolyte imbalances—symptoms include thirst, confusion, nausea, vomiting, muscle cramps, drowsiness, weakness, feeling faint, decreased urination, dry mouth, and a fast heart rate or weak pulse.

Geriatric

Seniors are at an increased risk of side effects from spironolactone and should be monitored closely.

Pregnant or breastfeeding

Spironolactone is considered a class C drug, which means that there is not enough evidence to determine whether the drug adversely affects a fetus. Patients should tell their doctor if they are pregnant or plan to become pregnant.

Spironolactone can pass into breast milk and may be harmful to a baby that is being breast fed. Women should not take this medication if they are breastfeeding.

Other conditions and allergies

Patients with a history of the following conditions should discuss their symptoms and medical history with their doctor before using spironolactone:

- kidney dysfunction
- liver dysfunction
- unstable or acute congestive heart failure
- high potassium (hyperkalemia)
- trouble urinating
- severe dehydration
- primary adrenal insufficiency (Addison's disease)

Side effects

In some cases, allergic reactions to spironolactone have occurred. Any patient who experiences symptoms of an allergic reaction, including swelling of the lips, throat, mouth, or face; difficulty breathing; hives; or rash, should seek emergency medical attention immediately.

Patients should seek emergency medical assistance if any of the following symptoms occur:

- allergic reaction including swelling of the face, lips, or tongue (angioedema)
- confusion
- dizziness or light-headedness
- slow, fast, or uneven heart rate
- palpitations (feeling of the heart pounding in the chest)
- signs of dehydration such as little or no urine output
- muscle pain or cramping

Other side effects include:

- mild muscle stiffness or cramps
- impotence
- tender or enlarged breasts (gynecomastia)
- dizziness
- drowsiness
- rash
- urinary frequency
- mild nausea or vomiting
- mild diarrhea
- headache

Interactions

Many medications may interact with spironolactone. Patients should tell their doctor and pharmacist about all

prescription medications, over-the-counter medications, vitamins, herbs, and supplements that they are taking. It may be necessary to stop taking some medications or switch to different medications to reduce the chance of serious interactions with spironolactone.

Drugs

Drug interactions including intensified electrolyte imbalance, hypotension, and decreased responsiveness have been noted when spironolactone is used concomitantly with the following:

- angiotensin-converting enzyme (ACE) inhibitors
- adrenocorticotrophic hormone (ACTH)
- barbiturates
- **digoxin**
- lithium
- muscle relaxants
- narcotics
- nonsteroidal anti-inflammatory (NSAIDs) drugs
- some **oral contraceptives**

Individuals who have been prescribed eplerenone (Inspra), another aldosterone antagonist, should not also take spironolactone.

Food and other substances

Patients should avoid too much salt in their diet because of the effects of water retention, which may decrease the effectiveness of spironolactone.

To minimize the potential for hyperkalemia, patients taking spironolactone should avoid potassium-rich foods and products that are high in potassium such as salt substitutes or potassium supplements.

Individuals taking spironolactone should avoid alcohol.

Resources

BOOKS

Whalen, Karen. *Lippincott Illustrated Reviews: Pharmacology*. 6th ed. Philadelphia: Wolters Kluwer, 2014.

Resources

PERIODICALS

Mahfoud, Felix, et al. "Aldosterone Antagonists and Renal Denervation: Friends or Foes?" *Hypertension* 65, no 2 (2015): 280–82.

Swedberg, Karl. "Heart Failure Therapies in 2014: Mixed Results for Heart Failure Therapies." *Nature Reviews Cardiology* 12, no. 2 (2015): 73–75.

Resources

OTHER

World Health Organization. *Review of the Role of Spironolactone in the Therapy of Children*. 18th Expert Committee on the Selection and Use of Essential Medicines. http://www.who.int/selection_medicines/committees/expert/18/applications/paediatric/16_Spironolactone.pdf (accessed March 11, 2015).

WEBSITES

American Association of Endocrine Surgeons (AAES). "Primary Hyperaldosteronism (Conn's Syndrome or Aldosterone-Producing Adrenal Tumor)." http://endocrine.diseases.org/adrenal/hyperaldosteronism_es.shtml (accessed January 26, 2015).

Mayo Clinic staff. "Heart Failure." MayoClinic.org. <http://www.mayoclinic.com/health/heartfailure/DS00061> (accessed March 11, 2015).

U.S. National Library of Medicine. "Aldactone—Spironolactone Tablet, Film Coated." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0fed2822-3a03-4b64-9857-c682fcd462bc> (accessed January 26, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.

Heart Foundation, 80 William Street, Level 3, East Sydney NSW, 2011, Australia, +61 02 9219 2444, 300 36 27 87, <http://www.heartfoundation.org.au/>.

National Heart, Lung, and Blood Institute (NHLBI), PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbinfo@nhlbi.org, <http://www.nhlbi.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Sterapred see **Prednisone**

Strattera see **Atomoxetine**

Suboxone see **Buprenorphine/naloxone**

Sulfamethoxazole/ trimethoprim

Definition

Sulfamethoxazole/trimethoprim is a prescription-only medication that combines two types of antibiotics: sulfamethoxazole and trimethoprim.



Sulfamethoxazole/trimethoprim, 800 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Sulfamethoxazole/trimethoprim is used to treat bacterial infections, primarily those of the urinary tract, ears, lungs, and intestines. The drug combination is active against a variety of bacteria, including *E. coli*, *Klebsiella enterobacter*, *M. morgani*, *P. mirabilis*, *P. vulgaris*, *H. influenzae*, *S. pneumoniae*, *Pneumocystis jirovecii*, *Shigella flexneri*, and *Shigella sonnei*.

Off-label use

Sulfamethoxazole/trimethoprim may be used off label to treat:

- encapsulated collections of infection (abscesses in the brain, the lining of the brain and spinal cord, or lungs)
- foot infections in individuals with diabetes
- head lice
- bone infections (including infections of both artificial or natural joints)
- prostate infections
- cholera
- salmonella
- typhoid fever
- methicillin-resistant *Staphylococcus aureus* (MRSA)

Description

Sulfamethoxazole/trimethoprim is available in tablet and liquid suspension forms. The medication is taken by

mouth and must be prescribed by a healthcare provider. Sulfamethoxazole/trimethoprim is used internationally, and is on the World Health Organization's list of essential medicines. It is also frequently used in veterinary medicine.

Sulfamethoxazole/trimethoprim is available in single- or double-strength tablets:

- Single-strength tablets contain 400 milligrams (mg) sulfamethoxazole and 80 mg trimethoprim.
- Double-strength tablets contain 800 mg sulfamethoxazole and 160 mg trimethoprim.

The drug combination is also available as a liquid suspension, with 200 mg sulfamethoxazole and 40 mg trimethoprim per 5 milliliters (mL) of liquid.

U.S. brand names

Sulfamethoxazole/trimethoprim is sold under the brand names Bactrim, Bactrim DS, Septra DS, and Sulfatrim. It is also manufactured as a generic by many different companies.

Canadian brand names

Sulfamethoxazole/trimethoprim is sold as Apo-Sulfatrim, Apo-Sulfatrim DS, Apo-Sulfatrim Pediatric, Protrin DF, Septra Injection, Teva-Trimel, Teva-Trimel DS, Trisulfa, Trisulfa DS, and Trisulfa S in Canada.

International brand names

Sulfamethoxazole/trimethoprim is sold under many different brand names internationally, including Actin (Thailand), Alcorim F (Kenya), Altavit (Italy), Bacris (Brazil), Chevi-Trim (Austria), Cotrim forte (Switzerland), D'Olatrim (Peru), Frocimole (Philippines), Trisul (New Zealand), and Zoltrim forte (Ecuador). In some countries, ampicillin is only one component of the medication, and there are other medications included in the formulation. In some locations, it is only available for veterinary use.

Recommended dosage

Recommended dosages are based on the amount of sulfamethoxazole/trimethoprim needed to treat the infection. In general, recommended adult dosages are one or two double-strength tablets, taken once or twice per day. The duration of treatment depends on the specific site of infection. Some urinary tract infections (UTIs) can be eradicated with only 3–5 days of treatment, while bronchitis may require a 10–14 day regimen.

Many off-label uses utilize higher doses for considerably longer periods of treatment.

KEY TERMS

Anaphylaxis—A severe, systemic allergic reaction that can be potentially life-threatening.

Methicillin-resistant *Staphylococcus aureus* (MRSA)—An infection with a Staph organism that has developed resistance to the common antibiotics that were previously used to treat such infections.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Pregnancy category—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk but no human studies exist, or adverse effects have been seen in animals but not in well-controlled human studies. Category C: No adequate human or animal studies exist, or adverse fetal effects have occurred in animal studies but there is no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk, and risks outweigh any benefits.

Pediatric

Children over the age of two months can be prescribed sulfamethoxazole/trimethoprim. The dose of the trimethoprim component dictates the pediatric dosing format. Sample dosing schedules include:

- Mild and moderate infections are treated with a total trimethoprim dose of 8 mg per kilogram (kg) of body weight per day, divided into two daily doses given every 12 hours.
- Serious infection is treated with a total trimethoprim dose of 15–20 mg/kg/day, divided into four daily doses given every 6 hours.
- Ear infections are treated with a total of 6–10 mg/kg/day, divided into two daily doses given every 12 hours for a total of ten days.

Other conditions and allergies

Individuals with a history of kidney problems or on dialysis should tell their healthcare provider before taking this drug, as a dosage reduction may be necessary.

Precautions

The following precautions apply to all individuals:

- This drug should be taken for the entire length of the prescription, even if symptoms cease. Failure to take a complete course of the medication can result in the return of symptoms.
- Sulfamethoxazole/trimethoprim can be taken with or without food.
- Use of this drug over a long period of time can increase the risk of developing another fungal or bacterial infection (secondary infection).
- *C. difficile*-associated diarrhea and pseudomembranous colitis have both been associated with long-term use of sulfamethoxazole/trimethoprim, even months after the drug has been discontinued.
- Women taking **oral contraceptives** should ask their healthcare provider if they should use a second form of contraception while taking sulfamethoxazole/trimethoprim, as this drug can interfere with the effectiveness of the birth control pill.
- Sulfamethoxazole/trimethoprim makes the skin more sensitive to sun exposure and tanning lights, resulting in more easily (and potentially severely) burned skin.

Sulfamethoxazole/trimethoprim has been associated with a variety of serious adverse reactions, including:

- blood disorders
- liver problems
- skin conditions
- high levels of potassium in the blood (hyperkalemia)
- low blood sugar (hypoglycemia)
- low levels of sodium in the blood (hyponatremia)

Pregnant or breastfeeding

Sulfamethoxazole/trimethoprim is a pregnancy category D drug, meaning that it is known to cause birth defects. Women who are pregnant should not use this drug unless the benefits very clearly outweigh the known risks to the fetus.

Sulfamethoxazole/trimethoprim also passes into breast milk. Women who are breastfeeding should tell their healthcare provider before taking sulfamethoxazole/trimethoprim, because this drug can cause diarrhea, yeast infections, or allergic reactions in the nursing child. Additionally, infants who are ill, premature, or have jaundice may experience more serious reactions.

Other conditions and allergies

Serious and sometimes fatal reactions can occur in individuals who are allergic to penicillin and penicillin-

like drugs. Anyone who has had a severe reaction to any drug should alert the healthcare provider before taking sulfamethoxazole/trimethoprim. Individuals who are allergic to sulfamethoxazole/trimethoprim (e.g., Septra, Bactrim, Sulfatrim), any form of sulfa drug, or trimethoprim should not take sulfamethoxazole/trimethoprim. Individuals with a history of severe allergies, asthma, or prior reactions involving anaphylaxis, hives, or angioedema (severe swelling) are at higher risk for serious reactions to sulfamethoxazole/trimethoprim.

Sulfamethoxazole/trimethoprim should be used with caution in individuals with the following conditions:

- asthma
- allergies
- thyroid disease
- liver impairment
- kidney impairment

Side effects

The most common adverse side effects of sulfamethoxazole/trimethoprim for all age groups tend to be mild. They include:

- upset stomach
- loose stools or diarrhea
- nausea and vomiting

These side effects should be brought to the healthcare provider's attention if they do not go away within a few days. Whitish vaginal discharge or white coating of the tongue and inside of the mouth should also be reported to the doctor.

The drug should be discontinued and a doctor should be notified immediately if any of these less common but more serious side effects occur:

- wheezing or difficulty breathing or swallowing (may indicate a severe allergic reaction and require immediate medical attention)
- skin reactions including rash, itching, hives, blistering, or peeling
- swelling (edema)
- yellowing of the skin (jaundice)
- vaginal itching or discharge (females)
- seizures
- abdominal pain with fever

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the

effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements including vitamin supplements.

Drugs

Sulfamethoxazole/trimethoprim is known to interact with the following pharmaceutical drugs. Other interactions are possible. An individual who develops any unusual or unexpected symptoms should contact their healthcare provider.

Sulfamethoxazole/trimethoprim may increase the blood levels of the following drugs, possibly increasing the risk of toxic effects:

- angiotensin-converting enzyme inhibitor (ACE) inhibitors
- amantadine
- angiotensin II receptor blockers
- antidiabetic agents
- azathioprine
- **cyclosporine**
- dapsone
- **digoxin**
- dofetilide
- eplerenone
- fosphenytoin
- lamivudine
- **memantine**
- mercaptopurine
- **metformin**
- **methotrexate**
- **phenytoin**
- pralatrexate
- procainamide
- repaglinide
- **spironolactone**
- sulfonyleureas
- **varenicline**
- verteporfin
- vitamin K antagonists

Sulfamethoxazole/trimethoprim may decrease the therapeutic effects of the BCG vaccine, sodium picosulfate, and the typhoid vaccine.

The risk of sulfamethoxazole/trimethoprim toxicity may be increased by simultaneous use of dexketoprofen and methenamine.

Use of leucovorin and potassium-p may decrease the effectiveness of sulfamethoxazole/trimethoprim.

Food and other substances

Individuals taking sulfamethoxazole/trimethoprim should avoid consuming alcohol.

Resources

BOOKS

- Bloom, Allyson K., and Edward T. Ryan. *Hunter's Tropical Medicine and Emerging Infectious Disease*. Philadelphia: Saunders; 2013.
- Cherry, J., et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Elsevier Saunders, 2014.
- Drug Information Handbook*. 23rd ed. Hudson, OH: Lexicomp, 2014.
- Mandell, G. L., et al. *Douglas and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. London: Churchill Livingstone, 2015.
- Rang, H. P. *Rang & Dale's Pharmacology*. 7th ed. London: Churchill Livingstone, 2012.

WEBSITES

- St. Vincent Hospital. "Sulfamethoxazole; Trimethoprim, SMX-TMP." <http://www.stvincent.org/Health-Library/Drug-Reference/Sulfamethoxazole;-Trimethoprim,-SMX-TMP.aspx> (accessed February 19, 2015).
- Steckelberg, James M. "What Are the Effects of Drinking Alcohol while Taking Antibiotics?" Mayo Clinic. <http://www.mayoclinic.org/healthy-living/consumer-health/expert-answers/antibiotics-and-alcohol/faq-20057946> (accessed February 19, 2015).
- U.S. National Library of Medicine. *Drugs and Lactation Database (LactMed)*. <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm> (accessed February 19, 2015).

ORGANIZATIONS

- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Sulfasalazine ER (extended release), 500 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

(GI) system and the joints. It is in a class of medications called anti-inflammatory drugs. The drug is made from a combination of salicylate, which is the main ingredient in aspirin, and an antibiotic called sulfa.

Purpose

People who have rheumatoid arthritis experience inflammation of their joints that causes stiffness, problems with movement, and pain. Sulfasalazine helps to relieve some of the inflammation and pain associated with mild to moderate rheumatoid arthritis in people whose symptoms have not responded to other medicines. The properties of sulfasalazine also work to relieve inflammation caused by ulcerative colitis. In this disease, a person's bowel becomes inflamed and ulcers, or sores, form in the lining of the colon and rectum, which form the lower intestine. The swelling and ulcers cause diarrhea, bleeding from the rectum, and pain in the stomach.

Description

Sulfasalazine comes in a tablet that is taken by mouth. The tablets may have enteric coating. The coating helps the tablet be absorbed in the small intestine, after it passes through the stomach. This helps prevent stomach irritation that can be caused by aspirin.

Sulfasalazine

Definition

Sulfasalazine is a drug used to treat inflammation, or swelling in the body, especially in the gastrointestinal

KEY TERMS

Colitis—Inflammation of the colon, a part of the intestine that extends down toward the rectum.

Gastrointestinal system—The gastrointestinal, or GI, system includes the stomach, esophagus, intestine, rectum, and anus. It also is called the digestive system.

Ulcer—A sore, usually in the thin lining of the stomach or part of the GI system.

U.S. brand names

In the United States, sulfasalazine is sold under the brand name Azulfidine and Azulfidine-EN-tabs (enteric coated).

Recommended dosage

Recommended dosage varies for each person who takes sulfasalazine, depending on how well the drug works at relieving symptoms and how well each individual tolerates the drug. Most patients receive sulfasalazine a few times a day in evenly divided doses. The tablets should be taken after meals when possible and swallowed whole, not chewed.

When treating ulcerative colitis in adults, doctors usually start an adult patient at a lower dose of 1 to 2 g per day to make sure that sulfasalazine does not cause too many problems in the stomach and GI tract. If the patient handles the drug well, the doctor may increase the dose to 4 g per day. Once symptoms are under control, maintenance therapy is implemented at a lower dose of 2 g of sulfasalazine a day.

Children age six and older may receive three to six equal doses in a day based on their body weight. The dosage should equal about 40 to 60 mg of sulfasalazine per kg of the child's body weight. Maintenance therapy for children is at a dose of 30 mg per kg of body weight per 24 hours, divided into four doses.

Patients who receive sulfasalazine for treatment of rheumatoid arthritis usually receive 500 mg of the drug each evening for one week, then 500 mg each morning and evening for a week. In the third week, doctors recommend 500 mg by mouth each morning and 1000 mg each evening. In week four, patients usually receive 100 mg each morning and evening. Many patients can stop taking the medicine after four weeks, but some must continue for up to 12 weeks.

Precautions

People who have asthma or severe allergies should use caution when taking sulfasalazine. Some people are

especially sensitive or allergic to ingredients in sulfasalazine and should watch for reactions when taking the medicine for the first time. It is important to inform the doctor of past allergic reactions, especially to antibiotics or aspirin.

It is important to drink plenty of water while taking sulfasalazine. Doctors also should monitor patients' kidney function while on the drug and perform other laboratory tests regularly to check for signs of adverse reactions.

Pediatric

Use of sulfasalazine in children younger than age two years old is not recommended. The drug has not been tested for safety or effectiveness in children this young.

Pregnant or breastfeeding

Sulfasalazine is a pregnancy category B drug. No adequate studies have been conducted to determine whether the drug is harmful to human fetuses. The drug can be passed from a mother to her infant in breast milk. Women who are taking sulfasalazine and breastfeeding should use extra caution and discuss use of the drug with their doctor.

Side effects

Sulfasalazine can cause side effects, including:

- headache
- upset stomach, vomiting, and loss of appetite
- diarrhea
- stomach pain

Some side effects of sulfasalazine can be severe or indicate a reaction to the drug. These side effects should be reported to a doctor immediately and include:

- itching, hives, or skin rash
- swelling
- sore throat
- fever
- pale or yellow skin
- fatigue or weakness
- aching in muscles or joints
- problems swallowing
- unusual bruising or bleeding

Interactions

Drugs can sometimes interact with one another, causing one drug to not work as it should or increasing side effects. It is important to tell the doctor about all

medications, herbal remedies, and supplements being taken before starting sulfasalazine.

Drugs

Sulfasalazine interacts with several drugs. Some of the important interactions are listed below:

- Taking sulfasalazine at the same time as the blood thinner warfarin (Coumadin) can interfere with how well the blood thinner works.
- Sulfasalazine can alter the effectiveness of a transplant medication called **cyclosporine** (Gengraf, Neoral, Sandimmune).
- Taking sulfasalazine can affect how the body absorbs **digoxin** (Cardoxin, Digitek, Lanoxin), a drug used to treat heart failure and abnormal heart rhythm.

Resources

PERIODICALS

- Karlsson, Johan A., et al. "Addition of Infliximab Compared with Addition of Sulfasalazine and Hydroxychloroquine to Methotrexate in Early Rheumatoid Arthritis." *Annals of Rheumatic Disease* vol. 72 (2013): 1927–33.
- Love, Bryan L., et al. "Extended-release Mesalamine Granules for Ulcerative Colitis." *Annals of Pharmacotherapy* vol. 46 (2012): 1529–36.

WEBSITES

- American Society of Health-System Pharmacists. "Sulfasalazine." MedlinePlus. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682204.html>
- American College of Rheumatology. Cannon, Michael. "Sulfasalazine (Azulfidine)." Available from: https://www.rheumatology.org/Practice/Clinical/Patients/Medications/Sulfasalazine_%28Azulfidine%29/
- Drugs.com. "Sulfasalazine." Available from: <http://www.drugs.com/cdi/sulfasalazine>
- Pfizer Pharmacia & Upjohn Co. "Azulfidine EN-Tabs." Pfizer. <http://labeling.pfizer.com/ShowLabeling.aspx?id=527>
- RXList. "Azulfidine EN-Tabs." RXList. Available from: <http://www.rxlist.com/azulfidine-drug.htm>

ORGANIZATIONS

- American College of Gastroenterology, 6400 Goldsboro Road, Suite 200, Bethesda, MD 20817, (301) 263-9000, <http://gi.org/>.
- National Institute of Arthritis and Musculoskeletal and Skin Diseases, 1 AMS Circle, Bethesda, MD 20892, (301) 495-4484, Fax: (301) 718-6366, (877) 226-4267, TTY: (301) 565-2966, NIAMSinfo@mail.nih.gov, <http://www.niams.nih.gov/>.

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Sumatriptan

Definition

Sumatriptan is a systemic medication used to treat the symptoms of migraine and cluster headaches. It is classified as an antimigraine agent in the drug family known as selective serotonin receptor agonists (SSRAs) or triptans.

Purpose

Sumatriptan is used to treat:

- acute migraine attacks: severe, throbbing headaches that may be accompanied by nausea and sensitivity to light and sound
- cluster headaches: severe pain usually on one side of the head or around one eye that typically occurs in episodes of several weeks
- new daily persistent headache (NDPH): a continuous headache that develops suddenly and persists, often for years
- cyclic vomiting syndrome (CVS): recurrent episodes of nausea, vomiting, and lethargy that are believed to be related to migraine, although they do not necessarily involve headaches

Sumatriptan is used to treat existing headaches. It does not prevent migraines or other headaches or reduce their frequency. It is sometimes prescribed for other uses.

Description

Migraine headaches are believed to be caused by the widening of cranial blood vessels that exert pressure on the brain. Migraines are associated with low levels of the neurotransmitter serotonin (5-hydroxytryptamine or 5-HT), which constricts blood vessels. Sumatriptan binds to specific serotonin receptors called 5-HT₁ receptors, located on blood vessels in the brain and sensory nerves leading to the brain. Sumatriptan is a selective 5-HT₁ receptor "agonist," because it binds with high affinity to these receptors and exerts the same effects as serotonin binding to the receptors, acting as a powerful vasoconstrictor that narrows the widened blood vessels. This reduces pressure on the brain and blocks the transmission of pain signals and the release of inflammatory neuropeptides that cause pain, nausea, sensitivity to light and sound, and other migraine symptoms. Studies reported in 2014 that a single 85 mg sumatriptan/500 mg naproxen sodium tablet used early in a migraine attack rapidly and consistently relieves symptoms and restores patient functioning.



Sumatriptan, 25 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

U.S. brand names

Sumatriptan is marketed under a variety of brand names including:

- Imitrex Tablets
- Imitrex Nasal Spray
- Imitrex Injection
- Alsuma Injection
- Sumavel Injection
- Zecuity, an iontophoretic transdermal system (TDS)
- Treximet, a sumatriptan/naproxen combination

Canadian brand names

Canadian brand names include:

- Imitrex
- CO Sumatriptan
- Apo-Sumatriptan
- Gen-Sumatriptan

International brand names

Sumatriptan is available in many different formulations from many different suppliers, so there are a large number of international brand names. Imigran is the most common international brand name.

Origins

Sumatriptan was the first commercially available triptan.

- It was originally approved by the U.S. Food and Drug Administration (FDA) as injectable Imitrex (sumatriptan succinate) in 1992. Sumatriptan injection is available in vials for use with disposable syringes and in autoinjectors. A single-use jet injector formulation that delivers 6 mg without a needle was approved in 2009. Injectable sumatriptan is useful for sudden migraine attacks with vomiting that prevent taking a tablet.
- Sumatriptan tablets were approved in 1995.
- Sumatriptan nasal spray was approved in 1997. Single-use nasal sprayers are useful for fast relief as well as for migraines accompanied by nausea and vomiting.
- Sumatriptan combined with naproxen, a nonsteroidal anti-inflammatory drug (NSAID), was approved in 2008 and has been shown to be more effective than either drug alone.
- Zecuity: a patch that uses low voltage controlled by a programmed microchip to deliver a single dose of sumatriptan through the skin received FDA approval in 2013.

Sumatriptan has been available as a generic drug since 2009. The generics are manufactured and marketed under a variety of names in various dosages. Although Sumatriptan is available only by prescription in the United States, 50 mg dosages are available over-the-counter in the United Kingdom and some other countries.

Recommended dosage

Sumatriptan is typically used at the first sign of a migraine or cluster headache or associated symptoms such as nausea, vomiting, or light sensitivity; however, it can be used at any stage of a headache. If symptoms do not improve after the first dose, a second dose should not be taken without consulting the doctor.

The usual adult dosages are:

- 25 mg, 50 mg, or 100 mg orally for migraine (50 or 100 mg may be more effective than 25 mg, but there is evidence that 100 mg is no more effective than 50 mg), swallowed whole with water; repeated after at least two hours if symptoms recur, for a maximum of 200 mg in 24 hours
- 5 mg, 10 mg, or 20 mg sprayed once into a nostril for migraine; repeated after at least two hours if symptoms recur, for a maximum of 40 mg per 24 hour period
- 6 mg injected subcutaneously (under the skin) for migraine, or 1 to 5 mg for people with dosage-limiting side effects; injection can be repeated after at least one hour if symptoms recur, for a maximum of 12 mg

KEY TERMS

5-hydroxytryptamine₁ (5-HT₁)—Serotonin receptors in blood vessels in the brain that bind sumatriptan.

Agonist—A drug, such as sumatriptan, that binds to a receptor and mimics the effects of the endogenous receptor-binding substance.

Cluster headache—Severe pain in one eye or temple.

Cyclic vomiting syndrome (CVS)—Recurrent episodes of nausea, vomiting, and lethargy that are sometimes treated with sumatriptan.

Iontophoretic—Introduction of an ionized drug through the skin by application of an electric current.

Migraine—A common primary headache characterized by debilitating neurological symptoms, especially severe throbbing pain on one or both sides of the head, lasting for several hours or more.

Monoamine oxidase A (MAO-A) inhibitor—A class of antidepressants that can interact with sumatriptan.

Monoamine oxidase inhibitor (MAOI)—A class of antidepressants that can interact with sumatriptan.

Naproxen—An NSAID that is available in combination with sumatriptan.

Neurotransmitter—A chemical that carries nerve impulses from one nerve cell to another across a synapse or from a nerve cell to a muscle cell.

New daily persistent headache (NDPH)—A treatment-resistant chronic headache that begins abruptly and may last for years.

NSAID—A nonsteroidal anti-inflammatory drug, such as ibuprofen or naproxen.

Receptor—A molecule, such as a protein, inside or on the surface of a cell, that binds a specific substance.

Selective serotonin receptor agonists (SSRAs)—A class of drugs, including sumatriptan, that bind to specific serotonin receptors, mimicking the effects of serotonin binding.

Selective serotonin reuptake inhibitors (SSRIs)—A class of antidepressants that increase levels of serotonin in the brain by preventing its reuptake by nerve-cell endings.

Serotonin—5-Hydroxytryptamine; a neurotransmitter in the brain and blood; low levels are associated with various disorders including migraines and depression.

Serotonin-norepinephrine reuptake inhibitors (SNRIs)—A class of antidepressants that increase the levels of the neurotransmitters serotonin and norepinephrine by preventing their reuptake.

Triptans—A class of drugs that bind to serotonin receptors and mimic the action of serotonin; believed to treat migraine headaches by constricting cranial blood vessels, inhibiting inflammatory neuropeptides, and blocking transmission of pain signals.

injected in 24 hours; or additional oral doses can be taken at intervals of at least two hours, up to a maximum of 100 mg orally per 24 hour period

- 6 mg injected subcutaneously for cluster headaches; the dose can be repeated after at least one hour if symptoms recur, for a maximum of 12 mg per 24 hour period

The nasal spray is used as follows:

- The nose is blown gently.
- The protective cap is removed from the sprayer.
- The sprayer is held between the thumb and fingers without pressing the plunger.
- One nostril is blocked with the other hand by pressing firmly on the side of the nose.
- With the head upright and mouth closed, the tip of the sprayer is inserted into the other nostril about 0.5 in. (1.3 cm).

- The plunger is pressed firmly with the thumb while breathing in gently through the nose.
- The tip is removed while holding the head level.
- The patient breathes gently, not deeply, in through the nose and out through the mouth for 10 to 20 seconds.
- Larger doses (10 mg or 20 mg) can be divided between the two nostrils.
- The response may be better with 20 mg than with 5 or 10 mg, but there is evidence that more than 20 mg does not provide increased benefit.
- The single-dose sprayer is discarded in the trash.

Sumatriptan solution is injected just under the skin, on the outer side of the thigh or upper arm. It should never be injected through clothing or into a vein or muscle. Prefilled injectors and vials are used only once. Doses other than 4 mg or 6 mg are administered using the

6 mg single-dose vial. Syringes are disposed of in puncture-resistant containers.

Other conditions and allergies

Patients with mild-to-moderate liver dysfunction should not exceed a single oral dose of 50 mg. No dose adjustment is necessary for sumatriptan injection.

Precautions

Sumatriptan should be avoided or prescribed with caution for:

- men over 40 and women over 55 or menopausal
- patients with heart disease risk factors such as smoking, obesity, diabetes, or high cholesterol
- patients with a family history of early heart disease or stroke

Patients should keep diaries of headache occurrence and sumatriptan use.

- The safety of treating more than an average of four headaches in a 30-day period has not been established.
- Headache medications should not be taken for more than ten days in a month. Overuse of migraine medications can worsen headaches or increase their frequency.
- Sumatriptan must not be taken within 24 hours of taking another SSRA or ergot-type medication.
- Sumatriptan must not be taken within 14 days of taking a monoamine oxidase inhibitor (MAOI) or a monoamine oxidase A (MAO-A) inhibitor.
- Sumatriptan can cause drowsiness: patients should not drive or operate machinery until they know how sumatriptan affects them.

Pediatric

The safety and effectiveness of sumatriptan have not been established in patients younger than 18 years.

Geriatric

Sumatriptan should be prescribed with caution in elderly patients.

Pregnant or breastfeeding

Sumatriptan is in the FDA pregnancy category C, meaning it is not known whether the drug poses harm to the fetus, but animal studies indicate that it might. However, it was reported in 2014 that the Sumatriptan, Naratriptan, and Treximet Pregnancy Registry detected no association between sumatriptan and major birth defects, consistent with observational studies. No conclusion could be drawn about the safety of the

sumatriptan/naproxen combination. Nevertheless, sumatriptan should be prescribed with caution during pregnancy, and women should use effective birth control while taking sumatriptan.

Sumatriptan is present at low levels in breast milk and has poor oral bioavailability, so infant exposure is expected to be minimal. Sumatriptan is not expected to cause adverse effects to most breastfed infants.

Other conditions and allergies

The doctor and pharmacist should be informed of any allergies to sumatriptan, any of the ingredients in sumatriptan, or any other medications. For patients with multiple cardiovascular risk factors, the first dose of sumatriptan should be administered by the doctor to monitor for adverse reactions. Patients with severe liver dysfunction should not use sumatriptan. The physician should be informed if the patient has ever had:

- heart disease
- heart attack
- angina (chest pain)
- irregular heartbeat
- stroke or mini-stroke (transient ischemic attack)
- circulation problems such as varicose veins, blood clots in the legs, Raynaud's disease, or ischemic bowel disease
- high blood pressure
- high cholesterol
- diabetes
- seizures
- liver or kidney disease

Side effects

The doctor should be contacted if the following symptoms are severe or persistent:

- drowsiness
- dizziness
- fatigue
- upset stomach
- diarrhea
- nausea
- muscle cramps
- flushing
- tingling
- feeling warm or cold
- weakness
- pain or redness at the injection site

The doctor should be notified if the following side effects of sumatriptan nasal spray are severe or persistent:

- sore or irritated nose
- sore throat
- dry mouth
- unusual taste in the mouth
- burning or tingling
- sensitivity to loud noise

Serious side effects that require immediately calling the doctor or getting emergency medical attention are:

- hives
- difficulty breathing or swallowing
- redness, itching, or swelling of the face, lips, tongue, eyes, or throat
- tightness, pain, pressure, or heaviness in the chest, throat, neck, or jaw
- rapid, pounding, or irregular heartbeat
- shortness of breath
- cold sweat
- weakness or numbness of an arm or leg
- sudden or severe stomach pain
- bloody diarrhea
- vomiting
- paleness or blue color to the fingers and toes
- rash
- slow or difficult speech
- hoarseness
- pain, burning, or tingling in the hands or feet
- faintness
- sudden weight loss
- vision changes
- seizures

Interactions

It is very important that the doctor and pharmacist be informed of any and all prescription and nonprescription medicines, herbs, vitamins, and dietary supplements being used by the patient.

Drugs

Sumatriptan must not be taken if:

- another SSRA—such as **almotriptan** (Axert), **eletriptan** (Relpax), **frovatriptan** (Frova), **naratriptan** (Amerge), **rizatriptan** (Maxalt), or **zolmitriptan** (Zomig)—has been taken in the past 24 hours
- ergot-type medications—such as **bromocriptine** (Parlo-dol), **cabergoline**, **dihydroergotamine** (D.H.E. 45, Migranal), **ergoloid mesylates** (Hydergine), **ergonovine** (Ergotrate), **ergotamine** (Cafergot, Ergomar, Wigraine),

methylergonovine (Methergine), **methysergide** (Sansert), or **pergolide** (Permax)—have been taken in the past 24 hours

- an MAO-A inhibitor—such as **isocarboxazid** (Marplan), **phenelzine** (Nardil), or **tranylcypromine** (Parnate)—has been taken in the past two weeks

Other drugs that can interact with sumatriptan include:

- **acetaminophen** (Tylenol)
- **aspirin** and other NSAIDs, such as **ibuprofen** (Advil, Motrin) and **naproxen** (Aleve, Naprosyn)
- selective serotonin reuptake inhibitors (SSRIs), such as **citalopram** (Celexa), **escitalopram** (Lexapro), **fluoxetine** (Prozac, Sarafem, Symbyax), **fluvoxamine**, **paroxetine** (Paxil), and **sertraline** (Zoloft)
- serotonin/norepinephrine reuptake inhibitors (SNRIs), such as **desvenlafaxine** (Pristiq), **duloxetine** (Cymbalta), **sibutramine** (Meridia), and **venlafaxine** (Effexor)
- other antidepressants, such as **amitriptyline** (Elavil), **amoxapine** (Asendin), **clomipramine** (Anafranil), **desipramine** (Norpramin), **doxepin** (Adapin, Sinequan), **imipramine** (Tofranil), **nortriptyline** (Aventyl, Pamelor), **protriptyline** (Vivactil), and **trimipramine** (Surmontil)

Resources

BOOKS

Smith, Howard S., et al. *Essential Pain Pharmacology: The Prescriber's Guide*. New York: Cambridge University, 2012.

PERIODICALS

- Cady, Roger, et al. "Treatment of Chronic Migraine: A 3-Month Comparator Study of Naproxen Sodium vs. SumaRT/Nap." *Headache* 54, no. 1 (January 2014): 80–93.
- Calhoun, Anne H., et al. "Injectable Sumatriptan for Cyclic Vomiting Syndrome in Adults: A Case Series." *Headache* 54, no. 9 (October 2014): 1526–30.
- Chessman, Alexander. "Review: Sumatriptan plus Naproxen Improves Acute Migraine More Than Placebo, Sumatriptan, or Naproxen." *Annals of Internal Medicine* 160, no. 4 (February 18, 2014): JC8.
- Ephross, Sara A., et al. "Final Results from the 16-Year Sumatriptan, Naratriptan, and Treximet Pregnancy Registry." *Headache* 54, no. 7 (July/August 2014): 1158–72.
- Landy, Stephen H., et al. "Consistency of Return to Normal Function, Productivity, and Satisfaction Following Migraine Attacks Treated with Sumatriptan/Naproxen Sodium Combination." *Headache* 54, no. 4 (April 2014): 640–54.
- Meadows, Kappa P., et al. "Sumatriptan Transdermal System Can Be Correctly Assembled and Applied During Migraine Attacks." *Headache* 54, no. 5 (May 2014): 850–60.

Pringsheim, Tamara, et al. "Triptans for Symptomatic Treatment of Migraine Headache." *British Medical Journal* 348, no. 7953 (April 12, 2014): 35.

Tepper, Deborah E. "Sumatriptan Iontophoretic Patch for Migraine." *Headache* 54, no. 9 (October 2014): 1563–4.

WEBSITES

American Society of Health-System Pharmacists, Inc. "Sumatriptan." MedlinePlus. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601116.html> (accessed November 29, 2014).

American Society of Health-System Pharmacists, Inc. "Sumatriptan Injection." MedlinePlus. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a696023.html> (accessed November 29, 2014).

American Society of Health-System Pharmacists, Inc. "Sumatriptan Nasal." MedlinePlus. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a614029.html> (accessed November 29, 2014).

Drugs.com. "Sumatriptan." Available from: <http://www.drugs.com/cdi/sumatriptan.html> (accessed November 29, 2014).

"Triptans: What You Should Know." *Consumer Reports*. Available from: http://www.consumerreports.org/health/resources/pdf/best-buy-drugs/BBD_Triptans_Summary.pdf (accessed November 29, 2014).

ORGANIZATIONS

American Headache Society, 19 Mantua Road, Mount Royal, NJ 08061, (856) 423-0043, Fax: (856) 423-0082, ahshq@talley.com, <http://www.americanheadachesociety.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY KEVIN GLAZA, RPH

Suprax see **Cefixime**

Symbicort see **Budesonide/formoterol**

Synthroid see **Levothyroxine**

T

Tacrolimus

Definition

Tacrolimus belongs to a group of medicines known as immunosuppressive drugs. It is used primarily to lower the body's natural immunity in order to prevent the rejection of organ transplants and to prevent graft-versus-host disease.

Purpose

Tacrolimus first saw use in transplant patients. By suppressing the activity of the immune system, tacrolimus makes it more likely that the recipient of a transplanted organ will accept that organ. It is especially used for kidney transplants.

In graft-versus-host disease, patients receiving transplants experience an adverse immune system reaction. To prevent this, grafts of stem cells from donors are sometimes given to the recipient to encourage the blood to begin production of normal cells. Tacrolimus may be given during the graft process because it seems to make the patient more receptive to the donated stem cells.

An ointment form is available as a treatment for severe atopic dermatitis. This form is to be used only when other treatment options have failed.

Description

Tacrolimus somehow suppresses, or prevents the activity of, the cells in the lymphatic system, which are known as T cells. Under normal circumstances, T cells mount an immune response to foreign materials in the body. However, during a transplant, T cells can cause a reaction that can lead to the rejection of a donor organ. The exact reason for the activity of tacrolimus is not understood.

U.S. brand names

Tacrolimus is sold under the brand names Prograf and Protopic (topical ointment). It is also known as FK506.

Recommended dosage

Given by mouth, in a capsule, or by intravenous line, tacrolimus doses range from about 0.03 milligrams (mg) to 0.05 milligrams per kilogram (kg, or 2.2 lb.) of body weight per day.

Other conditions and allergies

Individuals with liver or kidney problems require a lower dose.

Precautions

Use of tacrolimus greatly increases the likelihood a person will get skin cancer and lymphoma. Anyone using the drug should be monitored closely for changes in the skin, and all normal precautions for avoiding skin cancer, such as avoiding direct exposure to ultraviolet light, should be taken.

Side effects

Many serious side effects are associated with tacrolimus. Conditions affecting the brain brought on by the use of tacrolimus include coma (unconscious state) and delirium (uncontrolled and erratic conscious state). Usually, the brain conditions are reversible. Headache, skin rashes, hair loss (alopecia), pain, sensitivity to light, and shock (anaphylaxis) are all side effects. Kidney damage, which cannot be reversed, is also a danger.

Interactions

This drug interacts with a long list of other drugs. It is important to tell the physician in charge of the care plan each and every drug being taken so that interactions can be avoided.

Drugs

Tacrolimus prevents effective vaccination, and **vaccinations** should not be given while the drug is in use.



Tacrolimus, 1 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Food and other substances

Tacrolimus should be taken without food and long after a meal. If there is food in the stomach, it will interfere with the way the drug makes its way into the body. Grapefruit juice can increase the activity of tacrolimus and should be avoided.

Resources

PERIODICALS

Carenco, C., et al. "Tacrolimus and the Risk of Solid Cancers after Liver Transplant: A Dose Effect Relationship." *American Journal of Transplantation* 15, no. 3 (2015): 678–86.

WEBSITES

AHFS Consumer Medication Information. "Tacrolimus." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601117.html> (accessed February 27, 2015).

Leukemia & Lymphoma Society. "Graft Versus Host Disease." <http://www.lls.org/diseaseinformation/managingyourcancer/treatmentnextsteps/typesoftreatment/stemcelltransplantation/graftvshostdisease/> (accessed February 27, 2015).

U.S. Food and Drug Administration. "Tacrolimus (Marketed as Protopic Ointment) Information." <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107845.htm> (accessed February 27, 2015).

ORGANIZATIONS

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

REVIEWED BY KEVIN GLAZA, RPH

KEY TERMS

Graft-versus-host disease (GVHD)—A potentially life-threatening complication of bone marrow or stem cell transplants in which the donated cells attack the patient's own cells.

Immunosuppressive drugs—Medications used to suppress the immune system.

Intravenous line—A tube that is inserted directly into a vein to carry medicine directly to the blood stream, bypassing the stomach and other digestive organs that might alter the medicine.

Lymphatic system—The system that collects and returns fluid in tissues to the blood vessels and produces defensive agents for fighting infection and invasion by foreign bodies.

Stem cell—Cell that gives rise to a lineage of cells. Particularly used to describe the most primitive cells in the bone marrow from which all the various types of blood cell are derived.

T cells—White blood cells that originate in the thymus gland. T cells regulate the immune system's response to infections.

Transplant—The removal of tissue from one part of the body for implantation to another part of the body, or the removal of tissue or an organ from one individual and its implantation in another individual by surgery.

Tadalafil

Definition

Tadalafil is an oral medication for treating erectile dysfunction (ED), benign prostatic hyperplasia (BPH), and pulmonary arterial hypertension (PAH). Tadalafil is in the phosphodiesterase-5 (PDE5) inhibitor drug class.

Purpose

Tadalafil and other PDE5 inhibitors are the most common drug treatments for ED: the consistent inability to achieve or maintain an erection sufficient for satisfactory sexual activity. It is estimated that 15 to 30 million American men have some degree of ED, and 10 to 20 million have severe ED. The incidence of ED increases with advancing age. Taken as needed, tadalafil works within about 15 minutes. The effects can sometimes last as long as 36 hours. Although response varies, men taking once-daily tadalafil for ED may be



Cialis (tadalafil), 20 mg. (© Cengage Learning®.)

able to have successful intercourse after four or five days to one week of treatment.

Tadalafil is modestly effective for treating the symptoms of moderate-to-severe BPH: an enlarged prostate. BPH can cause lower urinary tract symptoms (LUTS), including difficult, painful, frequent, or urgent urination; incomplete bladder emptying; weak urinary stream; straining; or excessive urination at night (nocturia). BPH symptoms generally improve after two to four weeks of treatment.

Tadalafil is used to treat PAH: high blood pressure in the arteries carrying blood from the heart to the lungs in both men and women. PAH causes shortness of breath, dizziness, and fatigue. Tadalafil can improve the ability to exercise with PAH and delay worsening of symptoms. Tadalafil may be prescribed for other purposes. Clinical studies suggest that it may be useful for treating pediatric PAH.

Description

When men become sexually aroused, nitric oxide (NO) is released from specialized cells. NO causes the formation of cyclic guanosine monophosphate (cGMP), which dilates the blood vessels of the penis and relaxes the penile muscles, enabling increased blood flow and erection. Compression of the dilated blood vessels against the firm outer lining of the penis prevents the blood from

escaping and perpetuates the erection. PDE5 is an enzyme produced in the lungs and elsewhere in the body that breaks down cGMP and returns the penis to its flaccid state. Tadalafil and other PDE5 inhibitors decrease PDE5 activity, so that more cGMP is available to achieve and maintain an erection. This same blood-vessel-dilating effect eases pressure on the lower urinary tract, reducing LUTS caused by BPH, and reduces blood pressure in the pulmonary arteries, improving heart function and enabling people with PAH to be more active.

U.S. brand names

Tadalafil brand names in the United States (as well as Canada and most other countries) are Cialis for treating ED and BPH and Adcirca for improving symptoms of PAH.

Origins

PDE5 inhibitors emerged from Pfizer's search for a new angina drug that would relax constricted blood vessels supplying the heart and relieve chest pain. Pfizer was about to abandon disappointing clinical trials, when participants began reporting an unusual side effect—erections. The result was **sildenafil** (Viagra), launched in 1998 as the first oral drug for ED. Tadalafil (Cialis) was approved by the U.S. Food and Drug Administration (FDA) in 2003 as the third PDE5 inhibitor for ED as needed and the first and only oral ED drug for lower-dose once-daily use to produce erections on demand without regard for timing of sexual activity. Tadalafil (Adcirca) was approved in 2009 as the first once-daily PDE5 inhibitor for PAH. Cialis was approved in 2011 for treating symptoms of BPH and BPH plus ED. The French drug manufacturer Sanofi SA is seeking approval for an over-the-counter version of tadalafil for ED when patents begin expiring in 2017.

Cialis is available as almond-shaped, 2.5 mg, 5 mg, 10 mg, and 20 mg tablets in different shades of yellow and debossed with "C 2 1/2," "C 5," "C 10," and "C 20," respectively. Adcirca is an almond-shaped, orange, 20 mg tablet.

Recommended dosage

Recommended dosages are:

- daily ED treatment: 2.5 mg Cialis once daily; may be increased to 5 mg
- BPH or BPH plus ED: 5 mg Cialis once daily
- ED as needed: usually 10 mg Cialis at least 30 minutes prior to sexual activity; may be increased to 20 mg or decreased to 5 mg; maximum dosing frequency once per day
- PAH: 40 mg (two 20 mg tablets) Adcirca once daily, possibly beginning with 20 mg daily

KEY TERMS

Adcirca—The brand name of tadalafil for treating pulmonary arterial hypertension.

Alpha-blockers—Drugs for treating high blood pressure.

Angina—Chest pain that occurs when diseased blood vessels restrict the flow of blood to the heart.

Benign prostatic hyperplasia (BPH)—An overgrowth of a portion of the prostate gland, usually in men over 50, that can constrict the urethra and interfere with urination.

Cialis—The brand name of tadalafil for erectile dysfunction and benign prostate hyperplasia.

Creatinine—The metabolized by-product of creatine, an organic acid that assists the body in producing muscle contractions. Creatinine is found in the bloodstream and in muscle tissue. It is removed from the blood by the kidneys and excreted in the urine.

Cyclic guanosine monophosphate (cGMP)—A second messenger in the body that, among other functions, enables the achievement and maintenance of penile erections; tadalafil prevents its breakdown.

Cytochrome P450 3A4 (CYP3A4) inhibitors—Substances, such as a drug or grapefruit juice, that

inhibit a liver enzyme that is required to metabolize and detoxify drugs such as tadalafil.

Erectile dysfunction (ED)—The consistent inability to achieve or maintain a penile erection.

Finasteride—A drug used to treat benign prostatic hyperplasia.

Lower urinary tract symptoms (LUTS)—Symptoms such as difficult, painful, or frequent urination that may be caused by benign prostatic hyperplasia.

Nitric oxide (NO)—A regulator of various bodily processes including penile erection.

Phosphodiesterase-5 (PDE5)—An enzyme that interferes with penile erections by breaking down cyclic guanosine monophosphate (cGMP); inhibited by tadalafil.

Pulmonary arterial hypertension (PAH)—High blood pressure in the pulmonary arteries that carry blood from the heart to the lungs.

Ritonavir—An antiviral drug that inhibits cytochrome P450 and can prevent drugs such as tadalafil from being properly metabolized.

Sildenafil (Viagra)—The first phosphodiesterase-5 inhibitor for erectile dysfunction.

Daily doses should be taken at about the same time each day; a missed dose should be taken as soon as possible unless it is almost time for the next dose, in which case the missed dose should be skipped. Tadalafil should be stored at room temperature in the tightly closed container it came in, away from excess heat and moisture (not in the bathroom).

Geriatric

No dose adjustment is necessary based on age alone, although greater sensitivity to medications in some elderly patients should be considered.

Other conditions and allergies

For renal impairment:

- creatinine clearance less than 30 mL/minute or on dialysis: daily use not recommended; maximum dose for ED not to exceed 5 mg once every 72 hours
- creatinine clearance 30 to 50 mL/minutes starting at 2.5 mg daily, with possible increase to 5 mg for BPH or ED and BPH; 5 mg not more than once daily with a

maximum of 10 mg not more than once every 48 hours for ED as needed

- creatinine clearance 31 to 80 mL/minute to 20 mg once daily for PAH, may be increased to 40 mg

Tadalafil is not recommended for patients with severe liver impairment. Daily Cialis has not been well-studied in mild-to-moderate liver impairment and should be prescribed with caution. Cialis as needed should not exceed 10 mg once per day. For PAH, the dose is 20 mg once daily.

Other dose adjustments include:

- for ED in patients on stable alpha-blocker therapy: 2.5 mg once daily
- for patients taking CYP450 3A4 inhibitors (**ketoconazole** or **ritonavir**)—no more than 2.5 mg once daily for ED; no more than 10 mg every 72 hours as needed for ED
- for PAH: 20 mg once daily for patients on ritonavir; may be increased to 40 mg; should be stopped 24 hours

before starting ritonavir and may be resumed at 20 mg once daily after at least one week on ritonavir

Precautions

- Tadalafil does not cure ED, increase sexual desire, or prevent pregnancy or the spread of sexually transmitted diseases.
- If cardiovascular symptoms (such as chest pain, dizziness, or nausea) occur during sexual activity, patients should refrain from further activity and seek immediate medical attention.
- PDE5 inhibitors will not treat ED occurring after radiation therapy for prostate cancer.
- Tadalafil effects on BPH symptoms are relatively small, and long-term safety and effectiveness are unknown.
- For BPH treated with **finasteride**, 5 mg of Cialis may be taken once daily for up to 26 weeks, but benefits decrease from 4 to 26 weeks.
- Tadalafil helps control PAH but does not cure it. It should be continued even if symptoms disappear.
- Blood pressure should be monitored while taking tadalafil.
- All healthcare providers should be informed of tadalafil usage, especially before any surgery, including dental surgery.
- A sudden decrease or loss of vision, sometimes permanent, has occurred in some patients taking tadalafil or similar drugs.

Pediatric

The safety and effectiveness of tadalafil have not been established for patients younger than 18.

Pregnant or breastfeeding

Tadalafil is in the FDA pregnancy category B meaning that animal studies have not shown fetal harm, but there are no adequate human studies. Cialis is not intended for use by women. Adcirca should be used by pregnant women only if it is clearly needed. It should be used with caution in breastfeeding women, since animal studies indicate that tadalafil and/or its metabolites are excreted in breast milk, and potential effects on nursing infants are unknown.

Other conditions and allergies

Because tadalafil relaxes blood vessels throughout the body, blood pressure may drop. Caution must be used for patients with:

- low blood pressure, such as less than 90/50 mmHg
- dehydration

- left-sided heart diseases
- certain nervous-system abnormalities

Tadalafil should not be used by patients:

- taking any form of organic nitrate—such as **nitroglycerin** for heart problems—either regularly or intermittently, because of the risk of a sudden drop in blood pressure
- with severe liver or kidney dysfunction
- with unstable angina or angina during sexual activity
- with uncontrolled high blood pressure
- with uncontrolled heart arrhythmias
- who had a heart attack in the last 90 days
- who had heart failure or a stroke in the past six months
- with pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis; rare diseases often associated with PAH

Patients requiring emergency treatment for a heart problem must tell medical personnel of their last use of tadalafil. Patients with angina should only be administered nitrates within 48 hours of taking tadalafil under close medical supervision and monitoring. Patients should tell their doctors and pharmacists if they are allergic to tadalafil, any ingredients in tadalafil tablets, or any other medications. Patients should tell their doctors if they smoke; recently had diarrhea, vomiting, excessive sweating, or poor intake of fluids that could cause dehydration; or have been told to avoid sexual activity (if taking tadalafil for ED). They should also tell their doctors if they have ever had:

- an erection lasting more than four hours
- any condition that affects the shape of the penis
- chest pain during sexual activity
- diabetes
- high cholesterol
- high or low blood pressure
- irregular heartbeat
- heart, kidney, or liver disease
- heart attack or heart failure
- angina
- stroke
- stomach ulcers
- bleeding disorders
- circulatory problems
- blood cell disorders, such as sickle-cell disease, multiple myeloma, or leukemia
- sudden severe vision loss, especially vision loss caused by a blockage of blood flow

- eye disease or family members with an eye disease such as retinitis pigmentosa

Side effects

Tadalafil generally has few side effects, but the most common are:

- headache
- indigestion
- nasal congestion
- flushing
- leg or arm pain
- back pain
- muscle pain
- respiratory infection
- nausea

The doctor should be notified if any of the following side effects are severe or persistent:

- headache
- indigestion or heartburn
- nausea
- diarrhea
- flushing
- pain in the stomach, back, muscles, arms, or legs
- cough

Side effects that require immediate or emergency medical attention include:

- an erection lasting at least four hours
- sudden decrease or loss of vision in one or both eyes
- blurred vision
- changes in color vision
- ringing in the ears
- sudden decrease or loss of hearing
- dizziness
- chest pain
- hives
- rash
- difficulty breathing or swallowing
- swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs
- blistering or peeling of skin

Interactions

The doctor and pharmacist should be informed of any and all prescription and nonprescription medicines,

herbs, vitamins, minerals, and dietary supplements being used. Patients should bring a list of medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

Combining mild vasodilators can increase their individual effects, causing unsafe drops in blood pressure:

- PDE5 inhibitors should never be used in combination.
- Nitroglycerin and other nitrates for chest pain, such as **isosorbide** dinitrate or isosorbide mononitrate, in any form, or street drugs containing nitrates (“poppers”), such as amyl nitrate, butyl nitrate, or nitrite should never be used with tadalafil.
- Alpha-blockers including alfuzosin, doxazosin, **dutasteride**, prazosin, silodosin, **tamsulosin**, or **terazosin** should not be taken in combination with tadalafil for BPH, and patients should be stable on alpha-blocker therapy before initiating tadalafil for ED at the lowest recommended dose.

Other drugs that may interact with tadalafil and may require changing dosages or monitoring for side effects include:

- CYP3A4 inhibitors such as ketoconazole or ritonavir
- certain other antifungals such as **fluconazole**, **griseofulvin**, itraconazole, and voriconazole
- high-blood-pressure medications
- other PAH medications
- amiodarone
- aprepitant
- bosentan
- **carbamazepine**
- **clarithromycin**
- **diltiazem**
- efavirenz
- **erythromycin**
- HIV protease inhibitors including indinavir, nelfinavir, and **lovastatin**
- nefazodone
- nevirapine
- phenobarbital
- **phenytoin**
- rifabutin
- **rifampin**
- **sertraline**
- telithromycin
- verapamil

Herbs and supplements

The herbal supplement St. John's wort may interact with tadalafil.

Food and other substances

Tadalafil can be taken without regard for food. However, alcohol is a mild vasodilator. Large amounts of alcohol, such as five or more shots of whiskey or glasses of wine, increase the risk of tadalafil side effects such as dizziness, headache, fast heartbeat, and low blood pressure. Patients should discuss with their doctors safe alcohol use, as well as consumption of grapefruit or grapefruit juice.

Resources

PERIODICALS

Buvat, J., et al. "Continuation and Effectiveness of Tadalafil Once Daily during a 6-Month Observational Study in Erectile Dysfunction: The EDATE Study." *International Journal of Clinical Practice* 68, no. 9 (September 2014): 1087–99.

Carson, C. C., et al. "Tadalafil—A Therapeutic Option in the Management of BPH-LUTS." *Internal Journal of Clinical Practice* 68, no. 1 (January 2014): 94–103.

"ED Drugs after Cancer Treatment Don't Protect Erectile Function." *Harvard Men's Health Watch* (July 2014): 8.

Loftus, Peter. "Corporate News: Cialis over the Counter?—Lilly Strikes Deal with Sanofi to Sell Nonprescription Version, Pending Approval." *Wall Street Journal* (May 28, 2014): B3.

Seftel, A. D., et al. "Effect of Once-Daily Tadalafil on Confidence and Perceived Difficulty in Performing Sexual Intercourse in Men Who Were Incomplete Responders to As-Needed PDE5 Inhibitor Treatment." *International Journal of Clinical Practice* 68, no. 7 (July 2014): 841–9.

OTHER

Eli Lilly and Company. "Full Prescribing Information." Available from: <http://pi.lilly.com/us/ cialis-pi.pdf> (accessed December 12, 2014).

WEBSITES

American Society of Health-System Pharmacists, Inc. "Tadalafil." MedlinePlus. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a604008.html> (accessed December 10, 2014).

Erectile Dysfunction Health Center. WebMD. "Erectile Dysfunction: Cialis, Levitra, Staxyn, Stendra, and Viagra to Treat ED." Available from: <http://www.webmd.com/erectile-dysfunction/guide/ cialis-levitra-staxyn-viagra-treat-ed> (accessed December 14, 2014).

Lilly USA, LLC. "Dosing and Getting Patients Started." Available from: http://www.cialismd.com/CIALIS-dosing.aspx?srcid=ciasem_google_cialis&WT.srch=1&WT.mc_id=82159-931846-7308 (accessed December 10, 2014).

PHA's Scientific Leadership Council. "Tadalafil (Adcirca) Treatments for Pulmonary Hypertension." Pulmonary

Hypertension Association. Available from: <http://www.phassociation.org/Patients/Treatment/Tadalafil> (accessed December 10, 2014).

ORGANIZATIONS

Pulmonary Hypertension Association, 801 Roeder Road, Suite 1000, Silver Spring, MD 20910, (301) 565-3004, Fax: (301) 565-3994, (800) 748-7274, PHA@PHAssociation.org, <http://www.phassociation.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY JAMES E. WAUN, MD, RPH

Tamiflu see **Oseltamivir**

Tamoxifen

Definition

Tamoxifen is a synthetic compound similar to estrogen. It mimics the action of estrogen on the bones and uterus, but it blocks the effects of estrogen on breast tissue.

Purpose

Tamoxifen is used as an adjuvant hormonal therapy immediately after surgery in early stages of breast cancer and to treat advanced metastatic breast cancer (stages III and IV) in women and men. Adjuvant therapy is treatment added to curative procedures (such as surgery) to prevent the recurrence of cancer. Tamoxifen may also be used to reduce the chance of breast cancer development in high-risk patients.

Fertility preservation through ovarian stimulation is another important function of tamoxifen. Although originally developed in the 1960s as a contraceptive, tamoxifen was later found to stimulate ovarian follicle growth. High-dose tamoxifen is used as an ovarian stimulant to preserve fertility in women who have been treated for breast cancer.

Off-label use

Tamoxifen is sometimes used to treat malignant melanoma, brain and central nervous system tumors, and uterine cancer, but these uses are not indicated on the product label.

Description

Tamoxifen belongs to a family of compounds called antiestrogens. Antiestrogens are used in cancer therapy to



Tamoxifen, 20 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

inhibit the effects of estrogen on target tissues. Estrogen is a steroid hormone secreted by the ovaries. Depending on the target tissue, estrogen can stimulate the growth of female reproductive organs and breast tissue, play a role in the female menstrual cycle, and protect against bone loss by binding to estrogen receptors on the outside of cells within the target tissue. Antiestrogens act selectively against the effects of estrogen on target cells in a variety of ways; they are also called selective estrogen receptor modulators (SERMs).

Tamoxifen selectively inhibits the effects of estrogen on breast tissue, while selectively mimicking the effects of estrogen on bone (by increasing bone mineral density) and uterine tissues. These qualities make tamoxifen an excellent therapeutic agent against estrogen receptor-positive breast cancer. Tamoxifen competes with estrogen by binding to estrogen receptors on the membrane of target cells, which limits the effects of estrogen on breast tissue. Tamoxifen may also be involved in other antitumor activities affecting the expression of genes associated with cancer (oncogenes), promotion of cancer cell death (apoptosis), and growth factor secretion. Growth factors are hormones that influence cell division and proliferation, which may encourage the growth of cancer cells.

A newer group of drugs called aromatase inhibitors, including anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin), may be used after a course of tamoxifen. These drugs are forms of endocrine therapy that are considered alternatives to tamoxifen. When used

as adjuvant therapy, aromatase inhibitors reduce the risk of recurrence and death from breast cancer in women who have hormone receptor-positive breast cancer. Although tamoxifen has been the standard therapy for preventing recurrence and increasing survival, which is still true for premenopausal women, these drugs are able to prevent recurrence as effectively as tamoxifen and with fewer side effects (although only letrozole has been shown to improve survival). Therefore, aromatase inhibitors may be prescribed after a course of tamoxifen to improve overall treatment results in postmenopausal women.

U.S. brand names

Tamoxifen is marketed under the brand name Nolvadex.

Origins

Tamoxifen has been used to reduce the risk of breast cancer since it was approved by the U.S. Food and Drug Administration (FDA) in 1990. Studies in thousands of women have shown that the use of tamoxifen over a five-year period effectively reduced the risk for breast cancer in high-risk, postmenopausal women.

Recommended dosage

Tamoxifen is taken orally and is available in 10- and 20-milligram (mg) tablets. The standard dosage for metastatic breast cancer or ductal carcinoma in situ (DCIS) is 10 mg twice daily or 20 mg once daily for adult females and males. The response rate at this dosage is about 30%, and the response rate with complete remission occurs in 10% of patients. Patients 60 years and older tend to have higher response rates.

For patients using tamoxifen for adjuvant therapy after surgery, the typical dosage is 20 mg once daily for two to five years following surgery. Women at high risk for developing breast cancer usually take 20 mg daily for five years. If a scheduled dose is missed, patients are advised to take their next regularly scheduled dose, contact their doctor, and avoid doubling the dose. Tamoxifen can be taken with food.

The dosage of tamoxifen used for ovarian stimulation is 20 mg daily for five days.

Precautions

Tamoxifen may not work effectively for every patient, because certain tumors tend to become resistant to tamoxifen therapy. The development of tamoxifen resistance is believed to be due to the pharmacologic structure of tamoxifen and its effect on the structure and function of the estrogen receptor in breast cancer. Genetic

studies are being conducted to investigate what causes tamoxifen resistance and how it may influence the management of individual breast cancer patients.

A study conducted by the National Cancer Institute called the Breast Cancer Prevention Trial found that, although tamoxifen resulted in approximately 50% fewer diagnoses of breast cancer, the women taking the drug had more than twice the chance of developing endometrial cancer and an increased risk of developing blood clots, as compared to women taking a placebo.

Pediatric

Tamoxifen is not recommended for use in children.

Pregnant or breastfeeding

Women who are pregnant or nursing are advised not to use this drug since it has several side effects that, although rare, can be severe. It is known to cause miscarriages and birth defects. Women are encouraged to use birth control while taking tamoxifen. However, **oral contraceptives** can negatively alter the effects of tamoxifen, so women are advised to explore nonhormonal birth control options.

Other conditions and allergies

Patients who are predisposed to the formation of blood clots (thromboembolisms) are advised to use tamoxifen with caution. Smokers are at a higher risk for thromboembolism than nonsmokers.

Side effects

Although tamoxifen is usually well tolerated by patients, certain side effects may occur. About 25% of patients experience side effects such as mild nausea, vomiting, hot flashes, weight gain, bone pain, and hair thinning. These side effects are usually not severe enough to stop therapy, and most are short-term effects. Patients using adjuvant tamoxifen for long periods of time may face unwanted effects years into therapy, which may warrant discontinuing the drug. Possible long-term effects include:

- increased risk of developing liver adenoma and uterine (endometrial) cancer
- eye problems such as retinal lesions, macular edema, and corneal changes (most resolve after tamoxifen is discontinued)
- neurological problems such as depression, dizziness, confusion, and fatigue
- gynecologic problems such as vaginal bleeding, vaginal discharge, and endometriosis
- increased risk of developing blood clots, both in the lungs and major blood vessels

KEY TERMS

Adjuvant therapy—Therapy given in addition to the primary treatment. In cancer treatment, adjuvant therapy usually refers to chemotherapy or radiation therapy given after surgery to prevent recurrence of the cancer.

Antiestrogen—A drug that prevents the hormone estrogen from influencing the behavior of specific types of cells.

Aromatase inhibitors—Medications used for preventing or treating breast cancer in postmenopausal women by inhibiting the body's production of estrogen.

Estrogen—A female hormone produced by the ovaries that stimulates the growth of the lining of the uterus.

Estrogen receptor (ER)—A cell-surface protein that binds the female hormone estrogen; present on ER-positive breast cancer cells.

Menopause—The end of a woman's menstrual periods when a woman no longer can conceive a child.

Metastatic—Referring to a cancer that has spread to an organ or tissue from a primary cancer located elsewhere in the body.

Placebo—A pill or liquid given during the study of a drug or dietary supplement that contains no medication or active ingredient. Usually study participants do not know if they are receiving a pill containing the drug or an identical-appearing placebo.

Interactions

Individuals should discuss potential drug interactions with their healthcare provider, including interactions between tamoxifen and over-the-counter drugs or supplements.

Drugs

Tamoxifen is used with caution in patients taking the anticoagulant drug **warfarin**, because tamoxifen can interfere with the effects of warfarin, and dose adjustments may be necessary. It can also reduce blood levels of letrozole and anastrozole (aromatase inhibitors that may be used with tamoxifen). Phenobarbital and **rifampin** increase the breakdown of tamoxifen and may therefore reduce its level in the blood, decreasing its activity. Oral contraceptives also may interfere with the action of tamoxifen.

Resources

BOOKS

- Hirshaut, Yashar, and Peter I. Pressman. *Breast Cancer: The Complete Guide*. 5th ed. New York: Bantam, 2008.
- Miller, Kenneth D. *Choices in Breast Cancer Treatment: Medical Specialists and Cancer Survivors Tell You What You Need to Know*. Baltimore: Johns Hopkins University Press, 2008.

PERIODICALS

- Davies, C., et al. "Long-term Effects of Continuing Adjuvant Tamoxifen to 10 Years versus Stopping at 5 Years after Diagnosis of Oestrogen Receptor-positive Breast Cancer: ATLAS, A Randomized Trial." *Lancet* 38 (March 2013): 805–16.
- Oktay, K. "Fertility Preservation: We Are in This for a Long Haul." *American Journal of Obstetrics and Gynecology* 209 (August 2013): 77–79.
- Salama, M., et al. "Female Fertility Loss and Preservation: Threats and Opportunities." *Annals of Oncology* 24 (March 2013): 598–608.
- Schiavon, G., and I. E. Smith. "Status of Adjuvant Endocrine Therapy for Breast Cancer." *Breast Cancer Research* 16 (February 2014): 206–9.
- Smith, G. L. "The Long and Short of Tamoxifen Therapy: A Review of the ATLAS Trial." *Journal of Advanced Practice Oncology* 5 (January 2014): 57–60.
- van Agthoven, T., et al. "Selective Recruitment of Breast Cancer Anti-Estrogen Resistance Genes and Relevance for Breast Cancer Progression and Tamoxifen Therapy Response." *Endocrine-Related Cancer* 17 (February 2010): 215–30.

WEBSITES

- American Cancer Society. "Tamoxifen." <http://www.cancer.org/treatment/treatmentsandsideeffects/guidetocancerdrugs/tamoxifen> (accessed February 27, 2015).
- Macmillan Cancer Support. "Tamoxifen." <http://www.macmillan.org.uk/Cancerinformation/Cancertreatment/Treatmenttypes/Hormonaltherapies/Individualhormonaltherapies/Tamoxifen.aspx> (accessed February 27, 2015).
- National Cancer Institute. "Hormone Therapy for Breast Cancer." <http://www.cancer.gov/cancertopics/types/breast/hormone-therapy-fact-sheet> (accessed February 27, 2015).
- Susan G. Komen. "Tamoxifen." <http://www5.komen.org/BreastCancer/Tamoxifen.html> (accessed February 27, 2015).

ORGANIZATIONS

- American Cancer Society, 250 Williams Street NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org/>.
- National Cancer Institute, 9609 Medical Center Drive, BG 9609 MSC 9760, Bethesda, MD 20892-9760, (800) 4-CANCER (422-6237), <http://www.cancer.gov/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

L. Lee Culvert

REVIEWED BY KEVIN GLAZA, RPh

Tamsulosin

Definition

Tamsulosin is an alpha-1 adrenergic blocker. It works by affecting the smooth muscle of the prostate. This medication is taken to relieve symptoms of bladder outlet obstruction associated with benign prostatic hyperplasia (BPH), including weak urine stream, urinary frequency, or an inability to begin the flow of urine. It has also been prescribed to assist in the passage of kidney stones through the urinary tract.

Purpose

Tamsulosin is a medication used for the management of urination issues associated with an enlarged prostate condition called benign prostatic hyperplasia. Men who have BPH often have trouble urinating. Tamsulosin helps relax the muscles of the prostate and bladder neck so that urine is able to flow through more easily.

Description

Tamsulosin is available as a capsule and is to be taken by mouth (orally).



Flomax (tamsulosin), 0.4 mg. (© Cengage Learning®.)

KEY TERMS

Benign prostatic hyperplasia (BPH)—A noncancerous swelling of the prostate.

Hypotension—Low blood pressure.

Orthostatic hypotension—A drop in blood pressure when moving from a lying to a standing position. May cause dizziness or fainting upon standing.

Priapism—Condition in which the penis remains erect for four or more hours. Usually painful, requires immediate medical treatment to minimize potential for scarring and permanent erectile dysfunction.

Prostate—A male reproductive gland located near where the bladder joins the urethra. The prostate produces the fluid part of semen.

Syncope—Also called fainting, a loss of consciousness over a short period of time due to temporary insufficient blood flow to the brain.

U.S. brand names

Tamsulosin is sold under the brand name Flomax and is offered by prescription only.

Recommended dosage

The usual dose of tamsulosin is 0.4 milligrams (mg) taken by mouth (orally) once a day. Per physician order, the dose may be adjusted after a two- to four-week period, to a maximum dose of 0.8 mg per day if indicated.

Tamsulosin should be taken about 30 minutes following a meal. It should be taken whole, and not crushed, broken, or chewed. It is recommended that this medication be taken at the same time each day.

Geriatric

Dosing should be done conservatively in seniors. As the body ages, it becomes less efficient at eliminating drugs, which can lead to increased risk of side effects and an increased risk of overdose. Seniors should be given the lowest effective dosage.

Precautions

This medication may affect blood pressure causing orthostatic hypotension. It is advised that patients who are taking it move from lying to standing positions slowly so to avoid becoming dizzy or falling.

Tamsulosin may cause a pupil condition called intraoperative floppy iris syndrome (IFIS) during cataract or glaucoma surgery. Patients undergoing eye surgery should be sure to inform their surgeon that they are taking this medication.

Tamsulosin should be taken whole, and not crushed, broken, or chewed. Breaking down the pill can result in an inconsistent or unpredictable amount of the medication entering the bloodstream at one time.

Patients who discontinue use of tamsulosin should consult with their doctor before beginning to take it again as a change in dose may be warranted prior to taking it again.

Pediatric

Tamsulosin is not for use in children.

Geriatric

Seniors are at an increased risk of side effects from tamsulosin, especially if taking antihypertensive medications along with tamsulosin.

Pregnant or breastfeeding

Tamsulosin is not for use in women.

Other conditions and allergies

Any illness causing vomiting and diarrhea may cause a drop in blood pressure, which may be exaggerated by tamsulosin.

Patients should let their doctor know if they are on dialysis.

Should tamsulosin be needed for urinary symptoms associated with cancer of the prostate, additional treatment will likely be indicated.

Side effects

In some cases, allergic reactions to tamsulosin have occurred. Any patient who experiences symptoms of an allergic reaction, including swelling of the lips, throat, mouth or face; difficulty breathing; hives; or rash, should seek emergency medical attention immediately.

Patients should seek emergency medical assistance if any of the following symptoms occur:

- feeling faint (syncope)
- swelling of the face, lips, or tongue (angioedema)
- palpitations (a feeling of the heart pounding in the chest) or chest pain
- severe diarrhea or vomiting
- painful or prolonged penile erection (priapism) lasting four or more hours

Common but less serious side effects (which may diminish with continued use) include:

- mild weakness
- mild headache
- mild dizziness
- general (mild) aches including backache
- insomnia
- cough
- nasal congestion or runny nose
- hoarseness
- decreased sex drive
- abnormal ejaculation

Interactions

Other medications may interact with tamsulosin. Patients should tell their doctor and pharmacist about all prescription medications, over-the-counter medications, vitamins, herbs, and supplements that they are taking. It may be necessary to stop taking some medications or switch to different medications to reduce the chance of serious interactions with tamsulosin.

Drugs

Patients should not take tamsulosin if they are taking other medications designed to have a similar effect including:

- doxazosin (Cardura)
- **terazosin** (Hytrin)
- prazosin (Minipress)
- silodosin (Rapaflo)
- alfuzosin (Uroxatral)

Drug interactions have been noted when tamsulosin is used in conjunction with some medications used for the following conditions:

- stomach ulcers
- tuberculosis
- restless legs syndrome
- low sodium
- thyroid problems
- diabetes
- hypertension
- HIV or AIDS
- blood clot problems
- erectile dysfunction

Drug interactions have been noted when tamsulosin is used in conjunction with other medications in the following drug classifications:

- antibiotics
- antidepressants
- antifungals
- antimalarials
- antipsychotics

Patients should be sure to let their doctor know if they take heart medications, diuretics, or other medications designed to lower blood pressure, as taking tamsulosin may further lower blood pressure.

Food and other substances

Patients taking tamsulosin should not consume alcohol. Alcohol may increase or mimic potential side effects of tamsulosin such as a dizzy or light-headed feeling.

Resources

BOOKS

Carter, H. Ballentine, et al. *The Whole Life Prostate Book*. New York, NY: Free Press, 2013.

Resources

PERIODICALS

Bird, Steven T., et al. "Tamsulosin Treatment for Benign Prostatic Hyperplasia and Risk of Severe Hypotension in Men Aged 40–85 Years in the United States: Risk Window Analyses Using Between and Within Patient Methodology." *BMJ* 347 (November 5, 2013). <http://dx.doi.org/10.1136/bmj.f6320> (accessed March 11, 2015).

Resources

WEBSITES

U.S. National Library of Medicine. "FLOMAX—tamsulosin hydrochloride capsule." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c00d5f7b-dad7-4479-aae2-fea7c0db40ed> (accessed January 26, 2015).

ORGANIZATIONS

National Heart, Lung, and Blood Institute (NHLBI), PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573 nhlbinfo@nhlbi.org, <http://www.nhlbi.nih.gov/>.

Urology Care Foundation, 1000 Corporate Boulevard, Linthicum, MD 21090, (410) 689-3700, (800) 828-7866, info@urologycarefoundation.org, <http://www.urologyhealth.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Laura Jean Cataldo, RN, EdD

REVIEWED BY GREGORY A. PRATT, RPh

Tegretol see **Carbamazepine**

Telmisartan

Definition

Telmisartan is an angiotensin II receptor blocker. An angiotensin II receptor blocker blocks the effects of angiotensin II (a type 1 receptor) resulting in dilation of blood vessels. This dilation of blood vessels results in a lowering of blood pressure.

Purpose

Telmisartan is a medication used for the management of high blood pressure (hypertension). It is also used for cardiovascular risk reduction in patients 55 years of age or older at high risk of developing major cardiovascular events such as heart attack, stroke, or death.

Patients with a history of peripheral vascular disease, diabetes, stroke, or coronary artery disease (CAD) may benefit from use of telmisartan along with other antihypertensive, antiplatelet, or cholesterol-lowering drugs.

Description

Telmisartan is available as a tablet and is to be taken by mouth (orally). It is available in 20, 40, and 80 milligram (mg) tablet strengths. Tablets are individually sealed in blister packs.



Telmisartan, 40 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Some other common angiotensin II receptor blockers include:

- azilsartan (Edarbi)
- **candesartan** (Atacand)
- eprosartan (Teveten)
- **irbesartan** (Avapro)
- **losartan** (Cozaar)
- **olmesartan** (Benicar)
- valsartan (Diovan)

U.S. brand names

Telmisartan is sold under the brand name Micardis. It is offered by prescription only.

Recommended dosage

The initial dose of telmisartan for adults for the treatment of hypertension is 40 mg taken once a day. Later, a maintenance dose of 40 mg to 80 mg may be prescribed. Patients will be monitored closely to ensure the drug is well tolerated before progressing to a higher dosage. Patients who are on diuretics may be prescribed a lower initial or lower maintenance dose by their physician.

The dosing regimen of telmisartan when taken for cardiovascular risk reduction is 80 mg once a day. Telmisartan used for this purpose is usually recommended as an alternative for patients who are unable to take angiotensin-converting enzyme (ACE) inhibitors.

Telmisartan may be taken with or without food. It is recommended that patients take this medication at the same time each day.

Geriatric

Dosing should be done conservatively in seniors. As the body ages, it becomes less efficient at eliminating drugs, which can lead to increased risk of side effects and an increased risk of overdose. Seniors should be monitored closely and given the lowest effective dosage.

Other conditions and allergies

Dose adjustments may need to be made for patients who have poor kidney function (renal failure), for patients who have chronic heart failure, or for patients taking diuretics. For these patients, an overall lower daily dose may be prescribed.

Precautions

This medication affects blood pressure and may cause orthostatic hypotension, so it is advised that patients who are taking it move from lying to standing positions slowly to avoid becoming dizzy or falling.

Patients should call their doctor if they are experiencing vomiting, diarrhea, or excessive sweating, as these conditions may cause an additional drop in blood pressure, accentuating the effects of telmisartan and necessitating a temporary dose adjustment.

Telmisartan may affect kidney (renal) or liver (hepatic) function, so special caution should be taken for use in patients who have known kidney or liver impairment, especially patients with diabetes. Patients may need to have blood work done on a regular basis to check creatinine levels and liver enzymes.

High potassium (hyperkalemia) may occur while taking telmisartan. Symptoms of high potassium include weakness, a slow or weak pulse, and tingling in limbs. Patients should seek medical treatment if these side effects occur.

Telmisartan should be taken whole, and not crushed, broken, or chewed. Breaking down the pill can result in an inconsistent or unpredictable amount of the medication entering the bloodstream at one time.

Patients taking telmisartan should not discontinue use of the medication without first consulting with their doctor.

All patients taking telmisartan should be monitored closely, and the dosage should be re-evaluated regularly.

Pediatric

Telmisartan is not used in children.

Geriatric

Seniors are at an increased risk of side effects from telmisartan and should be monitored closely.

Pregnant or breastfeeding

Telmisartan is a U.S. Food and Drug Administration (FDA) pregnancy category class D drug. Class D drugs are those for which known evidence of serious risks to a fetus exist. Telmisartan should not be taken by anyone who is pregnant or plans to become pregnant. This drug may pass into breast milk and should not be taken if a mother is breastfeeding her baby.

Other conditions and allergies

Before beginning this drug regimen, patients should let their doctor know past or current dietary and medical information including but not limited to the following:

- a history of swelling (edema) in the legs, ankles, feet, or hands
- a history of unexplained weight gain
- any heart problems

KEY TERMS

Angiotensin-converting enzyme (ACE) inhibitor—Type of drug that blocks the conversion of angiotensin I to angiotensin II by inhibiting the angiotensin-converting enzyme, thereby preventing tightening (constriction) of blood vessels.

Coronary artery disease (CAD)—Also called atherosclerosis, it is a build-up of fatty matter and debris in the coronary artery wall that causes narrowing of the artery.

Diuretic—Type of medication that increases the body's output of urine.

Edema—Swelling in the body's tissues caused by excess fluids.

Heart attack—Also called myocardial infarction, myocardial means heart muscle and infarction means death of tissue from lack of oxygen.

Hyperkalemia—An abnormally high concentration of potassium in the blood. The usual reference range for potassium is 3.6-5.0 mmol/L (or mEq/L).

Orthostatic hypotension—A drop in blood pressure when moving from a lying to a standing position. May cause dizziness or fainting upon standing.

Syncope—Also called fainting, a loss of consciousness over a short period of time due to temporary insufficient blood flow to the brain.

- chronic kidney failure or dialysis treatments
- if they are taking diuretics
- if they experience recurrent diarrhea or vomiting episodes
- if they maintain a low salt or salt-free diet

Side effects

In some cases, allergic reactions to telmisartan have occurred. Any patient who experiences symptoms of an allergic reaction, including swelling of the lips, throat, mouth, or face; difficulty breathing; hives; or rash, should seek emergency medical attention immediately.

Patients should seek emergency medical assistance if any of the following symptoms occur:

- feeling faint or experiencing a fainting occurrence (syncope)

- swelling of the face, lips, or tongue (angioedema)
- difficulty swallowing
- confusion
- severe abdominal or back pain
- severe muscle cramps
- rapid or slowed heartbeat
- sudden weakness

Common but less serious side effects include:

- stuffy nose
- mild body aches
- mild back pain
- diarrhea
- sore throat
- mild dizziness
- fatigue

Interactions

Many medications may interact with telmisartan. Patients should tell their doctor and pharmacist about all prescription medications, over-the-counter medications, vitamins, herbs, and supplements that they are taking. It may be necessary to stop taking some medications or switch to different medications to reduce the chance of serious interactions with telmisartan.

Drugs

Telmisartan should not be used by people with diabetes who are taking aliskiren (Tekturna).

Telmisartan should be used with caution in patients who are taking **lithium**, as lithium toxicity has been reported when these drugs are used concomitantly.

Telmisartan should be used with caution in patients who are taking **digoxin**, as digoxin toxicity has been reported when these drugs are used concomitantly.

Patients taking diuretics or potassium supplements should take telmisartan with caution and only after discussion with their doctor.

Patients who are taking nonsteroidal anti-inflammatory (NSAIDs) medication should use telmisartan with caution, as the combination may increase their risk of renal impairment. This is especially important for seniors, patients on diuretic therapy, or patients with compromised renal function. Some common NSAIDs are:

- **ibuprofen** (Motrin)
- naproxen (Aleve)
- **celecoxib** (Celebrex)
- **aspirin** or aspirin-containing products such as Excedrin

Food and other substances

To minimize the potential for hyperkalemia, patients taking telmisartan should avoid potassium-rich foods and products that are high in potassium such as salt substitutes or potassium supplements.

Patients taking telmisartan should not consume alcohol. Alcohol may increase or mimic potential side effects of telmisartan such as a dizzy or light-headed feeling.

Resources

BOOKS

Mann, Douglas, et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 10th ed. Philadelphia: Saunders, 2014.

PERIODICALS

Chalmers, John. "Are the Effects of Telmisartan More Marked in Hypertensive Patients?" *Journal of Hypertension* 32, no. 6 (2014): 1201–2.

WEBSITES

Centers for Disease Control and Prevention, National Center for Health Statistics. "Fast Stats A to Z: Hypertension." Available from: <http://www.cdc.gov/nchs/fastats/hypertension.htm> (accessed January 26, 2015).

U.S. National Library of Medicine. "Micardis—Telmisartan Tablet." DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cfb9309f-e0df-4a55-9542-0e869fce05fb> (accessed January 26, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721, <http://www.heart.org/>.

Heart Foundation, 80 William Street, Level 3, East Sydney NSW 2011, Australia, +61 02 9219 2444/300 36 27 87, <http://www.heartfoundation.org.au/>.

National Heart, Lung, and Blood Institute (NHLBI), PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbiinfo@nhlbi.org, <http://www.nhlbi.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Laura Jean Cataldo, RN, EdD

REVIEWED BY GREGORY A. PRATT, RPH

Temazepam

Definition

Temazepam is a drug that belongs to a family of drugs known as benzodiazepines.



Temazepam, 7.5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Temazepam is given to patients with sleeping problems. It is often prescribed for insomnia characterized by frequent awakening during the night or by awakening early in the morning.

Description

Temazepam is one of several drugs in the class known as benzodiazepines. These drugs produce a variety of effects, but most cause some degree of drowsiness (sedation). Temazepam is used almost exclusively as a hypnotic, or drug given to help people fall asleep. It is nearly always taken just before bedtime. The drug works by slowing down certain impulses in the brain, allowing the patient to fall asleep.

U.S. brand names

Temazepam is sold under the brand name Restoril in the United States and is also available under its generic name.

Recommended dosage

The typical starting dose for adults is 7.5–15 milligrams (mg) taken just before bedtime. The maximum recommended dose is 30 mg.

Pediatric

The doctor should determine the dose in children 18 years of age and younger on an individual basis.

Geriatric

Elderly patients may need only 7.5 mg.

Precautions

Patients taking this drug should be monitored by their physicians to ensure that significant side effects do not develop. Insomnia that lasts longer than 7–10 days may point to a significant medical problem that should be thoroughly evaluated.

Individuals who are taking temazepam should not stop taking it abruptly. Instead, the dose should be reduced gradually. Withdrawal symptoms, including depressed mood, sweating, abdominal cramps, muscle cramps, vomiting, seizures, and shakiness, can develop if the medication is stopped suddenly.

Although patients are instructed to take temazepam in the evening before bedtime, they often experience side effects the next day, particularly drowsiness and loss of coordination or clumsiness. Patients should not operate heavy machinery or drive a car while they are taking temazepam or any other benzodiazepine.

Pregnant or breastfeeding

Pregnant women should not use this drug because it increases the risk of birth defects in the baby. Nursing mothers should not be given temazepam because it can make their babies drowsy and unable to nurse properly.

Other conditions and allergies

Anyone with a history of anemia, liver disease, kidney disease, drug abuse, serious psychological disorders, or suicide attempts should be given temazepam only after being thoroughly evaluated by their physician. This caution also applies to individuals with a history of lung disease, seizure disorders, and narrow-angle glaucoma.

Side effects

Temazepam is a relatively safe drug, safer than most of the benzodiazepines. Its less serious but more common side effects include clumsiness or unsteady behavior, dizziness, drowsiness, and slurred speech. Some patients taking temazepam experience abdominal cramps, dry mouth, constipation, diarrhea, headache, nausea, vomiting, a giddy sense of well-being, and changes in sexual drive.

A small number of patients taking temazepam have experienced anger outbursts, confusion, mental depression, unusually low blood pressure, memory difficulties, nervousness, irritability, and muscle weakness. Symptoms of a temazepam overdose include extreme drowsiness, significant confusion, breathing difficulties, a very slow heartbeat, and staggering.

Rebound insomnia is one of the more common side effects of tapering a patient's dose of temazepam. Rebound insomnia is a reaction characterized by the recurrence of the symptom that the drug was originally given to suppress, namely problems with falling or staying asleep. When a person takes a medication for sleep on a regular basis, the body adjusts to the presence of the drug. As a result, when the person stops taking the sleeping medication, the body will take a few nights to return to its normal condition. During this period of readjustment, the person may experience a few sleepless hours each night. People often mistake the rebound insomnia for regular insomnia and consider it a good reason to continue taking temazepam, even though the drug is no longer needed.

People can also develop withdrawal symptoms even when they are gradually decreasing their dose of temazepam, particularly if the original dose was high. The more common withdrawal symptoms include sleeping difficulties, irritability, and nervousness. Less common withdrawal side effects include abdominal cramps, confusion, sweating, nausea, trembling, increased heart rate, and mental depression.

Geriatric

Side effects of dizziness, light-headedness, and clumsiness after taking temazepam are especially common in elderly patients.

Interactions

Patients should always inform any healthcare provider that they see—doctors, dentists, nurses, and others—about all the medications they are taking before starting temazepam.

Drugs

Temazepam interacts with certain other drugs, including cimetidine (an antihistamine), disulfiram (a drug given to help patients control cravings for alcohol), and **clozapine** (an antipsychotic medication). **Rifampin**, which is an antibiotic, may decrease the effectiveness of the temazepam if the two are taken together.

Temazepam should not be combined with any other drugs that lower the level of activity in the central nervous system. Examples of such drugs include prescription pain medications, antihistamines, barbiturates, and muscle relaxants.

Food and other substances

Patients should avoid drinking alcohol while taking temazepam, because it will intensify the drug's sedative effects. Heavy smoking interferes with the effectiveness of temazepam.

KEY TERMS

Antihistamine—A medication used to alleviate allergy or cold symptoms such as runny nose, itching, hives, watering eyes, or sneezing.

Barbiturates—A class of medications that causes sedation and drowsiness. They may be prescribed legally but are also used as drugs of abuse.

Benzodiazepines—A group of central nervous system depressants used to relieve anxiety or to induce sleep.

Hypnotic—A type of medication that induces sleep.

Insomnia—A chronic inability to sleep or to remain asleep throughout the night.

Rebound—A physical reaction to stopping a medication characterized by the reappearance of the symptom(s) that the medication was given to suppress. For example, people who stop taking temazepam may experience rebound excitability and sleeping problems.

Sedation—A state of emotional or physical relaxation. The term is usually used to refer to this condition when it is produced by a medication.

Withdrawal—Symptoms experienced by a person who has become physically dependent on a drug, experienced when the drug use is discontinued.

Persons taking temazepam should not eat grapefruit or drink grapefruit juice, as the fruit may inhibit the metabolism of the drug, resulting in potentially toxic levels.

Resources

BOOKS

Brunton, Laurence, Bruce Chabner, and Bjorn Knollman. *Goodman & Gilman's The Pharmacological Basis of Therapeutics* 12th ed. New York: McGraw-Hill, 2010.

PERIODICALS

Kansagra, S., R. Walter, and B. Vaughn. "Nocturnal Temazepam in the Treatment of Narcolepsy." *Journal of Clinical Sleep Medicine* 9, no. 5 (2013): 499–500.

WEBSITES

Micromedex. "Temazepam (Oral Route)." <http://www.mayoclinic.org/drugs-supplements/temazepam-oral-route/description/drg-20072162> (accessed February 27, 2015).

UK National Health Service (NHS). "Temazepam (Temazepam 10mg Tablets)." <http://www.nhs.uk/Medicine-Guides/pages/MedicineOverview.aspx?>

condition=Insomnia&medicine=Temazepam&preparation=Temazepam%2010mg%20tablets (accessed February 27, 2015).

U.S. Food and Drug Administration. "Restoril (Temazepam) Capsules." American Society of Health-System Pharmacists. Available from: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm113808.htm> (accessed February 27, 2015).

ORGANIZATIONS

National Sleep Foundation, 1010 N. Glebe Road, Suite 310, Arlington, VA 20221, (703) 243-1697, nsf@sleepfoundation.org, <http://sleepfoundation.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Mark Mitchell, MD

REVIEWED BY KEVIN GLAZA, RPh

Tenex see **Guanfacine**

Tenofovir/efavirenz/emtricitabine see **Efavirenz/emtricitabine/tenofovir**

Tenormin see **Atenolol**

Terazosin

Definition

Terazosin is an oral medication for treating symptoms of an enlarged prostate—benign prostatic hyperplasia (BPH)—in men. It is also used to treat hypertension (high blood pressure) in both men and women. Terazosin is in the drug class of peripherally acting alpha-adrenergic blockers or antiadrenergic agents, also called alpha-blockers or alpha-1 blockers.

Purpose

The prostate—the male gland that produces semen for carrying sperm—surrounds the urethra, which carries urine. The prostate enlarges with age. BPH affects about half of all men over age 55, three-quarters of men over 65, and 90% of men by age 80. An enlarged prostate can pinch the urethra and cause urination difficulties, including a weak urine stream, dribbling, incomplete bladder emptying, painful urination, and frequent or urgent urination. Over time, BPH can cause problems such as urinary tract infections and kidney damage. Terazosin does not shrink the prostate or cure BPH, but it relaxes the muscles in the prostate and the neck of the bladder. This helps relieve symptoms such as difficulty



Terazosin, 5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

initiating urine flow, a weak stream, or the frequent or urgent need to urinate, including at night. Alpha-blockers such as terazosin, which have long been used to treat hypertension, can relieve BPH symptoms even in men with normal blood pressure.

Terazosin is also used alone or in combination with other drugs to help control high blood pressure. Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. Terazosin may lower blood pressure more effectively when used in combination with lifestyle changes such as exercise, quitting smoking, and lowering dietary fat.

Off-label uses

Terazosin may be prescribed for purposes not specifically approved by the U.S. Food and Drug Administration (FDA). For example, terazosin or another alpha-blocker that improves urine flow is typically prescribed for at least a few weeks following radiation therapy for prostate cancer and is gradually withdrawn as symptoms improve. Terazosin may also be prescribed to help pass kidney stones during urination, to help treat bladder problems in women, and for excessive perspiration (hyperhidrosis).

Description

Terazosin and other alpha-blockers relieve BPH symptoms by relaxing the smooth muscles of the prostate and neck of the bladder to improve urine flow and reduce

bladder blockage. They also relax blood vessels so that blood flows more easily, and blood pressure is lowered. Terazosin selectively blocks postsynaptic alpha-1 receptors. These are cell-surface receptors located throughout the body that bind certain adrenergic agents, such as **epinephrine** (adrenaline) and norepinephrine, to contract smooth muscles and constrict blood vessels to raise blood pressure, among other effects. By blocking these receptors, terazosin relaxes smooth muscles and dilates (relaxes) arteries and veins to lower blood pressure. Selective alpha-blockers, such as terazosin, are less likely to cause rapid heart rate (tachycardia).

Alpha-blockers such as terazosin are usually effective for BPH symptoms within a few days or weeks. Terazosin is active for 24 hours after ingestion and reaches its peak response for symptoms of BPH within four to six weeks. Terazosin and other alpha-blockers cost less than other BPH drugs, but they may not work for all men. The other main class of BPH drugs—5-alpha-reductase inhibitors—may be more effective for some men. Furthermore, older alpha-blockers such as terazosin can cause sudden drops in blood pressure, whereas newer alpha-blockers tend not to affect blood pressure.

Terazosin is available as 1 mg, 2 mg, 5 mg, and 10 mg capsules. The capsules come in a variety of colors depending on the strength and manufacturer. Terazosin is taken by mouth, with or without food, twice a day or once a day at bedtime. It is stored in the tightly closed container it is supplied in, at room temperature and away from light, heat, and moisture (not in the bathroom). The capsules may soften or melt if stored above 77°F (25°C).

U.S. brand names

Brand-name terazosin, known as Hytrin, has been discontinued in the United States. It has been replaced by generic terazosin hydrochloride manufactured by various companies including Sandoz, Apotex, Ivax, Jubilant Cadista, and Mylan.

Canadian brand names

Canadian brand names for terazosin are Apo-Terazosin and ratio-Terazosin.

International brand names

The most common international brand name for terazosin is Hytrin. Other common brand names include:

- Apo-Terazosin
- Hitrin
- Itrin
- Kornam

KEY TERMS

Adrenergic—Activated by epinephrine (adrenaline) or similar substances.

Alpha-blockers—Drugs, such as terazosin, that treat high blood pressure and other conditions by blocking alpha-adrenergic receptors.

Alpha-receptors—Receptors on the cell surfaces of organs and tissues that bind specific adrenergic agents to constrict blood vessels and contract smooth muscles; blocked by terazosin.

Benign prostatic hyperplasia (BPH)—An overgrowth of a portion of the prostate gland, usually in men over age 50, that can constrict the urethra and interfere with urination.

Hypertension—High blood pressure.

Hypotension—Low blood pressure.

Prostate—The walnut-shaped gland that surrounds the urethra at the neck of the bladder in males and supplies fluid for semen.

- Setegis
- Teranar
- Terasin
- Teraumon
- Terzosin Accord
- Terazosin HEXAL
- Zayasel

Origins

Terazosin capsules and tablets were originally approved by the FDA in 1987. Generic terazosin has been available since 1998.

Recommended dosage

Terazosin doses are increased gradually until the most effective dosage with minimal side effects is reached. The initial dosage for BPH is 1 mg once daily at bedtime. This can be gradually increased to 5 mg once daily at bedtime. Some patients may benefit from up to 20 mg per day. The initial dosage for hypertension is also 1 mg once daily at bedtime. Maintenance doses are 1–5 mg per day or every 12 hours, with a maximum of less than 20 mg per day. The initial dosage and subsequent increases are always taken at bedtime to minimize the risk of fainting from low blood pressure.

Terazosin must be taken regularly to get the most benefit. If it is stopped for a few days or more, the doctor will usually restart it at the lowest dose with gradual increases. A missed dose should be taken as soon as possible, unless it is almost time for the next dose, in which case the missed dose should be skipped and the regular schedule resumed. Patients should check with their doctor if they miss two or more doses.

Pediatric

Off-label dosages for pediatric hypertension are 1 mg once per day, gradually increased as necessary to a maximum of 20 mg per day.

Geriatric

For hypertension in geriatric patients, the initial dose is 0.5 mg once daily at bedtime, with gradual adjustments based on the response.

Other conditions and allergies

Terazosin doses should be increased with caution in patients with liver impairment.

Precautions

- Terazosin must be taken exactly as directed—no more, no less, and no more often—and should not be stopped without consulting the doctor.
- Terazosin can cause drowsiness, dizziness, lightheadedness, or fainting; patients should not drive, operate machinery, or perform other tasks that require alertness for 12 hours after the first dose or an increased dose or after restarting the drug, until they know how it affects them. Patients should rise from bed slowly, resting their feet on the floor for a few minutes before standing, and sit or lie back down if dizziness occurs. Taking terazosin at bedtime reduces the risk of injury from dizziness or fainting.
- It may take two weeks before BPH symptoms improve and four to six weeks or longer before terazosin's full benefit is realized. Patients should consult their doctor if symptoms do not improve or worsen.
- Blood pressure should be checked regularly. Patients taking terazosin for hypertension should call their doctor if their blood pressure remains high or increases.
- Laboratory or other tests, such as prostate exams, should be performed periodically to check for responses and side effects.
- Patients should tell their doctor or dentist that they are taking terazosin (and any other prescription or nonprescription drugs or herbal products) before having any type of surgery. Before having eye surgery, doctors

should be informed if the patient has ever taken terazosin.

Symptoms of terazosin overdose can include:

- dizziness
- lightheadedness
- fainting
- blurred vision

Geriatric

Geriatric patients are at higher risk of side effects from terazosin, especially low blood pressure, dizziness, and fainting when rising from a sitting or lying position, which can increase the risk of falls.

Pregnant or breastfeeding

Terazosin is in the FDA pregnancy category C, meaning that it should be used during pregnancy only if clearly needed. Women taking terazosin should call their doctor if they become pregnant and discuss the potential benefits and risks to the fetus. It is not known whether terazosin passes into breast milk, so caution is advised for nursing mothers.

Other conditions and allergies

Patients should tell their doctor and pharmacist if they have any allergies, including allergies to terazosin, any of the inactive ingredients in terazosin capsules, other alpha-blockers such as doxazosin or prazosin, or any other medications. Before taking terazosin, the doctor should be informed of the patient's medical history, especially any history of:

- liver problems
- prostate cancer
- low blood pressure or fainting
- certain eye problems such as cataracts or glaucoma

Side effects

Between 10% and 20% of patients taking terazosin are affected by dizziness. Weakness affects 2%–13% of patients. Side effects in 1%–10% of patients are (in decreasing frequency):

- hypotension (low blood pressure)
- nasal inflammation or congestion
- lightheadedness
- drowsiness
- rapid pulse
- nausea
- swelling (edema)

- sinus inflammation
- labored breathing
- fatigue
- headache
- back pain
- flu-like symptoms
- rapid heartbeat
- dimmed vision in one eye (amblyopia)
- blurred vision
- impotence
- fainting

Other possible side effects include stomach problems and reduced semen during ejaculation. The doctor should be notified immediately of severe, persistent, or worsening side effects and serious side effects such as:

- fainting
- fast, pounding, or irregular heartbeat
- pain, burning, numbness, or tingling in the hands or feet
- problems with sexual function or decreased sexual ability, inability to maintain an erection or ejaculate, or decreased sexual desire
- swelling of the feet, ankles, lower legs, or hands
- unexpected weight gain

Rarely, men taking terazosin have experienced painful or prolonged penile erections lasting four hours or more. If this occurs, the patient must stop using the drug and get immediate medical assistance to prevent permanent problems.

Geriatric

Geriatric patients are at high risk for low blood pressure and fainting upon standing. They also may be more bothered by side effects such as dry mouth or urinary complications.

Other conditions and allergies

Although very serious allergic reactions to terazosin are rare, the following symptoms require emergency medical attention:

- hives
- rash
- itching or swelling, especially of the face, tongue, or throat
- severe dizziness
- difficulty breathing or shortness of breath

Interactions

The doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used or planning to be used by the patient. Patients should bring a list of medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

Some drugs have serious interactions with terazosin and require changing medications or dosages or carefully monitoring for side effects. These include medications for erectile dysfunction (ED) or pulmonary hypertension—such as **sildenafil** (Viagra), **tadalafil** (Cialis), or **varde-nafil** (Levitra)—as well as other medications for high blood pressure, especially verapamil and other alpha-blockers, such as prazosin and **tamsulosin**.

An additional 90 drugs have significant interactions with terazosin and require close monitoring. Eight drugs have minor interactions. Patients should check the labels on all their medicines, including cough-and-cold medications, diet aids, and nonsteroidal anti-inflammatory drugs (NSAIDs) such as **ibuprofen** and naproxen, because these may have ingredients that can increase blood pressure.

Herbs and supplements

Yohimbe should never be taken in combination with terazosin, because there is a high likelihood of a serious or life-threatening interaction.

Food and other substances

Patients should follow their doctor's dietary instructions, including orders for a reduced salt (sodium) diet. Alcohol should be limited while taking terazosin.

Resources

PERIODICALS

"Drugs to Treat Hypertension." *Journal of Psychosocial Nursing & Mental Health Services* 52, no. 2 (2014): 11–12.

WEBSITES

MedlinePlus. "Terazosin." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a693046.html> (accessed March 10, 2015).

"Prostate Enlargement: Benign Prostatic Hyperplasia." National Kidney and Urologic Diseases Information Clearinghouse. <http://kidney.niddk.nih.gov/kudiseases/pubs/prostateenlargement> (accessed March 10, 2015).

“Terazosin (Rx).” Medscape.com. <http://reference.medscape.com/drug/hytrin-terazosin-342348#91> (accessed March 10, 2015).

U.S. Food and Drug Administration. “High Blood Pressure—Medicines to Help You.” FDA.gov. <http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118594.htm> (accessed March 10, 2015).

ORGANIZATIONS

National Kidney and Urologic Diseases Information Clearinghouse, 3 Information Way, Bethesda, MD 20892-3580, Fax: (703) 738-4929, (800) 891-5390, nkudic@info.niddk.nih.gov, <http://kidney.niddk.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY DENISE M. LINTON, DNS, FNP-BC

Terbinafine

Definition

Terbinafine is a topical and oral anti-fungal agent used to treat superficial fungal infections of the skin, fingernails, and toenails. It is in a drug class known as allylamine fungicides.

Purpose

Terbinafine is most effective against dermatophyte fungi (fungi that live on human skin). Terbinafine topical cream is effective against superficial fungal skin infections in about half the time required by other topical anti-fungal agents. Topical prescription-strength terbinafine formulations are used to treat fungal skin infections known as ringworm or tinea:

- tinea barbae: barber’s itch or beard ringworm that affects the face and neck
- tinea corporis: ringworm of the skin
- tinea cruris: jock itch that affects the groin and perineum
- tinea faciei: facial ringworm
- tinea pedis: athlete’s foot

Oral terbinafine is used to treat more extensive or serious ringworm infections and infections that do not improve with topical medication. Tinea capitis or scalp ringworm is a usually harmless infection of the hair and scalp that causes scaly spots and patches of broken hair. It most often occurs in children and is readily transmitted through contaminated objects such as combs or pillows. Although scalp ringworm is usually caused by dermatophytes that



Terbinafine, 250 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

preferentially grow on humans, it can also be contracted from animals (zoophilic dermatophytes) or from soil (geophilic dermatophytes). Kerions are inflamed, thickened, pus-filled areas of the scalp and may be accompanied by fever. Scalp ringworm and kerions require oral (systemic) treatment, because the fungi grow deep inside the hair follicles that cannot be penetrated by topical medications. Oral terbinafine is also used to treat fungal infections of the toenails or fingernails, known as tinea unguium or onychomycosis, which may be secondary to superficial dermatophyte infections. Onychomycosis is typically caused by a dermatophyte or *Candida* spp. Because these infections are deep under the nail in the cuticle, topical treatments cannot reach them in sufficient quantities. Oral terbinafine is more effective against fungal nail infections than two other commonly used medications, **griseofulvin** (Fulvicin, Gris-Peg) and itraconazole (Sporanox).

Terbinafine may be prescribed for other uses. For example, it is used to treat sporotrichosis, a chronic skin infection caused by the fungus *Sporothrix schenckii*. This fungus lives on vegetation, and infection occurs when the skin is broken while handling plants such as rosebushes or mulch. It often affects farmers and gardeners. Systemic or disseminated sporotrichosis can occur in people with compromised or deficient immune systems who inhale the fungal spores.

Description

Terbinafine is a synthetic allylamine. Because it is very hydrophobic (water-avoiding) it accumulates in

KEY TERMS

Allylamine—A very basic liquid used in the synthesis of drugs such as terbinafine.

Candida—Various species of yeast-like fungi, especially *C. albicans*, that are normal inhabitants of the human body but that can overgrow and cause infection.

Candidiasis—Yeast infection caused by *Candida* spp.

Dermatophyte—A fungal parasite on skin, hair, or nails.

Griseofulvin—An antifungal medication similar to terbinafine.

Itraconazole—An antifungal medication similar to terbinafine.

Kerion—An inflammatory ringworm infection of the hair follicles of the scalp or beard that is usually accompanied by a secondary bacterial infection.

Onychomycosis—A fungal disease of the fingernails or toenails.

Ringworm—Any of several contagious fungal diseases of the skin, hair, or nails characterized by ring-shaped patches.

Tinea barbae—Barber's itch: ringworm of the face and neck.

Tinea capitis—A contagious fungal infection (ringworm) of the scalp.

Tinea corporis—A fungal infection (ringworm) of the skin.

Tinea cruris—Jock itch: a fungal infection of the groin and perineum.

Tinea faciei—A superficial fungal infection of the skin of the face.

Tinea pedis—Athlete's foot: ringworm of the feet.

Tinea unguium—Onychomycosis: the most common fungal nail infection.

skin, nails, and fatty tissues. It is very effective against a variety of dermatophytes that infect the skin and nails, including *Epidermophyton floccosum*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum*. Like other allylamines, terbinafine interferes with the synthesis of a component of the fungal cell membrane by selectively inhibiting a fungal enzyme called squalene epoxidase. This changes the permeability of the cell membrane and weakens the cells, causing them to burst (lyse). Inhibition of squalene epoxidase may also cause squalene to accumulate to toxic levels that kill the fungus.

Nail infections treated with terbinafine may not be completely cured until several months after finishing the medication. This is because it takes time for healthy nails to grow back in.

U.S. and Canadian brand names

Lamisil is the U.S. and Canadian brand name for oral terbinafine tablets. Terbinafine is also available in generic versions in the United States and some other countries.

International brand names

Terbinafine is marketed under various international generic and brand names. Lamisil is the most common brand name. Other international brand names include:

- Corbinal
- mycoCeaze
- Terbisil
- Sebifin
- Zimig

Origins

Terbinafine was developed by the pharmaceutical company Novartis. The U.S. Food and Drug Administration (FDA) approved topical terbinafine in 1992 and oral terbinafine in 1998. Topical terbinafine is available as prescription-strength and over-the-counter 1% creams, lotions, gels, solutions, powders, and sprays for treating dermatophyte skin infections such as tinea corporis, tinea cruris, and tinea pedis. Oral 250 mg tablets are available by prescription for onychomycosis. In 2007, the FDA approved oral terbinafine hydrochloride as 125 mg and 187.5 mg granules that can be sprinkled on food to treat tinea capitis in children aged four and older. The contents of a packet are sprinkled on a spoonful of soft, non-acidic food, such as pudding or mashed potatoes, and the entire spoonful is swallowed without chewing. Terbinafine granules should not be used on fruit-based foods such as applesauce.

Recommended dosage

The dosage and duration of treatment depend on the condition and its response to terbinafine. Prescription-strength and over-the-counter creams, gels, sprays, powders, or solutions are applied to affected areas twice daily for athlete's foot and once daily for jock itch or other ringworm infections, for a duration of about one week.

The recommended adult oral dose of terbinafine is 250 mg once daily. Onychomycosis and other nail infections require daily treatment for six weeks for

fingernails and 12 weeks for toenails. Tinea capitis usually requires six weeks of treatment, although there is some evidence that tinea capitis caused by *Microsporum canis* requires a higher dosage or longer therapy. Although oral terbinafine is not approved by the FDA for cutaneous candidiasis (*Candida* skin infection), tinea corporis, tinea cruris, or tinea pedis, the usual dosages for these conditions are 250 mg once daily for 2–4 weeks, and 2–6 weeks for tinea pedis. Tinea capitis and kerions usually require 6–8 weeks of treatment with oral terbinafine or griseofulvin.

A missed dose is taken as soon as it is remembered; however, if it is almost time for the next dose, the missed dose should be skipped and the regular dosing schedule resumed. Terbinafine should be stored at room temperature, in the tightly closed container it came in, away from excess heat and moisture (not in the bathroom).

Pediatric

The usual pediatric oral granule dosages for tinea capitis in children ages four and older are once daily treatment for six weeks with:

- 125 mg for children weighing less than 25 kg (55 lb.)
- 187.5 mg for children weighing 25 to 35 kg (55 to 77 lb.)
- 250 mg for children weighing more than 35 kg (77 lb.)
- possibly higher doses or longer duration for tinea capitis caused by *M. canis*

Precautions

The full prescribed amount of terbinafine should be used. Stopping the medication too soon may not completely cure the infection, allowing it to return. The doctor should be notified if the infection persists or worsens with treatment.

Terbinafine can increase sun sensitivity. Patients should avoid prolonged exposure to sunlight and avoid tanning booths and sunlamps. Sunscreen and protective clothing should be worn outdoors.

In rare cases, oral terbinafine has been clearly linked to acute liver injury, including severe cases that require a liver transplant or result in death. Lab tests, including liver function tests, may be required to monitor responses to terbinafine.

Pregnant or breastfeeding

Terbinafine is in the FDA pregnancy category B—high-dose studies in animals have not shown any evidence of reduced fertility or fetal toxicity. However, there have been no controlled studies in human pregnancy, and the manufacturer recommends that oral treatment be postponed until after pregnancy. Oral

terbinafine passes into breast milk and should not be used by nursing mothers.

Other conditions and allergies

Patients should tell their doctor and pharmacist if they are allergic to terbinafine, any inactive ingredients in terbinafine, or any other medications or if they have any other allergies. Patients should tell their doctors if they have or have ever had kidney or liver disease or HIV/AIDS, lupus, or other immune system disorders. Terbinafine should not be taken by patients with active or chronic liver disease. Terbinafine may induce or worsen subacute cutaneous lupus erythematosus, an autoimmune disease of the skin.

Side effects

Most patients do not experience serious side effects from terbinafine. The most common side effects of oral terbinafine are:

- headache
- cough
- diarrhea
- abdominal pain
- hives, itching, or rash
- altered or lost senses of taste and smell

The doctor should be notified if any of these symptoms are severe or persistent:

- diarrhea
- stomach pain
- rash
- itching
- hives
- taste changes or loss of taste

The following uncommon side effects require calling the doctor immediately:

- persistent upset stomach
- vomiting
- unusual or extreme tiredness
- pain in the upper-right stomach
- pink or bloody urine
- pale stools
- severe and worsening skin rash
- fever, sore throat, chills, and other signs of infection
- swollen lymph glands
- vision changes
- mouth sores
- unusual change in the amount of urine

- chest pain
- fast or irregular heartbeat
- persistent dry cough
- symptoms of liver disease, including persistent nausea/vomiting, loss of appetite, severe stomach or abdominal pain, dark urine, yellowing eyes or skin
- rare serious allergic reactions, including rash, itching, or swelling, especially of the face, tongue, or throat; severe dizziness; or trouble breathing

Interactions

The doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

Drugs that affect liver enzymes that are involved in removing terbinafine from the body can seriously affect terbinafine blood levels and increase potential side effects. For example, the azole antifungal agent **fluconazole** (Diflucan) increases terbinafine blood levels by 52%–69%. Other drugs that may affect terbinafine blood levels include:

- **rifampin** (Rifadin, Rimactane)
- cimetidine (Tagamet)
- amiodarone
- the azole antifungal **ketoconazole**

Other drugs that can interact with oral terbinafine and may require changing doses and/or monitoring for side effects include:

- anticoagulants (blood thinners) such as **warfarin** (Coumadin)
- antidepressants such as **amitriptyline** (Elavil), amoxapine (Asendin), clomipramine (Anafranil), **desipramine** (Norpramin), **doxepin** (Adapin, Sinequan), **imipramine** (Tofranil), **nortriptyline** (Aventyl, Pamelor), protriptyline (Vivactil), rasagiline, and trimipramine (Surmontil)
- beta-blockers such as **atenolol** (Tenormin), labetalol (Normodyne), **metoprolol** (Lopressor, Toprol XL), nadolol (Corgard), and **propranolol** (Inderal)
- medications that suppress the immune system such as azathioprine (Imuran), **cyclosporine** (Neoral, Sandimmune), **methotrexate** (Rheumatrex), sirolimus (Rapamune), and **tacrolimus** (Prograf)
- selegiline (Eldepryl)

Food and other substances

Terbinafine may be taken with or without food, except for the oral granules, which must be taken with food. Alcoholic beverages must be limited while taking terbinafine. Daily alcohol use may increase the risk of serious side effects.

Resources

PERIODICALS

- Feinberg, Arthur N., et al. "Pediatric Dermatologic Disorders." *Journal of alternative Medicine Research* (suppl. Special Issue: "Dermatology and Psychiatry") 6, no. 2 (2014): 95–137.
- Verrier, Julie, et al. "Oral Terbinafine and Itraconazole Treatments against Dermatophytes Appear Not to Favor the Establishment of *Fusarium* spp. in Nail." *Dermatology* 228, no. 3 (June 2014): 225–32.

WEBSITES

- "Drug Record: Terbinafine." LiverTox. November 4, 2014. <http://livertox.nih.gov/Terbinafine.htm> (accessed December 20, 2014).
- "Fungal Nail Infection." MedlinePlus. November 20, 2012. <http://www.nlm.nih.gov/medlineplus/ency/article/001330.htm> (accessed December 20, 2014).
- "Sporotrichus." MedlinePlus. May 30, 2012. <http://www.nlm.nih.gov/medlineplus/ency/article/001338.htm> (accessed December 20, 2014).
- "Terbinafine Dosage." Drugs.com. <http://www.drugs.com/dosage/terbinafine.html> (accessed December 20, 2014).
- "Terbinafine—Oral, Lamisil." Medicine.Net. Available from: <http://www.medicinenet.com/terbinafine-oral/article.htm> (accessed December 20, 2014).

ORGANIZATIONS

- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY JAMES E. WAUN, MD, RPH

Tetracycline

Definition

Tetracycline is an antibiotic drug. It gives its name to an entire class of antibiotics that share characteristics of its central chemical structure.

Purpose

Tetracycline treats a variety of infections, particularly of the respiratory tract, urinary tract, and skin. Some of the organisms that tetracyclines are effective against include the



Tetracycline, 250 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

causes of anthrax, acne, Lyme disease, Rocky Mountain spotted fever and other tick-borne infections, syphilis, plague, cholera, gonorrhea, chlamydia, and stomach ulcers.

Description

Tetracycline is available as a capsule in 250 or 500 milligram (mg) strengths. They are two-toned, often blue and yellow, black and yellow, or orange and yellow. Imprint on capsules depends on manufacturer. The medication is taken by mouth and must be prescribed by a physician. Tetracycline is used internationally and is also frequently used in veterinary medicine.

For individuals who cannot take pills by mouth, the contents of capsules can be used by a licensed pharmacist to create a liquid suspension. The suspension is usually made to a ratio of 25 mg per milliliter (mL).

U.S. brand names

Tetracycline is manufactured as a generic by many different companies.

Canadian brand names

In Canada, tetracycline is sold as Apo-Tetra and Nu-tetracycline.

International brand names

Tetracycline is sold under a large variety of brand names internationally, including Bronchocine in Tunisia, Cicloteteryl in Argentina, Hostcycline in India,

Alcycline in Kenya, Ambramacina in Italy, Tefilin in Germany, and Tetrana in Thailand. In some countries, tetracycline is only one component of the medication, and there are other medications included in the formulation. In some locations, it is only available for veterinary use.

Recommended dosage

Recommended dosages are based on the amount of tetracycline needed to treat the infection. Dosing schedules depend on the specific infection being treated, although usual adult doses are 500 mg taken four times a day for 7–28 days. Treatment durations for specific conditions include:

- bronchitis, 7–10 days
- chlamydia, at least 7 days
- stomach ulcers, 14 days
- Lyme disease, 14–30 days
- pneumonia, 10–21 days
- upper respiratory infection, 7–10 days
- early syphilis, 10–15 days
- tertiary (advanced) syphilis, 28 days
- gonorrhea, 7 days
- bladder infection, 3–7 days

For acne, once control has been obtained, dosage may be decreased to 250 mg and frequency of dosing may decrease as well. Acne treatment may continue for months to years, depending on the severity of the condition.

Pediatric

Tetracycline is absolutely contraindicated in children under the age of eight, due to the fact that tetracycline causes permanent stains on developing teeth. In children over eight years, tetracycline is dosed by weight, as 25–50 mg per kilogram (kg) of body weight per day, divided into four equivalent doses.

Other conditions and allergies

Dose may need to be decreased in individuals with renal (kidney) impairment or on dialysis.

Precautions

The following precautions apply to all individuals.

- This drug should be taken for the entire length of the prescription. Failure to take a complete course of the medication can result in return of symptoms.
- Tetracycline should be taken on an empty stomach, one hour before or two hours after eating.

- Taking the medication with a large (at least 16 oz.) glass of water will help avoid irritation to the esophagus from the drug.
- Tetracycline makes the skin more sensitive to sun exposure and tanning lights, resulting in more easily (and potentially severely) burned skin.
- Use over a long period of time can increase the risk of developing another fungal or bacterial infection (secondary infection).
- *C. difficile*-associated diarrhea and pseudomembranous colitis have both been associated with long-term use of tetracycline, even months after the drug has been discontinued.
- Tetracycline should be discarded on its expiration date, as expired medications can cause an anemia syndrome.
- Tetracycline can cause an increase in pressure inside the skull. Women of child-bearing age are at particular risk, as are individuals who have had this type of adverse effect from tetracyclines or other agents previously. Individuals who develop headaches or vision changes should consult their healthcare provider immediately.

Pregnant or breastfeeding

This drug is a pregnancy category D drug, meaning that it is known to cause harm in a developing fetus. Tetracycline also passes into the breast milk. Women who are pregnant or breastfeeding should not use tetracycline. It is known to damage the development of teeth and bones.

Other conditions and allergies

Individuals should not take tetracycline if they are allergic to tetracycline or other drugs in its class (e.g., doxycycline, **minocycline**, or demeclocycline) or have developed jaundice and liver problems when taking tetracycline in the past. Individuals with a history of severe allergies, asthma, or prior reactions involving anaphylaxis, hives, or the severe swelling called angioedema are at higher risk for serious reactions to tetracycline.

Individuals with a history of kidney or liver problems or on dialysis should tell their doctor before taking this drug.

Side effects

Serious and sometimes fatal reactions can occur in individuals who are allergic to tetracycline drugs. Anyone who has had a severe reaction to any drug should alert the physician before taking this drug.

The most common adverse side effects of tetracycline for all age groups tend to be mild. They include:

- upset stomach
- loose stools or diarrhea

KEY TERMS

Anaphylaxis—A severe, systemic allergic reaction that can be potentially life-threatening.

Pregnancy category—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk, but no human studies; or adverse effects in animals, but not in well-controlled human studies. Category C: No adequate human or animal studies; or adverse fetal effects in animal studies, but no available human data. Category D: Evidence of fetal risk, but benefits may outweigh risks. Category X: Evidence of fetal risk. Risks outweigh any benefits.

Secondary infection—An infection by a microbe that occurs because the body is weakened by a primary infection caused by a different kind of microbe; also called an opportunistic infection.

- nausea and vomiting
- headache

These side effects should be brought to the doctor's attention if they do not go away within a few days.

Whitish vaginal discharge or white coating of the tongue and inside of the mouth should also be reported to the doctor.

A doctor should be notified immediately if any of these less common but more serious side effects occur.

- wheezing, difficulty breathing or swallowing (may indicate a severe allergic reaction and require immediate medical attention)
- hoarse voice
- severe skin rash, itching, or hives; blistering or separating skin
- swelling
- yellowing of the skin or the whites of the eyes
- nail discoloration
- difficulty swallowing or painful swallowing
- vaginal itching or discharge (females)
- severe headache
- vision changes
- seizures
- abdominal pain with fever
- sensation of an extra, skipped, or fast heartbeat
- dizziness, fainting

- severe or bloody diarrhea, even if it occurs two months after ending tetracycline treatment
- easy bruising or bleeding
- very dark urine
- severe muscle weakness or unusual loss of muscle control

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplement including vitamin supplements.

Drugs

Tetracycline is known to interact with the following pharmaceutical drugs. Other interactions are possible. An individual who develops any unusual or unexpected symptoms should contact a physician.

- The following drugs decrease the absorption of tetracycline: antacids, bile acid sequestrants, bismuth, calcium salts, lanthanum, magnesium Salts, **quinapril**, and sucralfate.
- Tetracycline may increase the serum concentration of the following drugs: **aripiprazole**, avanafil, **colchicine**, dapoxetine, doxorubicin, and quinine.
- Tetracycline may decrease the serum concentration of the following drugs: atovaquone and iron salts.
- Tetracycline may interfere with the effect of penicillins.

Women taking **oral contraceptives** should ask their healthcare provider if they should use a second form of contraception while using tetracycline, as this drug can interfere with the effectiveness of the birth control pill.

Individuals should take tetracycline two hours before or after taking antacids or laxatives.

Herbs and supplements

Individuals should take tetracycline two hours before or after taking iron supplements, multivitamins, and calcium supplements.

Food and other substances

Tetracycline should not be taken within a few hours of consuming dairy products.

Resources

BOOKS

- Bloom, Allyson K., et al. *Hunter's Tropical Medicine and Emerging Infectious Disease* Philadelphia: Saunders: 2013.
- Cherry J., et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Elsevier Saunders, 2014.
- Drug Information Handbook*. 23rd ed. Hudson, OH: Lexicomp Inc., 2014.
- Mandell G. L., et al. *Douglas and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. London: Churchill Livingstone, 2015.
- Rang, H P. *Rang & Dale's Pharmacology*. 7th ed. London: Churchill Livingstone, 2012.

WEBSITES

- AHFS Consumer Medication Information. "Tetracycline." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682098.html> (accessed March 12, 2015).

ORGANIZATIONS

- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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REVIEWED BY GREGORY A. PRATT, RPH

Tiazac see **Diltiazem**

Timolol

Definition

Timolol maleate is both an oral drug for treating high blood pressure (hypertension) and heart failure and an ophthalmic solution (eyedrops) for treating intraocular pressure from ocular hypertension and open-angle glaucoma. Timolol is an antihypertensive in the beta-blocker drug class, also known as beta-adrenergic receptor blockers or beta-adrenergic antagonists.

Purpose

Oral timolol maleate helps control high blood pressure and other conditions, but does not cure them. It has been shown to reduce mortality in patients with hypertension and improve survival following heart attacks. However, it is less effective than thiazide diuretics in black and geriatric patients. Oral timolol is sometimes prescribed for other conditions, including prevention of angina (chest pain) and migraine headaches.



Betimol (timolol maleate). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Ophthalmic timolol maleate is used to treat increased pressure in the eye from open-angle glaucoma and certain other eye diseases such as ocular hypertension. By lowering the amount of fluid within the eye, timolol reduces pressure and helps prevent gradual vision loss (especially side vision loss), optic nerve damage, and blindness. Both timolol eyedrops and gel-forming solutions control glaucoma without curing it. However, a combination medicine containing timolol and dorzolamide, as well as prostaglandin analogs, appears to lower eye pressure more effectively than either timolol alone or other glaucoma medications.

Description

Oral timolol relaxes (dilates) blood vessels and slows the heart rate. This decreases blood pressure and improves blood flow. Timolol blocks beta-1 and beta-2 adrenergic receptors that normally bind to epinephrine and norepinephrine to initiate a variety of responses throughout the body, including constricting blood vessels to raise blood pressure and increasing the heart rate. The blood pressure-lowering effects of oral timolol are evident within 15–45 minutes, peak within 30 minutes to 3 hours, and last about 4 hours.

Ophthalmic timolol is believed to reduce intraocular pressure by reducing production of the aqueous humor—the fluid in the space between the crystalline lens and cornea of the eye. Pressure-lowering effects of ophthalmic timolol are evident within 30 minutes, peak within 1 to 2 hours, and last 24 hours.

Oral timolol maleate is available in tablet form, in several different strengths. The 5 mg tablets are green and round, unscored, and debossed with “M 55”; 10 mg tablets are round, scored, and debossed with “M 221”; 20 mg tablets are oval, scored, and debossed with “M 715”. Oral timolol is also available in a combination drug with the diuretic **hydrochlorothiazide** (Timolide).

Ophthalmic timolol maleate is available in different forms and strengths:

- Generic timolol maleate and Betimol hemihydrate, which contain benzalkonium chloride, are available as 0.25% and 0.5% 5 mL, 10 mL, and 15 mL solutions.
- Istalol, containing benzalkonium chloride and potassium sorbate, is a 0.5% 10 mL solution.
- Timoptic, containing benzalkonium chloride, is available as 0.25% and 5% 5 mL and 10 mL solutions.
- Timoptic OcuDose is a preservative-free, single-use, 0.25% or 0.5% 0.2 mL solution.
- Timolol maleate extended-release (long-acting) gel-forming ophthalmic solutions are available as 0.25% in 5 mL or 0.5% in 2.5 mL or 5 mL. The solution thickens to a gel in the eye.

Timolol maleate is stored in the tightly closed container it comes in, at room temperature and away from excess heat and moisture (not in the bathroom). Timolol solutions are normally colorless to light yellow. Solutions that become discolored or cloudy or develop particles must be discarded. Timolol eyedrops are also available in combination with brimonidine (Combigan) and dorzolamide (Trusopt).

U.S. brand names

Oral timolol maleate is available under the brand name Blocadren and as a generic drug. Ophthalmic timolol maleate is available in generic formulations and under the brand names:

- Betimol
- Istalol
- Timoptic
- preservative-free Timoptic OcuDose for patients who experience eye irritation from preservatives in the medication
- Timoptic-XE or GRS—a longer-acting gel-forming solution

Canadian brand names

Canadian brand names for timolol maleate include:

- Apo-Timol
- Apo-Timop

- Gen-Timolol
- PMS-Timolol
- Sandoz Timolol
- Timoptic
- Timoptic-XE

International brand names

There are many international timolol brand names. The most common include:

- Apo-Timol
- Apo-Timop
- Arutimol
- Blocadren
- Blocadren Depot
- Driptimol
- Glaumol
- Globitan
- Lithimole
- Maleato de Timolol
- NyoGel
- Nyolol
- Oculpres
- Oftan
- Oftan Timolol
- Optimol
- Rysmon
- Tim-Ophtal
- Timabak
- Timo-Comod
- Timocomod
- Timogel
- TimoHEXAL
- Timolast
- Timolol-POS
- Timolol Sandoz
- Timoptic
- Timoptic-XE
- Timoptol
- Timoptol XE
- Timosan
- Timosan Depot
- Timosol
- Tiof
- Unitimolol
- Yesan

KEY TERMS

Angina—Chest pain that occurs when diseased blood vessels restrict the flow of blood to the heart.

Antagonist—A drug, such as timolol, that blocks the action of substances by binding to their receptors.

Beta-blocker—A drug, such as timolol, that slows heart rate and lowers blood pressure by blocking beta-receptors for the hormones epinephrine and norepinephrine.

Hypertension—High blood pressure.

Migraine—A common primary headache characterized by debilitating neurological symptoms, especially severe throbbing pain on one or both sides of the head, lasting for several hours or more.

Myocardial infarction—Heart attack; damage or death to heart muscle due to insufficient blood supply.

Open-angle glaucoma—A progressive form of glaucoma in which the drainage channel for the aqueous humor remains open and serious reduction in vision occurs only in advanced stages.

Receptor—A molecule, usually a protein, on the surface of or inside a cell, that binds a specific substance to initiate physiological events.

Thiazide diuretic—A type of diuretic (“water pill”) that removes water and salt from the body to treat high blood pressure.

Origins

Oral timolol maleate for lowering blood pressure was first approved by the U.S. Food and Drug Administration (FDA) in 1981. Ophthalmic timolol was first approved in 1995.

Recommended dosage

Recommended oral dosages for timolol are as follows:

- for hypertension: initially 10 mg every 12 hours; gradually increased every 7 days to 20–40 mg daily in 2 divided doses, with a maximum of 60 mg per day
- for prevention of further myocardial infarction (heart attack): 10 mg every 12 hours beginning within 1–4 weeks of infarction
- for migraine prevention: initially 10 mg every 12 hours; decreased to 10 mg per day or increased to a maximum of 30 mg per day

- for angina (off-label): 15–45 mg per day, divided into doses every 6–8 hours

Ophthalmic dosages for timolol are as follows:

- regular solution: initially 1 drop of 0.25% instilled in the affected eye(s) twice daily at evenly spaced intervals; increased to 0.5% if response is inadequate; decreased to 1 drop per day if glaucoma is controlled (usually after about 4 weeks); maximum of 1 drop of 0.5% twice daily
- Istalol: 1 drop of 0.5% once daily in the morning
- gel-forming solution: 1 drop of 0.25% or 0.5% once daily

Ophthalmic solutions are applied as follows:

- Contact lenses are removed and not replaced until at least 15 minutes after instillation.
- Timolol is instilled at least 10 minutes before any ointments and before or after any other topical eye medications.
- The hands are washed thoroughly with soap and water.
- The gel-forming solution container is inverted and shaken once; the other solutions do not require shaking.
- To avoid contamination, the dropper tip must not be chipped or cracked and must not touch hands, surfaces, or the eye.
- The head is tilted back and, while looking up, the lower eyelid is pulled down with the index finger to form a pouch.
- With the dropper held directly over the eye with the other hand, as close as possible to the eye without touching, 1 drop is placed in the pouch with a single gentle squeeze of the dropper or pressure on the bottom or side of the gel-forming-solution container according to the specific instructions.
- Looking down, with the eyes gently closed and without blinking for 1–3 minutes, a finger at the corner of the eye on the tear duct near the nose is used to apply gentle pressure without rubbing the eye.
- Any excess liquid is wiped from the face.
- The dropper cap is replaced without wiping or rinsing.
- The hands are washed.
- A second drop must not be applied to the same eye for at least 5 minutes.
- It takes several minutes for vision to clear.

A missed dose should be taken or instilled as soon as possible unless it is almost time for the next dose, in which case the dose should be skipped and the regular schedule resumed.

Pediatric

Pediatric dosages of the regular or gel-forming ophthalmic solutions are the same as adult dosages.

Precautions

Oral timolol has boxed warnings against interrupting or discontinuing the use of beta-blockers without the doctor's advice, since abrupt discontinuation may worsen angina and ischemic heart disease and sometimes causes myocardial infarction. Beta-blockers must be gradually discontinued over one to two weeks with close monitoring, even in patients being treated only for hypertension, since unrecognized coronary artery disease is common. If angina significantly worsens or acute heart insufficiency develops, beta-blockers must be re-administered, at least temporarily. Furthermore, hypersensitivity to catecholamines, such as **epinephrine** and norepinephrine, has occurred during withdrawal of beta-blockers.

Oral timolol can cause drowsiness, so patients should not drive or operate machinery until they know how the drug affects them and until their vision has cleared from ophthalmic timolol. Furthermore:

- Doctors and dentists should be informed of timolol use before performing any type of surgery. There is an increased risk of stroke following surgery.
- Patients who have eye surgery, eye injury, or eye infections while using ophthalmic timolol should consult their doctor before continuing to use the same solution.
- Patients using ophthalmic timolol should avoid rubbing their eyes.

Pediatric

The safety and effectiveness of oral timolol have not been established in pediatric patients.

Pregnant or breastfeeding

Although timolol is in the FDA pregnancy category C for use during pregnancy if clearly needed, expert analysis has placed it in the FDA pregnancy category D for the second and third trimesters because it may cause fetal harm. Women should call their doctor if they become pregnant while using timolol. Timolol is secreted in breast milk, and the manufacturer advises against nursing, although the American Academy of Pediatrics has rated it compatible with breastfeeding.

Other conditions and allergies

Timolol should not be used by patients with:

- hypersensitivity or allergic reactions to timolol or any ingredients in the medication
- bronchial asthma or chronic obstructive pulmonary disease

- certain types of heart failure or disease or an irregular heartbeat

Timolol should be used with caution in patients who are undergoing anesthesia or surgery that depresses heart activity or who have:

- congestive heart failure
- peripheral vascular disease
- cerebrovascular insufficiency (low blood flow to the brain)
- liver disease
- kidney impairment
- insulin-dependent (type 1) diabetes
- hyperthyroidism
- pheochromocytoma (tumor associated with hypertension)

In addition to telling their doctor and pharmacist if they are allergic to any other drugs, patients should tell their doctors if they have ever had:

- asthma or another lung disease
- heart, liver, or kidney disease
- diabetes
- severe allergies
- muscle weakness disorders or diseases
- thyroid problems
- myasthenia gravis

Timolol may prevent the fast/pounding heartbeat that is a symptom of low blood sugar in people with diabetes. Other symptoms of low blood sugar, such as dizziness and sweating, are unaffected by timolol.

Side effects

Many patients do not experience serious side effects from timolol. Side effects experienced by 1%–10% of patients taking oral timolol include:

- heart arrhythmia
- slowed heart rate
- fainting
- fatigue
- headache
- labored breathing

Patients should consult their doctor if any of the following symptoms are severe or persistent:

- dizziness or lightheadedness
- excessive tiredness
- heartburn
- headache
- cold hands and feet

Blurred vision lasting from 30 seconds to 5 minutes affects about 1/3 of patients using ophthalmic timolol. Temporary burning, stinging, or itching of the eye(s), watery or dry eye, a sensation of something in the eye, and headache may also occur. Although ophthalmic timolol appears to cause less eye redness than prostaglandin analogs used to treat intraocular pressure, it is more likely to cause side effects such as slowed heart rate and shortness of breath. Patients should call their doctor if any of the following side effects are severe or persistent:

- eye irritation
- double vision
- headache
- depression
- dizziness
- nausea

Patients should call their doctor immediately if they experience any of the following unlikely or rare but serious side effects:

- slow or irregular heartbeat
- chest pain
- unusual tiredness or weakness
- sudden weight gain
- swelling of the feet, lower legs, or hands
- cold, numbness, or pain in the hands or feet
- fainting
- eye pain, swelling, or discharge
- muscle weakness
- mental or mood changes
- vision changes
- weakness on one side of the body
- slurred speech
- confusion

Other conditions and allergies

Although very serious allergic reactions to timolol are rare, symptoms that require immediate medical attention include:

- rash
- itching or swelling, especially of the face, tongue, or throat
- severe dizziness
- difficulty breathing

Interactions

The doctor and pharmacist should be informed of all prescription and nonprescription medicines, vitamins,

minerals, herbs, and dietary supplements being used or planning to be used by the patient. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

Drugs with potentially serious or life-threatening interactions with timolol are:

- acebutolol
- artemether
- **atenolol**
- betaxolol
- bisoprolol
- **carvedilol**
- celiprolol
- **clonidine**
- **digoxin**
- **diltiazem**
- epinephrine
- esmolol
- **fluoxetine**
- labetalol
- lumefantrine
- **metoprolol**
- nadolol
- **nebivolol**
- **paroxetine**
- penbutolol
- pindolol
- **propranolol**
- quinidine
- **sotalol**
- inhaled umeclidinium bromide/vilanterol
- verapamil
- inhaled vilanterol/fluticasone furoate

Another 224 drugs have significant interactions with timolol and require close monitoring, and 31 drugs have minor interactions. Patients should tell their doctor and pharmacist if they are using:

- **aspirin** or other nonsteroidal anti-inflammatory drugs such as **ibuprofen** and naproxen
- other heart disease, high blood pressure, or glaucoma medications or oral beta-blockers or calcium channel blockers
- antidepressants
- fingolimod

- methyl dopa
- **nifedipine**
- reserpine
- theophylline

Herbs and supplements

Vitamin supplements may interact with timolol.

Food and other substances

Alcohol can increase timolol-induced drowsiness.

Resources

BOOKS

Smith, Howard S., Marco Pappagallo, and Stephen M. Stahl. *Essential Pain Pharmacology: The Prescriber's Guide*. New York: Cambridge University, 2012.

PERIODICALS

"Drugs to Treat Hypertension." *Journal of Psychosocial Nursing & Mental Health Services* 52, no. 2 (2014): 11–12.

"Drugs to Treat Hypertension." *Journal of Psychosocial Nursing & Mental Health Services* 53, no. 2 (2015): 21–22.

WEBSITES

"Medication Guide." Glaucoma Research Foundation. <http://www.glaucoma.org/treatment/medication-guide.php> (accessed March 10, 2015).

MedlinePlus. "Timolol Ophthalmic." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682043.html> (accessed March 10, 2015).

MedlinePlus. "Timolol Oral." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a684029.html> (accessed March 10, 2015).

Smith, Amelia Williamson, et al. "Treatments for Open-Angle Glaucoma: A Review of the Research for Adults." Effective Health Care Program, Agency for Healthcare Research and Quality. <http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1395&ECem=130214> (accessed March 10, 2015).

"Timolol." University of Maryland Baltimore Washington Health Library. <http://www.mybwmc.org/library/41/125400> (accessed March 10, 2015).

"Timolol Ophthalmic (Rx)." Medscape.com. <http://reference.medscape.com/drug/timoptic-timoptic-xe-timolol-ophthalmic-343603#91> (accessed March 10, 2015).

"Timolol (Rx)—Blocadren, Timol." Medscape.com. <http://reference.medscape.com/drug/blocadren-timol-timolol-342368#0> (accessed March 10, 2015).

"Types of Blood Pressure Medications." American Heart Association. <http://www.heart.org/HEARTORG/>

Conditions/HighBloodPressure/PreventionTreatmentof-HighBloodPressure/Types-of-Blood-Pressure-Medications_UCM_303247_Article.jsp (accessed March 10, 2015).

ORGANIZATIONS

Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, (301) 427-1364, <http://www.ahrq.gov/>.

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org/>.

Glaucoma Research Foundation, 251 Post Street, Suite 600, San Francisco, CA 94108, (415) 986-3162, (800) 826-669, question@glaucoma.org, <http://www.glaucoma.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

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Timolol/dorzolamide see **Dorzolamide/timolol**

Timoptic see **Timolol**

Tiotropium

Definition

Tiotropium bromide is a medicine used in inhalers to help prevent and manage symptoms of chronic obstructive pulmonary disease (COPD). It is in a class of medications called bronchodilators.

Purpose

When a person has trouble breathing because of the COPD, the airways, which also are called bronchi, are tight and contracted. Bronchodilator drugs such as tiotropium bromide help expand and relax the airways, making it easier to breathe and relieving symptoms such as wheezing, shortness of breath, and coughing. Tiotropium bromide is taken regularly to help prevent COPD symptoms, not as a rescue medication once symptoms occur.

Description

A capsule of tiotropium bromide powder is placed into a special inhaler that delivers the premeasured amount. Until September 2014, the medicine was available only as a powder that was inhaled through the handheld inhaler as maintenance therapy for COPD.



Spiriva (tiotropium bromide). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Maintenance therapy is designed for regular, everyday use to help keep airways relaxed and manage symptoms. In September 2014, the U.S. Food and Drug Administration (FDA) approved a form of tiotropium bromide delivered in a mist that was designed to make it easier for patients with COPD to inhale the medication.

U.S. brand names

In the United States, tiotropium bromide is sold as the brand Spiriva. The powder form of the medicine is sold in a product called Spiriva HandiHaler, and the newer mist form is sold as Spiriva Respimat.

Recommended dosage

Each capsule of dry powder that is released from an oral inhaler contains 18 mcg of powder. Patients receive the full dose through two inhalations of the powder once a day. The mist is delivered in two inhalations of 2.5 mcg of tiotropium taken once per day. If a regular dose is missed, it should be taken as soon as possible, unless it is nearly time for the next regular dose. In that case, the missed dose should be skipped.

Precautions

Anyone taking tiotropium bromide should carefully follow instructions from healthcare providers, pharmacists, and package inserts to use the medication and

KEY TERMS

Bronchodilator—A medicine that relaxes the muscles around the airways, or bronchi, helping to open the airways and making it easier to breathe.

Chronic obstructive pulmonary disease—A group of diseases of the lungs and airways such as chronic bronchitis and emphysema that become progressively worse.

inhalers correctly. Some individuals may be allergic or sensitive to tiotropium bromide.

Pediatric

To date, tiotropium bromide only has been approved for use in maintenance of COPD, which occurs in adults. Although some research has been done on the use of tiotropium in children who have asthma, accurate and complete clinical trials have not verified how well the drug would work or how safe it would be in children.

Pregnant or breastfeeding

Tiotropium bromide is a pregnancy category C drug. No clinical studies have been conducted in pregnant women to show possible harm to an unborn child if the mother uses tiotropium bromide while pregnant, but animal studies have shown some effects. Pregnant women should only use tiotropium if the possible benefits outweigh potential risks. Women who are nursing could pass tiotropium bromide to their infants through breast milk and should use caution. A mother who wants to breastfeed while taking tiotropium should discuss it carefully with her healthcare provider first.

Other conditions and allergies

Patients with moderate to severe kidney disease need extra monitoring while taking tiotropium bromide.

Side effects

Tiotropium bromide may cause side effects in individuals who take the medication, including:

- dry mouth
- nosebleed or runny nose
- sneezing
- stomach problems such as pain, indigestion, and vomiting
- muscle pain
- sore, white spots in the mouth

Some side effects of tiotropium can be severe and should be reported to a doctor immediately, including:

- itchy rash or hives
- problems breathing or swallowing
- swelling of the throat, lips, face, eyes, lower limbs, or hands
- chest pain
- hoarseness and sore throat
- fever and signs of infection
- rapid heartbeat
- changes in vision or eye pain

Interactions

Sometimes drugs can interact with one another or with herbal remedies or supplements. Anyone taking tiotropium should inform their healthcare provider of any other medications and supplements that they are taking.

Drugs

Taking tiotropium at the same time as other bronchodilators that perform the same actions can increase side effects and is not advised.

Resources

PERIODICALS

- Bollmeier, Suzanne Gielow, and Shin-Yu Lee. "The Emerging Role of Tiotropium for Patients with Asthma." *The Annals of Pharmacotherapy* 47, no. 5 (2013): 704–13.
- Cook, Anna L., T. Bernard Kinane, and Benjamin A. Nelson. "Tiotropium Use in Pediatric Patients with Asthma or Chronic Cough: A Case Series." *Clinical Pediatrics* 53, no. 14 (2014): 1393–5.

WEBSITES

- Boehringer Ingelheim Pharmaceuticals, Inc. "Boehringer Ingelheim Announces FDA Approval of Spiriva Respimat (Tiotropium Bromide) Inhalation Spray for the Maintenance Treatment of COPD." *Us.boehringer-ingelheim.com*. http://us.boehringer-ingelheim.com/news_events/press_releases/press_release_archive/2014/09-25-14-boehringer-ingelheim-announces-fda-approval-spiriva-respimat-tiotropium-bromide-inhalation-spray-maintenance-treatment-copd.html (accessed February 28, 2015).
- Boehringer Ingelheim Pharmaceuticals, Inc. "Highlights of Prescribing Information: Spiriva HandiHaler." *Biodocs.boehringer-ingelheim.com*. <http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Spiriva/Spiriva.pdf>
- Boehringer Ingelheim Pharmaceuticals, Inc. "Highlights of Prescribing Information: Spiriva RespiMat." *Boehringer Ingelheim*. <http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/>

Prescribing+Information/PIs/Spiriva+Respimat/
spirivarespimat.pdf

MedlinePlus. "Tiotropium Oral Inhalation." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a604018.html> (accessed February 28, 2015).

"Spiriva." Rxlist.com. <http://www.rxlist.com/spiriva-drug.htm> (accessed February 28, 2015).

"Tiotropium." Drugs.com. <http://www.drugs.com/cdi/tiotropium.html> (accessed February 28, 2015).

ORGANIZATIONS

American Academy of Allergy, Asthma & Immunology, 555 East Wells Street, Suite 1100, Milwaukee, WI 53202-3823, (414) 272-6071, <http://www.aaaai.org/home.aspx>.

American Lung Association, 55 West Wacker Drive, Chicago, IL 60601, (202) 452-1805, (800) 586-4872, <http://www.lung.org/>.

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Tizanidine

Definition

Tizanidine hydrochloride (HCl) is an oral medication for treating muscle spasms and pain. It is in the drug class of skeletal muscle relaxants.

Purpose

Tizanidine HCl is used to relieve muscle spasms and pain caused by a variety of conditions. It can help relieve tight muscles, cramping, and spasms caused by increased muscle tone in multiple sclerosis (MS) and similar muscle-tone and spasticity problems caused by stroke and brain or spinal-cord injuries. Tizanidine is also a first-line treatment for muscle problems associated with cerebral palsy and is used to treat dystonia (muscle-tone abnormalities) associated with Wilson's disease, an inherited disorder of copper metabolism. Tizanidine does not cure these conditions, but it can relax stiff, contracted, and overactive muscles.

Tizanidine may be prescribed for other conditions, such as cluster headaches. Some studies have shown that tizanidine may be effective for relieving tension-type headaches, back pain, nerve pain, and myofascial pain—a chronic pain disorder in which sensitive points in muscles trigger pain in other parts of the body.



Tizanidine, 4 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

Tizanidine is an alpha-2 adrenergic agonist that acts on alpha-2 adrenergic receptors to mimic the nervous system-inhibiting activities of **epinephrine** and norepinephrine. This slows down activity in the brain and nervous system and inhibits motor neurons that activate muscles, enabling the muscles to relax. Because alpha-2 adrenergic receptors are involved in many different processes throughout the body, tizanidine has a variety of muscle-relaxing and pain-reducing effects. Tizanidine is similar to the alpha-2 adrenergic agonist **clonidine**, but tends to be better tolerated and, unlike clonidine, rarely reduces blood pressure.

Tizanidine is sold in tablet and capsule forms in different strengths. The 2 mg and 4 mg tablets and 2 mg, 4 mg, and 6 mg capsules all contain the same active tizanidine, but the formulations differ somewhat. Capsules and tablets of the same potency are not interchangeable because the medication is absorbed differently. Tizanidine is also absorbed differently depending on whether it is taken with food, on an empty stomach, or as the contents of a capsule sprinkled on food. Depending on the manufacturer and dosage, tizanidine capsules vary in color, and the tablets vary in color, shape, labeling, and scoring. The medication is stored in the tightly closed container it comes in, at room temperature, and away from excess heat and moisture (not in the bathroom). Tizanidine HCl is also available in several different combination medicines.

KEY TERMS

Alpha-2 adrenergic agonist—A drug, such as tizanidine, that mimics the effects of the binding of endogenous substances, such as epinephrine and norepinephrine, to the alpha-2 subtype of adrenergic receptors.

Cerebral palsy—Muscular incoordination and speech disturbances resulting from brain damage before, during, or shortly after birth.

Cluster headache—Severe pain in one eye or temple.

Dystonia—Abnormal muscle tone.

Hypotension—Low blood pressure.

Multiple sclerosis (MS)—An autoimmune disorder of the central nervous system that causes progressive paralysis, usually marked by periods of exacerbation and remission.

Receptor—A molecule, usually a protein, inside or on the surface of a cell, that binds to specific substances, such as hormones, to affect physiological processes.

Spasticity—Hypertonic (overly toned) muscles with increased tendon reflexes.

Wilson's disease—An inherited disorder of abnormal copper metabolism that causes dystonia.

that the patient is taking. It is taken by mouth, consistently with or without food, usually 2–3 times per day or every 6–8 hours. The drug is usually initiated with a low dose, which is gradually increased to determine the most effective dose while minimizing side effects, not to exceed 36 mg per day or more than 3 doses in a 24-hour period. For muscle spasticity associated with MS or spinal-cord injury, the initial recommended dosage is 4 mg every 6–8 hours as needed, with a maximum of 3 doses every 24 hours. The dose is increased in increments of 2–4 mg per day.

Tizanidine capsules can be opened and sprinkled on soft food, such as applesauce. This must be done in consultation with the doctor, because the effects may differ from swallowing an intact capsule.

Patients who have been instructed to take tizanidine at regular intervals should take a missed dose as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the regular dosing schedule resumed.

Other conditions and allergies

Caution should be used in prescribing tizanidine for patients with kidney impairment. For those with creatinine clearance of less than 25 mL per minute, clearance of tizanidine from the body is reduced by more than 50%.

Precautions

- Tizanidine must be taken exactly as prescribed—no more or less and no more often.
- Tizanidine must not be stopped without consulting the doctor. The dose will probably be decreased gradually, since suddenly stopping the drug can cause rapid heartbeat, increased blood pressure, muscle tightening or tenseness, anxiety, or tremor, especially if it has been used regularly for a long period or at high doses.
- Tizanidine may cause drowsiness, sedation, or blurred vision in some people; patients should not drive, operate machinery, or perform any activities that require alertness until they know how the drug affects them.
- Tizanidine may cause dizziness, lightheadedness, and fainting when rising too rapidly from lying down, especially when first taking the drug; patients should rise from bed slowly, resting their feet on the floor for a few minutes before standing.
- Tizanidine can decrease muscle tone, so patients must exercise caution when walking or performing other activities that require muscle tone for posture or balance.

U.S. brand names

The U.S. brand name for tizanidine HCl is Zanaflex.

Canadian brand names

The Canadian brand name for tizanidine HCl is Zanaflex.

International brand names

Tizanidine is sold internationally under a variety of brand names, of which Sirdalud is the most common.

Origins

Tizanidine HCl was originally approved by the U.S. Food and Drug Administration (FDA) as Zanaflex oral tablets in 1996. Zanaflex oral capsules were approved in 2002, and various generic forms have been available since 2002.

Recommended dosage

Tizanidine HCl dosage depends on the medical condition, response to the drug, and other medications

- Tizanidine may cause low blood pressure (hypotension) or visual hallucinations.
- Patients should consult their doctor if their condition does not improve or worsens.
- Laboratory and/or medical tests, such as blood pressure and liver function, will be performed periodically to monitor progress and side effects.
- Doctors and dentists should be told of tizanidine use (and of all prescription and nonprescription drugs and herbal products) before performing any type of surgery.
- Infrequently, tizanidine has caused very serious, rarely fatal, liver disease.

Symptoms of tizanidine overdose can include:

- drowsiness
- extreme tiredness
- dizziness
- fainting
- slowed heartbeat
- slow or shallow breathing
- confusion
- loss of consciousness

Pediatric

Tizanidine is not recommended for pediatric patients.

Geriatric

Older adults can be more sensitive to tizanidine side effects, especially drowsiness and dizziness, which can increase the risk of falling.

Pregnant or breastfeeding

Tizanidine is in the FDA pregnancy category C, meaning that it has not been studied in pregnant women, but animal studies at extremely high doses have caused damage in offspring. Thus, tizanidine should not be used during pregnancy unless it is clearly needed. Women who become pregnant while taking tizanidine should contact their doctor immediately. Tizanidine may be excreted in breast milk, so women will probably be advised against breastfeeding while taking it.

Other conditions and allergies

Before taking tizanidine, patients should tell their doctor and pharmacist if they are allergic to tizanidine, any inactive ingredients in the medication, or any other medications and if they have any other allergies. Patients should tell their doctor if they have or have ever had liver or kidney disease or low blood pressure or are taking any type of blood-pressure medication. Caution is advised in

prescribing tizanidine for patients with kidney or liver impairment, and it should not be used by patients with severe liver impairment.

Side effects

Many people do not experience serious side effects from tizanidine, and many common side effects disappear as the body adjusts to the medication. Patients should tell their doctor about any side effects that are severe or persist for more than two weeks. Dry mouth and drowsiness affect up to 50% of patients. Weakness affects 10%–45%, and dizziness or lightheadedness affects 16%–20%. Side effects affecting 1%–10% of patients include:

- blurred vision
- constipation
- vomiting
- frequent urination
- speech abnormalities
- urinary tract or other infections
- abnormal liver-function tests

Other possible side effects include:

- low blood pressure, especially upon standing
- depression
- diarrhea
- stomach pain
- heartburn
- increased muscle spasms, cramps, or tightness
- back pain
- rash
- sweating

The doctor should be contacted immediately in case of serious side effects including:

- fainting
- mental or mood changes or visual or auditory hallucinations
- slow or irregular heartbeat
- vision changes
- extreme tiredness
- unusual bleeding or bruising
- lack of energy
- loss of appetite
- pain in the upper right stomach
- unexplained flu-like symptoms
- burning, prickling, or tingling sensations
- fever
- nervousness
- painful or burning urination

- skin sores
- signs of liver disease such as persistent nausea or vomiting, severe stomach or abdominal pain, dark urine, or yellowing of the skin or eyes

Other conditions and allergies

Very serious allergic reactions to tizanidine are rare. However, immediate medical help should be sought for symptoms of an allergic reaction, such as:

- rash
- itching or swelling, especially of the face, tongue, or throat
- severe dizziness
- difficulty breathing

Some tizanidine side effects may be difficult to distinguish from common symptoms of MS. Patients should consult their doctor if abrupt changes occur in the following symptoms:

- weakness
- tiredness or fatigue
- burning, prickling, or tingling sensations
- blurred vision

Interactions

The doctor and pharmacist should be informed of all prescription and nonprescription medicines, vitamins, minerals, herbs, and dietary supplements being used. Patients should not start, stop, or change dosages of any medicines without their doctor's approval. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

Tizanidine should not be used by patients taking **ciprofloxacin** (an antibiotic used to treat urinary tract infections in MS patients), **fluvoxamine** (an antidepressant), or other potent inhibitors of cytochrome P450 1A2 (CYP1A2). Inducers of CYP1A2 may decrease tizanidine levels. Oral contraceptives may slow the removal of tizanidine from the body; tizanidine dosages should be lowered in women using birth control pills. Tizanidine may increase the drowsiness-inducing effects of other central nervous system depressants, including antihistamines such as **cetirizine** or **diphenhydramine**, sedatives, tranquilizers, prescription pain medications such as codeine, seizure medications, other muscle relaxants, and sleep or anxiety medications such as **alprazolam**, **diazepam**, and **zolpidem**. Other alpha agonists for treating high blood pressure, such as clonidine and methyldopa, may also interact with tizanidine. Patients

should check the labels on all of their medications, including allergy and cough-and-cold products, because the ingredients may cause further drowsiness.

Other drugs that can interact seriously with tizanidine and require the use of alternatives, if possible, include:

- amobarbital
- **armodafinil**
- butabarbital
- butalbital
- **carbamazepine**
- cimetidine
- **diltiazem**
- **erythromycin**
- hexobarbital
- isoniazid
- mefloquine
- mephobarbital
- mexiletine
- **modafinil**
- norfloxacin
- pefloxacin
- peginterferon alfa-2a
- pentobarbital
- phenobarbital
- pipemidic acid
- primidone
- **rifampin**
- secobarbital
- tacrine
- verapamil
- zileuton

Additional drugs that can significantly interact with tizanidine and may require adjusting dosages or closely monitoring for side effects include:

- **acyclovir**
- amiodarone
- **baclofen**
- **candesartan**
- **citalopram**
- clobazam
- dantrolene
- deferasirox
- eprosartan
- ethinyl estradiol
- **famotidine**
- **fentanyl** intranasal

- fluoroquinolones such as gemifloxacin, **levofloxacin**, **moxifloxacin**, and ofloxacin
- **irbesartan**
- **losartan**
- lurasidone
- maraviroc
- **nitroglycerin** rectal
- **olmesartan**
- propafenone
- **telmisartan**
- ticlopidine
- teriflunomide
- valsartan
- vemurafenib

Food and other substances

Cigarette smoking or other tobacco use will decrease the level of effectiveness of tizanidine by affecting CYP1A2 metabolism in the liver, with possibly serious or life-threatening results. Alcoholic beverages should be avoided while taking tizanidine because they can increase drowsiness.

Resources

BOOKS

Smith, Howard S., Marco Pappagallo, and Stephen M. Stahl. *Essential Pain Pharmacology: The Prescriber's Guide*. New York: Cambridge University, 2012.

WEBSITES

MedlinePlus. "Tizanidine Hydrochloride." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601121.html> (accessed March 10, 2015).

"Tizanidine (Rx)." Medscape.com. <http://reference.medscape.com/drug/zanaflex-tizanidine-343071#91> (accessed March 10, 2015).

"Zanaflex." National Multiple Sclerosis Society. <http://www.nationalmssociety.org/Treating-MS/Medications/Zanaflex> (accessed March 10, 2015).

ORGANIZATIONS

National Institute of Neurological Disorders and Stroke, NIH Neurological Institute, PO Box 5801, Bethesda, MD 20824, (301) 496-5751, <http://www.ninds.nih.gov/>.

National Multiple Sclerosis Society (800) 344-4867, <http://www.nationalmssociety.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY GREGORY A. PRATT, RPH

Tobradex see **Tobramycin/dexamethasone**

Tobramycin/dexamethasone

Definition

Tobramycin/dexamethasone is a combination topical medicine that contains both an antibiotic (tobramycin) and an anti-inflammatory steroid (dexamethasone).

Purpose

Tobramycin/dexamethasone is used to treat eye infections. The antibiotic kills susceptible bacteria, and the steroid medication calms inflammation in the eye.

Description

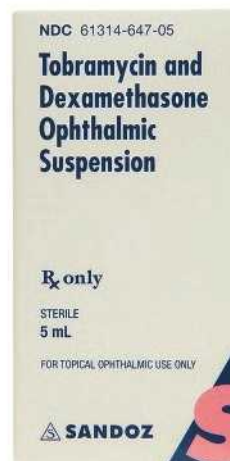
Tobramycin/dexamethasone is available as an ointment and an eyedrop.

U.S. brand names

Tobramycin/dexamethasone is sold under the brand name Tobradex. It is also manufactured as a generic by a number of companies.

Canadian brand names

Tobramycin/dexamethasone is sold under the brand name Tobradex in Canada.



Tobramycin/dexamethasone. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

International brand names

Tobramycin/dexamethasone is sold as Tobradex in a number of countries around the world.

Recommended dosage

Ointment: Use about a 1/2-inch long strip of ointment in the affected eye, three to four times per day.

Drops (suspension): Use one to two drops in the affected eye every four to six hours. Depending on severity of infection, individuals may use one to two drops every two hours for the first one or two days, then go back to the four- to six-hour dosing schedule.

Dosing is the same for adults, geriatric population, and pediatric population. Should only be used in children over the age of two years.

Precautions

The following precautions apply to all individuals.

- Individuals who are allergic or who have had reactions to Tobramycin or to dexamethasone should not use this drug.
- Do not use this drug for viral, mycobacterial, or fungal infections of the eye.
- This drug should be taken for the entire length of the prescription. Failure to take a complete course of the medication can result in return of symptoms.
- Use over a long period of time can increase the risk of developing another fungal or bacterial infection, as well as steroid-related complications involving the optic nerve, potential glaucoma, cataract formation, and visual changes.
- Should not be used following cataract surgery.
- Contact lenses should not be worn during treatment.
- Always wash hands before using eyedrops or ointment.
- Care must be taken not to contaminate the container or the ointment or solution.

Pregnant or breastfeeding

Tobramycin/dexamethasone has not been well studied in pregnant women. This drug is a pregnancy category B drug. Women who are pregnant or breastfeeding should tell their doctor before taking Tobramycin dexamethasone.

Side effects

Serious and sometimes fatal reactions can occur in individuals who are allergic to penicillin and penicillin-like drugs. Anyone who has had a severe reaction to any drug should alert the physician before taking this drug.

KEY TERMS

Anaphylaxis—A severe, systemic allergic reaction that can be potentially life-threatening.

MRSA—Methicillin-resistant *Staphylococcus aureus*, a staphylococcal organism that has developed the ability to resist killing by many conventional antibiotics.

Pregnancy category—A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk, but no human studies; or adverse effects in animals, but not in well-controlled human studies. Category C: No adequate human or animal studies; or adverse fetal effects in animal studies, but no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk. Risks outweigh any benefits.

Resistance—A characteristic that can be developed by some organisms, and which allows them to escape the effects of certain antibiotics.

The most common adverse side effects of tobramycin/dexamethasone for all age groups tend to be mild. They include:

- Burning, stinging, or pain in the affected area being treated.
- Tearing.
- Itching.
- Eyelid swelling.
- Eye redness.
- Brief blurred vision directly following administration (should not last).
- Keratitis: Swelling of the cornea, the front clear portion of the eyeball.

These side effects should be brought to the doctor's attention if they do not go away within a few days.

A doctor should be notified immediately if any of these less common but more serious side effects occur.

- Wheezing, difficulty breathing or swallowing. These side effects may indicate a severe allergic reaction and require immediate medical attention. Call the doctor or go to the emergency room.
- Severe skin rash, itching, or hives.
- Swelling.

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements including vitamin supplements.

Drugs

Because tobramycin/dexamethasone is not systemic, there have been few reported drug interactions. Tobramycin/dexamethasone may interact with other topical eye medications. Individuals should always check with their doctor before using more than one product in their eyes.

Resources

BOOKS

- Bloom, Allyson K, and Edward T. Ryan. *Hunter's Tropical Medicine and Emerging Infectious Disease*. Philadelphia: Saunders, 2013.
- Cherry, J., et al. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia: Elsevier Saunders, 2014.
- Drug Information Handbook*. 23rd ed. Hudson: Lexicomp Inc., 2014.
- Mandell, G. L., et al. *Douglas and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. London: Churchill Livingstone, 2015.
- Rang, H. P., et al. *Rang and Dale's Pharmacology* 7th ed. London: Churchill Livingstone, 2012.

WEBSITES

- Micromedex. "Tobramycin And Dexamethasone (Ophthalmic Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/tobramycin-and-dexamethasone-ophthalmic-route/side-effects/DRG-20062827> (accessed April 10, 2015).

ORGANIZATIONS

- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Tobrex see **Tobramycin/dexamethasone**

Tofranil see **Imipramine**

Tolterodine

Definition

Tolterodine tartrate is a medication used to treat problems caused by an overactive bladder. It is available only by prescription and is in a class of drugs called anticholinergics.

Purpose

When someone has an overactive bladder, that individual has the urge to urinate more often and strongly than normal and may have problems with uncontrollable leakage of urine. Drugs such as tolterodine tartrate help relax the muscles of the bladder by affecting nerve impulses. This eases the symptoms of the overactive bladder.

Description

Tolterodine tartrate, or simply tolterodine, is taken by mouth in a tablet. It comes in a tablet that is usually taken twice a day, or once if the drug is taken in an extended-release, or long-lasting, form.

U.S. brand names

In the United States, tolterodine is sold under the brand name Detrol. The extended-release tablet is sold as Detrol LA.



Detrol LA (tolterodine), 4 mg. (© Cengage Learning®.)

Recommended dosage

Healthcare providers usually recommend starting tolterodine at 2 milligrams (mg) twice a day. The extended-release tablets are usually taken in 4 mg doses once a day. All tolterodine tablets should be swallowed whole and taken with water.

For maintenance therapy of problems with urinary frequency or incontinence, healthcare providers may recommend a slightly lower dose (1 mg twice a day or a 2 mg extended-release tablet once a day).

Other conditions and allergies

Patients who have kidney or liver function problems also might receive reduced doses of tolterodine.

Precautions

Some patients who have taken tolterodine have reported angioedema, or swelling just under the skin. A severe allergic reaction called anaphylactic shock also has been reported from the drug's use. Patients who have an obstruction in the bladder should use caution with taking tolterodine because it can cause the bladder to retain urine. Because the drug can cause drowsiness, it is important to avoid driving a vehicle or operating heavy machinery until the drug's effects are known.

Pediatric

The safety and effectiveness of tolterodine have not been tested in children, and the medicine should only be given to adults.

Pregnant or breastfeeding

Tolterodine is a pregnancy category C drug, which means that it is unknown whether the drug can adversely affect a human fetus. It has only been tested in animals, not in people. Pregnant women should only use the medicine if its potential benefits outweigh the risk of possible harm to the unborn child.

Animal studies show that tolterodine is passed in breast milk. Women who want to breastfeed should either stop taking tolterodine while nursing or choose not to breastfeed their infant while on the drug.

Other conditions and allergies

Individuals who have certain kinds of cataracts should take tolterodine with caution. Anyone who has a condition called myasthenia gravis should also use special care if considering the use of tolterodine.

KEY TERMS

Anticholinergic—A type of drug that affects nerve impulses from parasympathetic nerves, which control involuntary movements such as organ functions.

Myasthenia gravis—A disease of the immune system that causes muscles under a person's control to weaken.

Overactive bladder—A problem with many causes, such as age, pregnancy, and obesity, that results in frequent and urgent trips to the restroom to urinate and sometimes in leakage of urine.

Urinary incontinence—A loss of bladder control, usually with symptoms that vary from minor leaking to wetting that cannot be controlled.

Side effects

Tolterodine can cause side effects, including:

- dry mouth and eyes
- headache
- upset stomach and constipation
- stomach pain
- blurry vision
- dizziness

Some side effects can be severe and should be reported to a healthcare provider doctor immediately. They include:

- rash
- chest pain
- problems urinating

Interactions

Certain drugs and other substances can cause interactions with tolterodine that either decrease one drug's effectiveness or increase unwanted side effects. It is important to tell the healthcare provider about all drugs, herbal remedies, and supplements being taken before using tolterodine.

Drugs

Some drugs used to treat antifungal infections such as ketoconazole (Bizoral) or **carbamazepine** (Tegretol) can cause increased concentrations of tolterodine. Taking

other anticholinergic medications at the same time as tolterodine increases the incidence of adverse effects.

Resources

PERIODICALS

Marinkovich, Serge P., et al. "The Management of Overactive Bladder Syndrome." *British Medical Journal* 344 (April 17, 2012): e2365. <http://dx.doi.org/10.1136/bmj.e2365> (accessed March 4, 2015).

Robinson, Dudley, and Linda Cardozo. "Antimuscarinic Drugs to Treat Overactive Bladder." *British Medical Journal* 344 (March 27, 2012): e2130. <http://dx.doi.org/10.1136/bmj.e2130> (accessed March 4, 2015).

WEBSITES

DetrolLA.com. <http://www.detrolLA.com/> (accessed February 28, 2015).

MedlinePlus. "Tolterodine." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699026.html> (accessed February 28, 2015).

Physicians' Desk Reference. "Detrol." PDR Health. <http://www.pdrhealth.com/drugs/detrol> (accessed March 4, 2015).

"Tolteridone." Drugs.com. <http://www.drugs.com/cdi/tolteridone.html> (accessed February 28, 2015).

U.S. Food and Drug Administration. "Detrol (Tolterodine Tartrate) Tablets and Detrol LA (Tolterodine Tartrate) Extended-Release Capsules." <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm316317.htm> (accessed March 4, 2015).

ORGANIZATIONS

American Geriatrics Society, 40 Fulton Street, 18th Floor, New York, NY 10038, (212) 308-1414, Fax: (212) 832-8646, info.amger@americangeriatrics.org, <http://www.americangeriatrics.org/>.

Urology Care Foundation, 1000 Corporate Boulevard, Linthicum, MD 21090, (410) 689-3700, Fax: (410) 689-3998, (800) 828-7866, info@urologyhealth.org, <http://www.urologyhealth.org/>.

Teresa G. Odle, BA, ELS

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Topamax see **Topiramate**

Topiramate

Definition

Topiramate is an anticonvulsant used alone or with other medications for the control of certain types of seizures due to epilepsy, including partial and tonic-



Topamax (topiramate), 15 mg. (© Cengage Learning®.)

clonic seizures, and those caused by Lennox-Gastaut syndrome.

Topiramate is also used to help prevent migraine headaches. This medication does not cure seizure disorders or migraines and only works as long as it is taken as prescribed.

Purpose

Topiramate is thought to decrease and balance the abnormal electrical activity within the brain that may trigger seizures. While topiramate controls some types of seizures associated with epilepsy, there is no known cure for the disorder.

Off-label uses

Doctors prescribe topiramate for the psychiatric treatment of bipolar affective disorders, though the FDA has not approved this medication for that use. In patients with bipolar disorder, topiramate stabilizes mood without producing a euphoric feeling or inducing manic episodes.

Another off-label use for topiramate is in the treatment of alcohol dependency. Topiramate has been shown to decrease cravings for alcohol in double-blind studies.

KEY TERMS

Bipolar disorder—Any of several mood disorders characterized by alternating episodes of depression and mania, or by episodes of depression alternating with mild nonpsychotic excitement.

Epilepsy—A neurological dysfunction in which excessive surges of electrical energy are emitted in the brain.

Lennox-Gastaut syndrome—A disorder that causes seizures and developmental delays.

Metabolic acidosis—A disturbance in the body's acid-base balance that results in excessive acidity of the blood.

Seizure—An abnormal electrical discharge in the brain, resulting in spasms or convulsions.

Description

Topiramate is most commonly prescribed to treat patients who do not respond to other anticonvulsant medications, or as part of a combination of anticonvulsant medications used to treat intractable seizures. Although the precise mechanisms by which it exerts its therapeutic effects on epilepsy and other seizure disorders are unknown, topiramate has three specific seizure-reducing actions:

- decreases nerve cell excitation by blocking targeted neurotransmitters from binding to certain receptors in the brain
- blocks sodium channels in nerve cells, thus decreasing excessive nerve cell firing
- increases the availability of GABA (gamma-aminobutyric acid), a neurotransmitter that inhibits nerve cell excitation in the brain

Topiramate is available as tablets in strengths of 25 mg, 100 mg, and 200 mg and as sprinkle capsules in strengths of 15 mg and 25 mg.

U.S. brand names

In the United States, topiramate is sold under the brand names Qudexy XR, Topamax, Topiragen, and Trokendi XR.

Canadian brand names

In Canada, topiramate is sold under the brand names CO Topiramate, Gen-Topiramate, PMS-Topiramate, ratio-Topiramate, Sandoz Topiramate, Teva-Topiramate, and Topamax.

International brand names

Internationally, topiramate is sold under a wide variety of brand names.

Recommended dosage

Topiramate is taken by mouth in tablet or sprinkle form. The drug is usually taken twice daily. Typical total daily doses are 200–400 mg for the treatment of seizure disorders. For the treatment of bipolar disorder or migraine headache prevention, dosages vary.

Beginning a course of treatment that includes topiramate requires a gradual dose-increasing regimen. The prescribing physician determines the proper beginning dosage and may raise a patient's daily dosage gradually over the course of several weeks. It may take several weeks to realize the full seizure-reducing benefits of topiramate.

A double dose of topiramate should not be taken to make up for a missed or forgotten dose. If a daily dose is missed, it should be taken as soon as possible, but if it is almost time for the next dose, the missed dose is skipped.

When discontinuing treatment with topiramate, physicians typically direct patients to gradually taper their daily dosages. Stopping the medicine suddenly may cause seizures to return or occur more frequently.

In the treatment of bipolar disorder, persons should not stop taking topiramate without consulting the prescribing physician. Stopping the medicine suddenly may cause seizures, or severely and suddenly alter a patient's mood.

Pediatric

The safety and efficacy of topiramate have not been established for seizure management in children under the age of 2. Dosing for migraine headaches has not been established for children younger than age 12.

Geriatric

Elderly patients are more likely to have age-related kidney problems with the use of topiramate. The doctor should monitor dosage and kidney function closely during treatment.

Precautions

Topiramate should be used cautiously in people with metabolic acidosis. This condition can be determined with a blood test prior to beginning this medication.

Topiramate is not habit forming. A physician should be consulted before combining topiramate with certain nonprescription medications.

Patients should avoid alcohol and CNS depressants (medicines that can make one drowsy or less alert, such as antihistamines, sleep medications, and some pain medications) while taking topiramate. Because topiramate may cause drowsiness, persons should not drive or operate heavy machinery until they know how they will react to the drug.

Persons taking topiramate, particularly those with predisposing factors, should maintain an adequate fluid intake in order to minimize the risk of kidney stone formation. Approximately 1.5% of people taking topiramate develop kidney stones.

Topiramate may not be suitable for persons with a history of liver or kidney disease, mental illness, high blood pressure, angina (chest pain), irregular heartbeat, or other heart problems. Before beginning treatment with topiramate, patients should notify their physician if they consume a large amount of alcohol, have a history of drug use, are pregnant, or are planning to become pregnant.

Topiramate may inhibit perspiration, causing body temperature to increase. Persons taking topiramate are at a greater risk for heat stroke and should use caution during strenuous exercise, prolonged exposure during hot weather, and while using saunas or hot tubs. People taking this medication should drink plenty of fluids and notify the doctor of any fever, headache, muscle cramps, or upset stomach.

Topiramate may cause osteoporosis in adults.

Topiramate and other antiepileptic medications are associated with an increased risk of suicidal thoughts or attempts.

Pediatric

Topiramate may slow physical growth when used in children. A doctor should track height and weight when this medication is used in a child. This medication may also cause rickets in children.

Pregnant or breastfeeding

Topiramate carries the FDA pregnancy category C, meaning that there is positive evidence of risk to the fetus. Topiramate increases the risk of birth defects including cleft lip and/or cleft palate, and animal studies have provided evidence of a heightened risk of craniofacial defects and reduced fetal weights. Topiramate should be used during pregnancy only if potential benefits outweigh potential risks to the fetus. Women who become pregnant while taking topiramate should contact their physician immediately.

Topiramate is known to be excreted into breast milk. Women who intend to breastfeed should consult their

physician about whether benefits outweigh risks to the infant.

Side effects

Patients and their physician should weigh the risks and benefits of topiramate before beginning treatment. Topiramate is usually well tolerated, but may cause a variety of usually mild side effects. Dizziness and drowsiness are the most frequently reported side effects of topiramate. Other possible side effects include:

- double vision
- tingling or prickly feeling of the extremities
- language problems, described as “trouble finding the right word”
- thinking and memory problems
- weight loss
- loss of appetite and nervousness (in children)

Many of these side effects disappear or occur less frequently during treatment as the body adjusts to the medication; however, if any symptoms persist or become too uncomfortable, the prescribing physician should be consulted.

Other uncommon side effects of topiramate can lead to serious complications. A person taking topiramate who experiences any of the following symptoms should immediately contact their physician:

- blurred vision and eye pain
- glaucoma
- extreme mood or mental changes
- shakiness or unsteady walking
- kidney stones
- difficulty breathing
- chest pain
- irregular heartbeat
- faintness or loss of consciousness

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

Topiramate may have negative interactions with some antihistamines, antidepressants, antibiotics, and

monoamine oxidase inhibitors (MAOIs). Other medications such as **diazepam** (Valium), phenobarbital (Luminal, Solfoton), nefazodone, **metronidazole**, acetazolamide (Diamox), lanoxin (**Digoxin**, Digitek), **phenytoin** (Dilantin), primidone, and propranolol (Inderal) may also need to be adjusted and closely monitored if taken with topiramate. Topiramate, like many other anticonvulsant medications, may decrease the effectiveness of **oral contraceptives** (birth control pills).

Resources

BOOKS

- Aminoff, Michael J., editor. *Neurology and General Medicine*. 4th ed. New York: Churchill Livingstone, 2007.
- Devinsky, Orrin. *Epilepsy: Patient and Family Guide*. 3rd ed. New York: Demos Medical, 2007.
- Diamond, Seymour, and Merle Lea Diamond. *A Patient's Guide to Headache and Migraine*. 2nd ed. Newtown, PA: Handbooks in Health Care, 2009.
- Mauskop, Alex. *Migraine and Headache*. New York: Oxford University Press, 2009.
- Panayiotopoulos, C. P. *Antiepileptic Drugs, Pharmacopoeia*. New York: Springer, 2010.
- Patsalos, Philip N., and Blaise F. D. Bourgeois. *The Epilepsy Prescriber's Guide to Antiepileptic Drugs*. New York: Cambridge University Press, 2010.
- Shorvon, Simon. *Handbook of Epilepsy Treatment*. 3rd ed. New York: Wiley-Blackwell, 2010.
- Tatum, William O., Peter W. Kaplan, and Pierre Jallon. *Epilepsy A to Z: A Concise Encyclopedia*. 2nd ed. New York: Demos Medical, 2009.

Resources

WEBSITES

- MedlinePlus. "Topiramate." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a697012.html> (accessed March 6, 2015).
- Micromedex. "Topiramate (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/topiramate-oral-route/before-using/drg-20067047> (accessed March 6, 2015).
- Schachter, Steven C., Patricia O. Shafer, and Joseph I. Sirven. "Seizure Medicines." Epilepsy Foundation. <http://www.epilepsy.com/learn/treating-seizures-and-epilepsy/seizure-and-epilepsy-medicines> (accessed March 6, 2015).

ORGANIZATIONS

- American Academy of Neurology (AAN), 1080 Montreal Avenue, Saint Paul, MN 55116, (651) 695-2717, (800) 879-1960, Fax: (651) 695-2791, memberservices@aan.com, <http://www.aan.com/>.
- American Epilepsy Society, 342 North Main Street, West Hartford, CT 06117-2507, (860) 586-7505 <http://www.aesnet.org/>.

American Neurological Association, 1120 Route 73, Suite 200, Mount Laurel, NJ 08054, (856) 380-6892, info@myana.org, <http://myana.org/>.

American Psychiatric Association (APA), 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, (888) 35-PSYCH, apa@psych.org, <http://www.psychiatry.org/>.

Epilepsy Foundation, 8301 Professional Pl., Landover, MD 20785-7223, (800) 332-1000, <http://www.epilepsy.com/>.

Family Caregiver Alliance, 785 Market Street, Suite 750, San Francisco, CA 94103, (800) 445-8106, <http://www.caregiver.org/>.

National Institute of Neurological Disorders and Stroke (NINDS), PO Box 5801, Bethesda, MD 20824, (301) 496-5751, (800) 352-9424, <http://www.ninds.nih.gov/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Revised by Tracy Gardner Beno, RN

REVIEWED BY GREGORY A. PRATT, RPh

Toprol-XL see **Metoprolol**

Toradol see **Ketorolac**

Torsenide

Definition

Torsenide is an oral or injected drug that reduces water retention and swelling caused by various medical conditions. Torsenide is in the pyridine-sulfonylurea class of loop diuretics, sometimes referred to as "water pills."

Purpose

Torsenide is used to help reduce water in the body and associated swelling (edema) resulting from conditions such as congestive heart failure, severe liver disease (cirrhosis), or kidney disease. Torsenide is also used to treat high blood pressure (hypertension). Controlling edema can lessen symptoms such as shortness of breath and swelling in the arms, legs, or abdomen. High blood pressure forces the heart and arteries to work harder and, over time, can damage blood vessels in the brain, heart, and kidneys and lead to stroke or heart or kidney failure and increase the risk of heart attacks. Torsenide does not cure high blood pressure, but it can help control it and reduce the risk of resulting problems. Torsenide is often used in combination with other medications and is sometimes prescribed for other purposes.



Torsemide, 20 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Description

Torsemide is a sulfonyleurea diuretic that causes the kidneys to excrete excess water and salt in the urine. It is called a loop diuretic because it acts on the thick ascending limb of Henle's loop, a structure in the kidney that reabsorbs sodium, potassium, and chloride, as well as magnesium and calcium. Torsemide binds reversibly to a carrier protein in the sodium/chloride/potassium cotransport system or reabsorptive pump in the loop. This reduces or eliminates sodium and chloride reabsorption by the kidney and increases excretion of water, sodium, and chloride in the urine. It also reduces calcium and magnesium reabsorption and potassium excretion. The other two types of diuretics—thiazide and potassium-sparing diuretics—affect different parts of the kidneys. Torsemide is often used when thiazide diuretics are ineffective or inappropriate.

The diuretic effects of torsemide peak one to two hours after taking a pill and last for six to eight hours. The diuretic effects of intravenous (IV) torsemide last about six hours. However, the full blood pressure-lowering effects of torsemide are not evident until 4 to 6 weeks after beginning treatment—and sometimes not until about 12 weeks. Torsemide may work better when combined with lifestyle changes including dietary modifications, exercise, quitting smoking, and stress reduction.

Torsemide is supplied as 5, 10, 20, or 100 milligram (mg) white, scored oral tablets. The 100 mg tablets are

capsule shaped; the others are elliptical. They are debossed with "5," "10," "20," or "100" to indicate the dose and are generally supplied in bottles of 100 tablets. The tablets are stored at room temperature and away from excess heat and moisture (not in the bathroom).

Torsemide for injection is supplied at a concentration of 10 mg per milliliter (mL), 20 mg/2 mL, or 50 mg/5 mL. It is either added to an IV fluid that is dripped through a needle or catheter in a vein as a continuous infusion or is administered directly into a vein or catheter over a period of at least two minutes. If torsemide is administered through an IV line, the line should be flushed with normal saline before and afterwards. The patient may be given a several-day supply that should be stored as directed. The IV supplies should be kept in a clean, dry place and needles, syringes, tubing, and containers disposed of properly.

U.S. brand names

The U.S. brand names for torsemide are Demadex Tablets and Demadex Injection. Generic torsemide is also available.

Canadian brand names

Only generic torsemide is available in Canada.

International brand names

There are many international brand name and generic forms of torsemide. Among the more common brand names are:

- Britomar
- Diuver
- Dytor
- Luprac
- Toragamma
- Torasemid
- Torasemida
- Torem
- Trifas

Origins

Torsemide is a white to off-white crystalline powder. The tablets and injection were originally approved by the U.S. Food and Drug Administration (FDA) in 1993. Generic torsemide has been available since 2002.

Recommended dosage

Dosage and duration of treatment depends on the medical condition and response to torsemide.

KEY TERMS

Cirrhosis—Liver damage and destruction, usually caused by chronic alcohol abuse or hepatitis infection.

Congestive heart failure—A condition in which the heart is unable to maintain adequate circulation or pump out the venous blood.

Dehydration—Abnormal depletion of body fluids, as from vomiting, diarrhea, or a diuretic.

Demadex—The U.S. brand name for torsemide.

Edema—Excess fluid accumulation in tissue, causing swelling.

Hypertension—High blood pressure.

Intravenous (IV)—Administered into a vein.

Loop diuretic—A “water pill,” such as torsemide, that increases urine excretion and removes water and salt from the body by interfering with sodium and chloride reabsorption in the kidney’s thick ascending limb of Henle’s loop.

- For congestive heart failure, the initial dose is 10–20 mg orally or IV once daily. If the diuretic response is inadequate, the doses can be approximately doubled until an adequate response is obtained, not exceeding 200 mg in a single dose.
- For chronic renal failure, the initial dose is 20 mg orally or IV once daily, with approximate doubling until the desired diuretic response is obtained, but not to exceed 200 mg in a single dose.
- For liver cirrhosis, the initial dose is 5–10 mg orally or IV once daily along with an aldosterone antagonist or potassium-sparing diuretic. The doses are doubled until the appropriate diuretic response is obtained, up to a maximum of 40 mg per individual dose.
- For hypertension, the initial dose is 2.5–5 mg orally once daily. The dose can be increased to 10 mg orally once daily if adequate blood-pressure reduction is not achieved within four to six weeks. If a 10 mg dose is insufficient, an additional antihypertensive agent must be added.

Torsemide is usually taken in the morning, at the same time each day. It should not be taken within four hours of bedtime so as to avoid interrupting sleep to urinate. A missed dose should be taken as soon as possible, but if it is almost time for the next dose, the missed dose should be skipped and the regular dosing schedule resumed.

Precautions

Some precautions while taking torsemide include:

- Patients should check their blood pressure regularly while taking torsemide.
- Periodic kidney function tests and blood tests, including levels of minerals such as potassium, and physical exams are used to monitor effectiveness and side effects.
- Doctors and dentists should be told about torsemide use before performing any type of surgery.
- The doctor should be notified if the condition does not improve or worsens or if blood pressure remains high or increases.
- Torsemide may cause dizziness: patients should not drive, operate machinery, or perform any activity that requires alertness until they know how the drug affects them.
- Patients should not stop using torsemide without talking to their doctor.
- Severe sweating, diarrhea, or vomiting increases the risk of dehydration (severe water loss) with torsemide. The doctor should be consulted in case of prolonged diarrhea or vomiting.

Before administering IV torsemide, the solution should be examined to ensure that it is clear and free of any floating material. The bag or container should be checked for leaks. A leaking container or a solution that is discolored or has particles should not be used. A mechanical problem, such as a blockage in the tubing, needle, or catheter, may require stopping the infusion and calling the healthcare provider immediately.

Pediatric

The safety and effectiveness of torsemide have not been established in pediatric patients.

Geriatric

No specific age-related differences have been observed in the effectiveness and safety of torsemide between younger and geriatric patients. However, older adults may be more sensitive to torsemide effects.

Pregnant or breastfeeding

Torsemide is in the FDA pregnancy category B. Its use may be acceptable during pregnancy, but it should only be used if clearly needed. Women should consult their doctors if they become pregnant or are planning to become pregnant while using torsemide. It is not known whether torsemide is passed into breast milk. It should be avoided or used with caution by nursing mothers.

Other conditions and allergies

Patients should tell their doctor and pharmacist if they are allergic to torsemide, sulfa drugs, or any other medications. Chronic use of torsemide or any other diuretic has not been adequately studied in patients with liver disease. Patients should tell their doctors if they have or have ever had:

- diabetes
- gout
- kidney or liver disease or other kidney or liver problems
- inability to make urine

Side effects

Many people take torsemide without experiencing serious side effects. Frequent urination can last up to six hours after a dose of torsemide, but this effect usually decreases after taking the drug for a few weeks. Torsemide may cause dizziness or headache as the body adjusts to it. Rising slowly from sitting or lying down reduces the risk of dizziness or lightheadedness. The doctor or pharmacist should be consulted promptly if dizziness or headache are persistent or worsen.

Torsemide may cause dehydration and loss of salt and minerals. The doctor should be called immediately if any of these uncommon but serious side effects occur:

- unusual decrease in the amount of urine
- unusual dry mouth or thirst
- nausea
- vomiting
- muscle cramps
- weakness
- drowsiness, unusual tiredness, or fatigue
- severe dizziness
- fainting
- fast or irregular heartbeat
- confusion

Rare but serious side effects that require calling the doctor immediately include:

- numbness, tingling, pain, redness, or swelling in the arms or legs
- hearing changes, such as ringing in the ears, temporary or permanent decrease in hearing, or deafness
- rapid, excessive weight loss
- vomiting blood

Injected torsemide carries a risk of infection at the injection site. The doctor should be called if any of the following occur near the site of injection:

- tenderness
- warmth
- irritation
- redness
- swelling
- drainage
- pain

Geriatric

Older adults may be more likely to experience dizziness or water and/or mineral loss from torsemide.

Other conditions and allergies

Infrequently, torsemide can affect blood sugar levels in people with diabetes. Patients should check their blood sugar regularly. It may be necessary to make adjustments to the diet or diabetes medications.

Very serious allergic reactions to torsemide are rare. However, emergency medical assistance is necessary for symptoms such as:

- rash, itching, or swelling, especially of the face, tongue, or throat
- severe dizziness
- trouble breathing

Interactions

The doctor and pharmacist should be informed of all prescription and nonprescription medicines, vitamins, minerals, herbs, and dietary supplements being used or planning to be used by the patient. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Drugs

The labels of all medications—including cough and cold medicines, diet aids, and nonsteroidal anti-inflammatory drugs (NSAIDs) such as **ibuprofen** and **naproxen**—should be checked, because these drugs may contain ingredients that could increase blood pressure and worsen swelling. Cholestyramine and colestipol can decrease torsemide absorption. Each dose of either of these drugs should be taken at least two hours before or after torsemide. Other drugs that may interact with torsemide include:

- other high blood pressure medications
- corticosteroids such as **prednisone** and especially dexamethasone (Decadron)
- **digoxin** (Lanoxin)

- **indomethacin** (Indocin)
- **lithium** (Eskalith, Lithobid)
- **probenecid** (Benemid)

Herbs and supplements

Vitamin supplements may interact with torsemide.

Food and other substances

Torsemide may be taken with or without food. The doctor may prescribe a low-sodium or low-salt diet along with a daily exercise program. Torsemide may reduce blood potassium levels, and potassium supplements or increased amounts of potassium-rich foods—such as bananas, prunes, raisins, and orange juice—may be required. The doctor will provide instructions on the amount of fluids to drink. Alcoholic beverages should be limited.

Resources

PERIODICALS

“Drugs to Treat Hypertension.” *Journal of Psychosocial Nursing & Mental Health Services* 52, no. 2 (February 2014): 11–12.

OTHER

U.S. Food and Drug Administration. “Demadex (Torsemide) Tablets.” http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020136s0231b1.pdf (accessed February 28, 2015).

WEBSITES

Mayo Clinic staff. “Diuretics.” MayoClinic.org. <http://www.mayoclinic.org/diseases-conditions/high-blood-pressure/in-depth/diuretics/art-20048129?pg=1> (accessed February 28, 2015).

Medscape Reference. “Torsemide (Rx)—Demadex.” <http://reference.medscape.com/drug/demadex-torsemide-342424#0> (accessed February 28, 2015).

Micromedex. “Torsemide (Oral Route).” MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/torsemide-oral-route/description/drg-20067926> (accessed February 28, 2015).

U.S. Food and Drug Administration. “High Blood Pressure—Medicines to Help You.” <http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118594.htm> (accessed February 28, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY KEVIN GLAZA, RPh

Tramadol

Definition

Tramadol is a prescription-only painkiller (analgesic) that belongs to the family of drugs called opioid analgesics. Tramadol is a type of synthetic narcotic drug.

Purpose

Tramadol is used to treat moderate to severe pain.

Description

Tramadol is classified by the Drug Enforcement Administration (DEA) as a Schedule IV drug. This means that tramadol:

- carries a low potential for abuse (less than drugs categorized as Schedule III)
- is medically accepted as a therapeutic agent
- carries a low potential for initiating psychological or physical dependence if abused

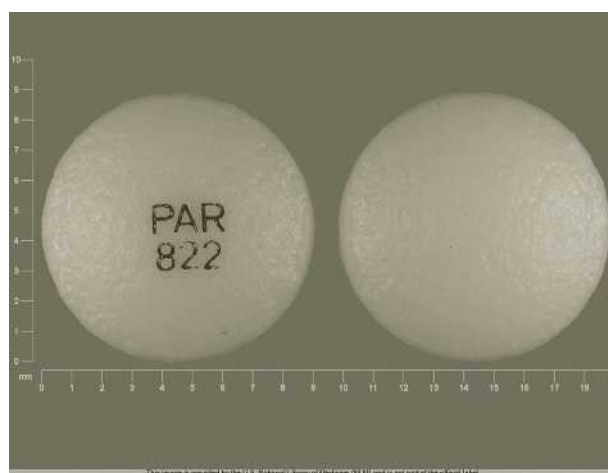
Tramadol is available as 50 mg scored tablets, with varying shapes and imprints depending on the manufacturer.

U.S. brand names

Tramadol is sold in the United States under the brand names Active-Tramadol, ConZip, EnovaRX-Tramadol, Synapryn FusePaq, Ultram, and Ultram ER.

Canadian brand names

In Canada, Tramadol is sold under the brand names Apo-Tramadol, Durela, Ralivia, Tridural, Ultram, and Zytram XL.



Extended-release tramadol, 200 mg. (U.S. National Library of Medicine, Pillbox)

KEY TERMS

Analgesic—A drug used to control pain.

Creatinine—The metabolized by-product of creatine, an organic acid that assists the body in producing muscle contractions. Creatinine is found in the bloodstream and in muscle tissue. It is removed from the blood by the kidneys and excreted in the urine.

Narcotics—A class of chemicals that contain opium or opium derivatives. These drugs decrease pain, often cause drowsiness, may induce a sense of euphoria or well-being, and have profound side effects that include respiratory depression in overdoses and addictive potential.

Opioid—A substance that resembles opium and binds to the same types of receptors in the body, producing similar effects in pain relief, pleasure, and addictiveness. These substances do not actually contain opium, but are synthetically produced to mimic its therapeutic benefits.

International brand names

Tramadol is sold under a variety of brand names internationally, including Acugesic (Pakistan), Domadol (India), Modsenal (Thailand), Noax (Romania), Souladol (Tunisia), and Zafin (Peru). In some countries, tramadol is only one component of the medication, and there are other medications included in the formulation.

Recommended dosage

In adults or children over 17 years of age, for the relief of moderate to severe pain, the recommended oral dosage is 50 to 100 mg every 4–6 hours, with a maximum daily dose of 400 mg.

Geriatric

Due to the potential for more profound side effects, the tramadol dose in elderly patients (over the age of 75 years) should be carefully titrated, beginning at the lowest possible dose, and should not exceed a total daily dose of 300 mg.

Other conditions and allergies

For patients with renal impairment, if creatinine clearance is less than 30 mL per minute, tramadol should be dosed 50–100 mg every 12 hours, not to exceed a total daily dose of 200 mg. Extended-release tramadol should not be used in these individuals. For patients with liver

impairment, tramadol should be dosed 50 mg every 12 hours, not to exceed a total daily dose of 200 mg. Extended-release tramadol should not be used in individuals with severe liver impairment.

Precautions

Tramadol should not be given to individuals with a known sensitivity to tramadol or other ingredients within a specific delivery formulation.

Tramadol should be used with caution in individuals who have had previous reactions to opiates or opioids.

Tramadol should not be used in patients with severe respiratory problems, including asthma (unless the patient is concurrently mechanically ventilated).

Tramadol can cause drowsiness and can impair physical abilities as well as mental processing and alertness.

Tramadol can induce seizures in vulnerable individuals, including those with head trauma, metabolic disorders, CNS infection, malignancy, or during alcohol/drug withdrawal, as well as in individuals who are also using medications that lower the seizure threshold, such as selective serotonin reuptake inhibitors (SSRIs), other opioids, tricyclic antidepressants, neuroleptics, MAO inhibitors, or drugs that impair the metabolism of tramadol (e.g., CYP2D6 and 3A4 inhibitors).

Tramadol should be avoided or carefully monitored in people with specific conditions, such as:

- history of substance abuse or alcoholism; because of tramadol's abuse potential, individuals with a prior history of addiction may have an increased risk of becoming addicted to tramadol
- head injury; tramadol and other opioid drugs may complicate the assessment and course of traumatic brain injuries and other causes of brain swelling; respiratory status may also be severely affected when used in the setting of head injury or coma

Because of tramadol's addictive potential, sudden discontinuation of the drug can lead to symptoms of withdrawal, including nausea, vomiting, diarrhea, teary eyes, runny nose, severe sweating, itchy skin, twitchy muscles, and uncontrollable yawning.

Geriatric

Elderly and debilitated patients are at particular risk of complications from tramadol use, especially effects on the central nervous system, respiratory system, and constipating effects. Tramadol should be used with extreme caution and close monitoring in this population.

Pregnant or breastfeeding

Tramadol is a pregnancy category C drug, meaning that risk cannot be ruled out in pregnant individuals. If possible, use of this drug should be avoided. Babies who have been exposed to tramadol acutely before birth may be born with decreased respiratory drive and a weak suck. Babies who have been exposed to tramadol chronically before birth may experience withdrawal syndrome (neonatal abstinence syndrome) after birth when they are no longer receiving tramadol through the placenta. These babies may require treatment to avoid severe symptoms of withdrawal.

Tramadol is known to pass into breast milk. It should be avoided by breastfeeding women.

Side effects

The most common side effects of tramadol treatment include:

- flushing
- headache, drowsiness, confusion, unclear thinking, depression
- sweating, itching
- dehydration
- constipation
- dry mouth
- urinary retention
- weak muscles
- shortness of breath, respiratory depression
- euphoria
- agitation, hallucinations
- upset stomach, nausea, vomiting
- blurred vision, ringing in the ears

Rare but serious signs of a significant allergic reaction to tramadol should prompt the individual to seek immediate medical care. These include:

- difficulty breathing or swallowing
- hoarse voice
- wheezing, shortness of breath, cough
- fever
- pain in the abdomen
- blue skin or lips
- yellow cast to the skin or the whites of the eyes
- headache
- stiff neck
- confusion
- seizures
- swollen face, lips, tongue, or throat

- rash, hives, blisters, or peeling skin
- dizziness

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

The following may increase tramadol's side effects:

- alpha- and beta-agonists
- opioid analgesics
- amphetamines
- anticholinergic agents
- antiemetics
- **aripiprazole**
- antipsychotic agents
- cannabis
- crizotinib
- droperidol
- hydrocodone
- **hydroxyzine**
- magnesium sulfate
- methotrimeprazine
- mifepristone
- **zolpidem**

CYP3A4 inhibitors have a profound effect on tramadol, and may greatly increase the risk of potentially fatal side effects. There are many drugs in this group, including:

- amiodarone
- anastrozole
- **azithromycin**
- cannabinoids
- cimetidine
- **clarithromycin**
- clotrimazole
- **cyclosporine**
- danazol
- delavirdine
- dexamethasone

- diethyldithiocarbamate
- **diltiazem**
- disulfiram
- entacapone
- **erythromycin**
- ethinyl estradiol
- **fluconazole**
- **fluoxetine**
- **fluvoxamine**
- gestodene
- indinavir
- isoniazid
- **ketoconazole**
- **metronidazole**
- mibefradil
- miconazole
- nefazodone
- nelfinavir
- nevirapine
- norfloxacin
- norfluoxetine
- **omeprazole**
- oxiconazole
- **paroxetine**
- propoxyphene
- quinidine
- quinine
- **ranitidine**
- ritonavir
- saquinavir
- sertindole
- **sertraline**
- troglitazone
- troleandomycin
- **valproic acid**

Tramadol may increase the side effects of the following:

- opioid analgesics
- antiemetics
- antipsychotic agents
- beta-blockers
- buprenorphine
- calcium channel blockers
- desmopressin
- diuretics
- hydrocodone

- hydroxyzine
- MAO inhibitors
- methotrimeprazine
- **metoclopramide**

Herbs and supplements

Kava kava may increase the side effects of tramadol. Tramadol may increase the side effects of kava kava.

Food and other substances

Alcohol may increase the side effects of tramadol. Tramadol may increase the side effects of alcohol.

Resources

BOOKS

- Aronson, J. K. *Meyler's Side Effects of Analgesics and Anti-inflammatory Drugs*. Oxford: Elsevier, 2010.
- Benzon, Honorio T. *Essentials of Pain Medicine*. 3rd ed. Philadelphia: Saunders, 2011.
- Smith, Howard S. *Current Therapy in Pain*. Philadelphia: Saunders, 2009.
- Waldman, Steven D. *Pain Management*. 2nd ed. Philadelphia: Saunders, 2011.

WEBSITES

- MedlinePlus. "Tramadol." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a695011.html> (accessed March 3, 2015).
- "Tramadol." Drugs.com. <http://www.drugs.com/tramadol.html> (accessed March 3, 2015).
- U.S. National Library of Medicine. "LactMed: Tramadol." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+391> (accessed March 3, 2015).

ORGANIZATIONS

- American Chronic Pain Association, PO Box 850, Rocklin, CA 95677, (800) 533-3231, APAC@theacpa.org, <http://www.theacpa.org/>.
- American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.
- National Pain Foundation, 14828 W 6 Avenue, Suite 16-B, Room 1, Golden, CO 80401-5000, (720) 541-6808, Fax: (720) 541-6809, <http://www.thenationalpainfoundation.org/>.
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Rosalyn S. Carson-DeWitt, MD

REVIEWED BY CHRISTY McDONALD LENAHA, DNP, MSN,
APRN, FNP-BC

Tramadol/acetaminophen

Definition

Tramadol/acetaminophen is a prescription-only medication that combines acetaminophen, a nonprescription painkiller (analgesic), and **tramadol**, an opioid analgesic.

Purpose

Tramadol/acetaminophen is used to treat acute pain. It is intended to be used for five days or fewer.

Description

Tramadol/acetaminophen is classified by the Drug Enforcement Administration (DEA) as a Schedule IV drug. This means that tramadol/acetaminophen:

- carries a low potential for abuse (less than drugs categorized as Schedule III)
- is medically accepted as a therapeutic agent
- carries a low potential for initiating psychological or physical dependence if abused

Tramadol/acetaminophen is available as a capsule-shaped tablet in orange, beige, yellow, or white, with varying imprints depending on the manufacturer. Each tablet contains 325 milligrams (mg) of acetaminophen and 37.5 mg of tramadol.



Tramadol/acetaminophen, 37.5 mg/325 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

U.S. brand names

Tramadol/acetaminophen is sold in the United States under the brand name Ultracet.

Canadian brand names

In Canada, tramadol/acetaminophen is sold under the brand names ACT Tramadol/Ace, Apo-Tramadol/Acet, JAMP-ACET-Tramadol, Mar-Tramadol/Acet, Mint-Tramadol/Acet, Pat-Tramadol/Acet, PMS-Tramadol/Acet, Priva-Tramadol/Acet, RAN-Tramadol/Acet, TEVA-Tramadol/Acetaminophen, Tramacet, and Tramaphen-Odan.

International brand names

Tramadol/acetaminophen is sold under a variety of brand names internationally, including Analgam-Tram (Ecuador), Didol-P (India), Duodol (Colombia), Supracalm Duo (Peru), Tolmus (Dominican Republic), and Zaldiar (Costa Rica).

Recommended dosage

In adults and children over 17 years of age, for the relief of moderate to severe pain, the recommended oral dose is two tablets every 4–6 hours, with a maximum dose of eight tablets per day. The duration of treatment should not be greater than five days.

Other conditions and allergies

In individuals with kidney impairment whose creatinine clearance is less than 30 milliliters (mL) per minute, the maximum dose should be two tablets taken every 12 hours. Creatinine is a waste material that is filtered out of the body by the kidneys; measuring the amount of creatinine in a patient's urine helps determine kidney function.

In individuals with liver impairment, tramadol/acetaminophen should not be used.

Precautions

A boxed warning is included with this product stating that the medication includes acetaminophen, which has the potential to damage the liver, usually due to overdose of the product. Overdose has sometimes occurred unintentionally, when more than one acetaminophen-containing product has been taken concurrently. Several over-the-counter drugs contain acetaminophen, including pain relievers and cough and cold medicines. Acute liver failure may result in the need for a liver transplant or death.

Tramadol/acetaminophen should be used with caution in individuals who have had previous reactions to opiates or opioids, and it should not be used in patients

KEY TERMS

Analgesic—A drug used to control pain.

Boxed warning—A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Drug schedule—A method of classifying drugs including narcotics, sedatives, hallucinogens, and other drugs that are restricted under federal and state laws in the United States. Schedule I substances have no approved medical use, while Schedules II, III, and IV have approved uses. The higher the schedule, the lower the degree of restriction.

Narcotics—A class of chemicals that contain opium or opium derivatives. These drugs decrease pain, often cause drowsiness, may induce a sense of euphoria or well-being, and have profound side effects that include respiratory depression in overdoses and addictive potential.

Opioid—A substance that resembles opium and binds to the same types of receptors in the body, producing similar effects in pain relief, pleasure, and addictiveness. These substances do not actually contain opium, but are synthetically produced to mimic its therapeutic benefits.

who are acutely intoxicated with ethanol, hypnotics, centrally acting analgesics, opioids, or psychotropic drugs.

Tramadol/acetaminophen can cause drowsiness and can impair physical abilities as well as mental processing and alertness.

Because of tramadol/acetaminophen's addictive potential, sudden discontinuation of the drug can lead to symptoms of withdrawal, including nausea, vomiting, diarrhea, teary eyes, runny nose, severe sweating, itchy skin, twitchy muscles, and uncontrollable yawning.

Geriatric

Elderly and debilitated patients are at particular risk of complications from tramadol/acetaminophen use, especially effects on the central nervous system, respiratory system, and constipating effects. Tramadol/acetaminophen should be used with extreme caution and close monitoring in this population.

Pregnant or breastfeeding

Tramadol/acetaminophen is a pregnancy category C drug, meaning that risk cannot be ruled out in pregnant individuals. If possible, use of this drug should be avoided. Babies who have been exposed to tramadol/acetaminophen acutely before birth may be born with decreased respiratory drive and a weak suck. Babies who have been exposed to tramadol/acetaminophen chronically before birth may experience withdrawal syndrome (neonatal abstinence syndrome) after birth when they are no longer receiving tramadol/acetaminophen through the placenta. These babies may require treatment to avoid severe symptoms of withdrawal.

Tramadol/acetaminophen is known to pass into breast milk. It should be avoided by breastfeeding women.

Other conditions and allergies

Tramadol/acetaminophen can induce seizures in vulnerable individuals, including those with head trauma, metabolic disorders, central nervous system infections, or cancer, or individuals who are undergoing alcohol/drug withdrawal. It should not be used in patients with severe respiratory problems, including asthma.

Tramadol/acetaminophen should be avoided or carefully monitored in people with specific conditions, such as:

- history of substance abuse or alcoholism
- head injury
- liver or kidney disease
- suicidality

Tramadol/acetaminophen should not be given to individuals with a known sensitivity to tramadol, acetaminophen, or other ingredients within a specific delivery formulation.

Side effects

The most common side effects of tramadol/acetaminophen treatment include:

- flushing
- headache, drowsiness, confusion, unclear thinking, depression
- sweating, itching
- dehydration
- constipation
- dry mouth
- urinary retention
- weak muscles
- shortness of breath, respiratory depression

- euphoria
- agitation, hallucinations
- upset stomach, nausea, vomiting
- blurred vision, ringing in the ears

Rare but serious signs of a significant allergic reaction to tramadol/acetaminophen should prompt the individual to seek immediate medical care. These include:

- difficulty breathing or swallowing
- hoarse voice
- wheezing, shortness of breath, cough
- fever
- pain in the abdomen
- blue skin or lips
- yellow cast to the skin or the whites of the eyes
- headache
- stiff neck
- confusion
- seizures
- swollen face, lips, tongue, or throat
- rash, hives, blisters, or peeling skin
- dizziness

Interactions

Pharmaceutical drugs may interact with other pharmaceuticals, herbs, dietary supplements, and foods. Drug interactions can increase or decrease the effectiveness of the drug or increase the risk of serious side effects. Patients must tell the prescribing doctor about all the medications they are taking, including nonprescription (over-the-counter) medications, herbs, and dietary supplements, including vitamin supplements.

Drugs

The risk of seizures is increased in patients who are taking tramadol/acetaminophen and medications that lower the seizure threshold, such as selective serotonin reuptake inhibitors (SSRIs), other opioids, tricyclic antidepressants, neuroleptics, monoamine oxidase inhibitors (MAOIs), or drugs that impair the metabolism of tramadol/acetaminophen (e.g., CYP2D6 and 3A4 inhibitors).

The following may increase tramadol/acetaminophen's side effects:

- alpha- and beta-agonists
 - opioid analgesics
 - amphetamines
 - anticholinergic agents
 - antiemetics
 - **aripiprazole**
 - antipsychotic agents
 - cannabis
 - crizotinib
 - droperidol
 - hydrocodone
 - **hydroxyzine**
 - magnesium sulfate
 - methotrimeprazine
 - mifepristone
 - **zolpidem**
- Drugs classified as CYP3A4 inhibitors have a profound effect on tramadol/acetaminophen, and may greatly increase the risk of potentially fatal side effects. There are many drugs in this group, including:
- amiodarone
 - anastrozole
 - **azithromycin**
 - cannabinoids
 - cimetidine
 - **clarithromycin**
 - clotrimazole
 - **cyclosporine**
 - danazol
 - delavirdine
 - dexamethasone
 - diethyldithiocarbamate
 - **diltiazem**
 - disulfiram
 - entacapone
 - **erythromycin**
 - ethinyl estradiol
 - **fluconazole**
 - **fluoxetine**
 - **fluvoxamine**
 - gestodene
 - indinavir
 - isoniazid
 - **ketoconazole**
 - **metronidazole**
 - mibefradil
 - miconazole
 - nefazodone
 - nelfinavir
 - nevirapine

- norfloxacin
- norfluoxetine
- **omeprazole**
- oxiconazole
- **paroxetine**
- propoxyphene
- quinidine
- quinine
- **ranitidine**
- ritonavir
- saquinavir
- sertindole
- **sertraline**
- troglitazone
- troleandomycin
- **valproic acid**

Tramadol/acetaminophen may increase the side effects of the following:

- opioid analgesics
- antiemetics
- antipsychotic agents
- beta blockers
- buprenorphine
- calcium channel blockers
- desmopressin
- diuretics
- hydrocodone
- hydroxyzine
- MAOIs
- methotrimeprazine
- **metoclopramide**

Herbs and supplements

Kava kava may increase the side effects of tramadol/acetaminophen, and tramadol/acetaminophen may increase the side effects of kava kava.

Food and other substances

Alcohol may increase the side effects of tramadol/acetaminophen, and tramadol/acetaminophen may increase the side effects of alcohol.

Resources

BOOKS

- Aronson, J. K. *Meyler's Side Effects of Analgesics and Anti-inflammatory Drugs*. Oxford: Elsevier, 2010.
- Benzon, Honorio T. *Essentials of Pain Medicine*. 3rd ed. Philadelphia: Saunders, 2011.

Smith, Howard S. *Current Therapy in Pain*. Philadelphia: Saunders, 2009.

Waldman, Steven D. *Pain Management*. 2nd ed. Philadelphia: Saunders, 2011.

WEBSITES

"Acetaminophen." Drugs.com. <http://www.drugs.com/acetaminophen.html> (accessed March 3, 2015).

MedlinePlus. "Acetaminophen." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a681004.html> (accessed March 3, 2015).

MedlinePlus. "Tramadol." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a695011.html> (accessed March 3, 2015).

"Tramadol." Drugs.com. <http://www.drugs.com/tramadol.html> (accessed March 3, 2015).

U.S. National Library of Medicine. "LactMed: Acetaminophen." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+330> (accessed March 3, 2015).

U.S. National Library of Medicine. "LactMed: Tramadol." TOXNET. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@term+@DOCNO+391> (accessed March 3, 2015).

ORGANIZATIONS

American Chronic Pain Association, PO Box 850, Rocklin, CA 95677, (800) 533-3231, APAC@theacpa.org, <http://www.theacpa.org/>.

American Society of Health-System Pharmacists (ASHP), 7272 Wisconsin Avenue, Bethesda, MD 20814, (866) 279-0681, <http://www.ashp.org/>.

National Pain Foundation, 14828 W 6 Avenue, Suite 16-B, Room 1, Golden, CO 80401-5000, (720) 541-6808, Fax: (720) 541-6809, <http://www.thenationalpainfoundation.org/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Tranexamic acid

Definition

Tranexamic acid delays fibrinolysis, or the step in the blood coagulation process that dissolves blood clots. It is classified as an antifibrinolytic drug.



Tranexamic acid. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

Purpose

Oral tranexamic acid was approved for use as a nonhormonal treatment for abnormal uterine bleeding, such as is associated with uterine fibroids. An injectable form of tranexamic acid was approved by the U.S. Food and Drug Administration (FDA) for use in preventing excessive bleeding during dental procedures or surgery in patients with hemophilia.

Tranexamic acid has been available in Europe for many years. The injectable formulation is on the World Health Organization's list of essential medicines shown to be safe, effective, and necessary worldwide.

Off-label uses

Tranexamic acid is often used to encourage hemostasis and normal blood coagulation (clotting) in order to prevent blood loss and reduce the need for blood transfusion during different types of surgery, various clinical conditions, and major trauma injuries that are associated with excessive bleeding. Surgeries with a high risk of excess blood loss include vascular surgeries, prostate surgery, cardiac and liver surgeries, and certain extensive orthopedic surgeries, such as back surgery. In craniofacial and orthopedic surgeries, tranexamic acid may help reduce the need for transfusion, especially in children undergoing these surgeries.

Description

Tranexamic acid is a synthetic (man-made) derivative of the amino acid lysine. It is a white, crystalline

powder that can be prepared as a tablet or in a solution for injection. In either form, tranexamic acid exhibits antifibrinolytic activity to inhibit the destruction of fibrin, which is part of the normal anticoagulation process that prevents blood clot formation. This means that tranexamic acid blocks the natural breakdown of blood clots in the body.

At concentrations as low as 1 milligram per milliliter (mg/mL), tranexamic acid prolongs thrombin times to effectively stop bleeding, and in concentrations up to 10 mg/mL, it does not affect platelet counts, coagulation times, or other coagulation factors. The antifibrinolytic activity of tranexamic acid continues for about 17 hours in body tissues and 7–8 hours in blood serum.

Reports have shown that tranexamic acid, aside from reversing excess bleeding in surgery or trauma patients, reduces inflammation. Patients treated with tranexamic acid soon after a serious injury are more likely to survive their injuries than those who receive multiple blood transfusions.

Tranexamic acid is prepared as a 500 mg oral tablet and as an injectable form of 100 mg/mL.

U.S. brand names

Tranexamic acid is sold in the United States under the brand names Lysteda and Cyklokapon.

Canadian brand names

Tranexamic acid is sold in Canada under the brand name Cyklokapon.

International brand names

Tranexamic acid is sold under a wide variety of brand names worldwide.

Origins

Tranexamic acid was first approved for use by the FDA in 2009.

Recommended dosage

The injectable solution of tranexamic acid is typically given at 10 mg per kilogram (kg) of body weight. In tablet form, a single 500 mg tablet is given every 24 to 48 hours.

Pediatric

Tranexamic acid has only limited use in pediatric patients, which may be related to tooth extraction or certain surgeries with high risk of bleeding. In these circumstances, dosing recommendations for adults have been used successfully in children.

KEY TERMS

Arterial thrombosis—Blood clots that have developed in arteries anywhere in the body.

Coagulation—The entire process of blood clotting.

Coagulation factors—Proteins in blood plasma that serve to activate various parts of the blood-clotting process by being transformed from inactive to active forms.

Deep vein thrombosis (DVT)—A blood clot in the calf's deep vein. This frequently leads to pulmonary embolism if untreated.

Disseminated intravascular coagulation (DIC)—The abnormal and extensive activation of the coagulation cascade that finally results in small blood clots forming in blood vessels throughout the body. If not stopped, this can compromise the flow of blood throughout the body and lead to multiple organ damage.

Embolism—The blocking of the flow of blood in an artery by an embolus. When an embolism blocks the blood supply to a tissue or organ, the tissue the artery feeds dies (infarction). Without immediate and appropriate treatment, an embolism can be fatal.

Fibrin—The protein formed as the end product of the blood clotting process when fibrinogen (another blood protein) interacts with thrombin (an enzyme).

Fibrinolysis—The clot-dissolving portion of the coagulation process.

Fibroids—Benign (noncancerous) growths that arise from the smooth muscle layer and connective tissue of the uterus. They sometimes cause secondary dysmenorrhea.

Hemophilia—An inherited bleeding disorder caused by a deficiency of factor VIII, one of a series of blood proteins essential for blood clotting.

Hemostasis—The process of how the body stops bleeding from an injured blood vessel.

Neuraxial system—Nerves of the central nervous system.

Thrombin—An enzyme in blood plasma that helps to convert fibrinogen to fibrin during the last stage of the clotting process.

Thrombosis—Formation of a clot in the blood that either blocks or partially blocks a blood vessel. The thrombus may lead to infarction, or death of tissue, due to the blocked blood supply.

Geriatric

The use of tranexamic acid has not been adequately studied in patients older than 65 years of age, so it is not known whether response to the drug differs from that in younger adult patients. Tranexamic acid may be started at the low end of the dosing range, especially if the patient has cardiac, pulmonary, kidney, or liver disease or is taking other medications.

Other conditions and allergies

In patients with kidney disease, the dosage of tranexamic acid is determined based on serum creatinine levels. Creatinine is a waste material that is filtered out of the body by the kidneys. Measuring the amount of creatinine in a patient's urine helps determine kidney function. Since tranexamic acid is primarily excreted by the kidneys, the risk of toxic reactions may be higher in patients with impaired kidney function. For example, if creatinine is between 250 and 500 mg per deciliter (dL), 10 mg/kg may be given every 48 hours, while 5 mg/kg is given every 24 hours if the creatinine level is over 500 mg/dL.

Precautions

Tranexamic acid should not be given at the same time as other coagulant concentrates such as factor IX complex or anti-inhibitor coagulant concentrates, which may increase the risk of clot development. Administration of tranexamic acid more than three hours after a patient has suffered major trauma may increase the risk of death due to excess blood loss. However, when administered closer to the time of blood loss due to trauma, the risk of death is decreased.

The risk of clotting (venous or arterial thrombosis) is increased in patients receiving tranexamic acid, especially in patients with a history of blood clots. Patients with upper urinary tract bleeding are at risk of ureteral obstruction due to clot formation after receiving injected tranexamic acid. The use of tranexamic acid injections must be under the strict observation and supervision of a physician experienced in treating coagulation disorders, including disseminated intravascular coagulation (DIC).

Hyperplasia (increased cell production) of the biliary tract (the path by which bile is secreted by the liver) and cancers of the intrahepatic biliary system (cholangioma

and adenocarcinoma) have been reported in animal studies of tranexamic acid administration, but long-term dietary administration of tranexamic acid has failed to cause hyperplasia or neoplastic changes in the liver during or after treatment. No associations have been investigated between tranexamic acid administration and cancers in humans.

Pregnant or breastfeeding

Tranexamic acid is in the FDA pregnancy category B, meaning that no impaired fertility or adverse effects to the fetus have been reported in reproductive studies conducted in animals. Although no well-controlled studies have been conducted with pregnant women, it is known that tranexamic acid passes the placenta and appears in cord blood in concentrations equal to maternal concentration. Tranexamic acid passes into breast milk and should only be used by pregnant or breastfeeding women if benefits clearly outweigh risks to the fetus or infant.

Side effects

Nausea, vomiting, and diarrhea may occur with the use of oral or injectable tranexamic acid and may diminish with dose reduction. Tranexamic acid may also cause dizziness, which can influence a patient's ability to drive or operate machinery. Giddiness and low blood pressure (hypotension) have been reported; hypotension may occur if the intravenous injection is done rapidly. Convulsions have been reported in patients receiving tranexamic acid for cardiovascular surgery, or when tranexamic acid has inadvertently been injected into the neuraxial system.

The most serious adverse reactions associated with tranexamic acid include thromboembolic events such as deep vein thrombosis, pulmonary embolism, and cerebral thrombosis.

Retinal degeneration has occurred in animal studies conducted in cats, dogs, and rats receiving oral or injectable tranexamic acid. However, in clinical trials, no retinal changes have been noted in patients treated with tranexamic acid for weeks or months. Poorly characterized visual disturbances, such as the obstruction of retinal arteries or veins, have been reported in isolated studies. Patients receiving tranexamic acid for a period of weeks or months are advised to undergo ophthalmological examinations for visual acuity and color vision.

Other conditions and allergies

The only allergic reaction that has been reported with the use of tranexamic acid is allergic dermatitis.

Interactions

Before receiving tranexamic acid either orally or by injection, the doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

Interactions between tranexamic acid and other drugs have not been studied and remain unknown. However, patients receiving tranexamic acid should not be receiving any other coagulation medications at the same time.

Resources

BOOKS

American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda, MD: ASHP, 2015.

PERIODICALS

Bouet, P. E., et al. "High-dose Tranexamic Acid for Treating Postpartum Haemorrhage after Vaginal Delivery." *British Journal of Anesthesia* 114, no. 2 (2015): 339–41.

Falana, O., and G. Patel. "Efficacy and Safety of Tranexamic Acid versus Epsilon-Aminocaproic Acid in Cardiovascular Surgery." *Annals of Pharmacotherapy* 48, no. 12 (2014): 1563–69.

Roberts, I., et al. "The CRASH-2 Trial: A Randomised Controlled Trial and Economic Evaluation of the Effects of Tranexamic Acid on Death, Vascular Occlusive Events and Transfusion Requirement in Bleeding Trauma Patients." *Health Technology Assessment* 17, no. 10 (2013): 1–79.

WEBSITES

AHFS Consumer Medication Information. "Tranexamic Acid." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a612021.html> (accessed March 2, 2015).

PubMed Health. "Tranexamic Acid." U.S. National Library of Medicine, National Institutes of Health. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0001840/> (accessed March 2, 2015).

ORGANIZATIONS

American Society for Clinical Pharmacology and Therapeutics, 528 N. Washington Street, Alexandria, VA 22314, (703) 836-6981, info@ascpt.org, <http://www.ascpt.org/>.

L. Lee Culvert

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Trazodone

Definition

Trazodone is an oral antidepressant.

Purpose

Trazodone is used to treat depression and to treat the combination of symptoms of anxiety and depression.

Off-label use

Like most antidepressants, trazodone has also been used in limited numbers of patients to treat panic disorder, obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), enuresis (bed-wetting), eating disorders such as bulimia nervosa, cocaine dependency, and the depressive phase of bipolar disorder, but it should be noted that trazodone is not approved by the U.S. Food and Drug Administration (FDA) for these uses.

Description

Trazodone acts to change the balance of naturally occurring chemicals in the brain that regulate the transmission of nerve impulses between cells. Its action primarily increases the concentration of norepinephrine and serotonin (both chemicals that stimulate nerve cells) and, to a lesser extent, blocks the action of another brain

chemical, acetylcholine. Trazodone is classified as an atypical antidepressant, but it shares many of the properties of tricyclic antidepressants (amitriptyline, clomipramine, **desipramine**, **doxepin**, **imipramine**, nortriptyline, protriptyline, and trimipramine). It also shares some of the properties of selective serotonin reuptake inhibitor (SSRI) antidepressants (such as **fluoxetine**, **paroxetine**, and **sertraline**).

The therapeutic effects of trazodone, like other antidepressants, appear slowly. Maximum benefit is often not evident for at least two weeks after starting the drug. People taking trazodone should be aware of this and continue taking the drug as directed even if they do not see immediate improvement.

U.S. brand names

Trazodone is sold in the United States under the brand name Desyrel and is also available under its generic name.

Recommended dosage

As with any antidepressant, the dosage of trazodone must be carefully adjusted to produce the desired therapeutic effect. Trazodone is available as 50-, 100-, and 150-milligram film-coated tablets that cannot be divided, as well as in 150 mg and 300 mg oral tablets that can be split. Therapy is usually started at a total of 150 mg per day divided into two or three doses. This dose is increased by 50 mg every three or four days until the desired effects are seen. Daily doses may be increased to a maximum of 400 mg per day, or sometimes up to 600 mg per day in hospitalized patients. In cases of extreme depression, daily doses of up to 800 mg have been used in hospitalized patients. To minimize daytime drowsiness, a major portion of the daily dose can be given at bedtime.

Precautions

Children and adults up to age 24 are at increased risk of developing suicidal thoughts and actions when taking antidepressant drugs, including trazodone. Patients of any age taking an antidepressant medication should be monitored for signs of worsening depression or changes in behavior. Trazodone is not approved for use in children younger than 18.

Trazodone may increase heart rate and stress on the heart. Trazodone is associated with an increased risk of death in patients with heart disease. Trazodone is also associated with an increased risk of bleeding, especially internal bleeding within the gastrointestinal tract.

The most common problem with trazodone is sedation (drowsiness and lack of mental and physical alertness). This side effect is especially noticeable early



Trazodone hydrochloride, 150 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Acetylcholine—A naturally occurring chemical in the body that generally produces effects that are the opposite of those produced by dopamine and norepinephrine. Central nervous system well-being is dependent on a balance between acetylcholine, serotonin, dopamine, and norepinephrine.

Anticholinergic—Related to the ability of a drug to block the nervous system chemical acetylcholine. When acetylcholine is blocked, patients often experience dry mouth and skin, increased heart rate, blurred vision, and difficulty urinating. In severe cases, blocking acetylcholine may cloud thinking and cause delirium.

Anxiety—A psychological state characterized by strong feelings of worry, nervousness, apprehension, or agitation; may also be accompanied by physical symptoms, including sweating, tension, and increased pulse.

Depression—A mental state characterized by excessive sadness and loss of interest in life; other symptoms may include altered sleep or eating patterns, loss of concentration, agitation, lack of energy, and, in severe cases, attempts at self-harm or suicide.

Norepinephrine—A neurotransmitter in the brain that acts to constrict blood vessels and raise blood pressure. It works in combination with serotonin.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to prescribe these drugs, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Selective serotonin reuptake inhibitors (SSRIs)—A class of antidepressants that works by blocking the reabsorption of serotonin in brain cells, raising the level of the chemical in the brain.

Serotonin—A widely distributed neurotransmitter that is found in blood platelets, the lining of the digestive tract, and the brain, and that works in combination with norepinephrine. It causes very powerful contractions of smooth muscle, and is associated with mood, attention, emotions, and sleep. Low levels of serotonin are associated with depression.

Tricyclic antidepressants—An older group of antidepressant drugs.

in therapy. In most patients, sedation decreases or disappears entirely with time, but until then patients taking trazodone should not perform hazardous activities requiring mental alertness or coordination, including driving or operating machinery. The sedative effect is increased when trazodone is taken with other central nervous system depressants, such as alcoholic beverages, sleeping medications, other sedatives, or antihistamines. It may be dangerous to take trazodone in combination with these substances.

Other conditions and allergies

In rare cases where patients with cardiovascular disease must take trazodone, they should be monitored closely for cardiac rhythm disturbances and signs of cardiac stress or damage.

Although lower in anticholinergic side effects than the tricyclic antidepressants, trazodone should be used cautiously and with close physician supervision in people, especially the elderly, who have benign prostatic hypertrophy, urinary retention, and glaucoma, especially angle-closure glaucoma (the most severe form). Before starting treatment, people with these conditions should

discuss the relative risks and benefits of treatment with their doctors to help determine if trazodone is the right medication for them.

Side effects

Trazodone shares side effects common to many antidepressants. The most frequent of these are dry mouth, constipation, and urinary retention, though these are less common than with tricyclic antidepressants. Increased heart rate, sedation, irritability, dizziness, and decreased coordination can also occur. As with most side effects associated with antidepressants, the intensity is highest at the beginning of therapy and tends to decrease with continued use.

Dry mouth, if severe to the point of causing difficulty in speaking or swallowing, may be managed by dosage reduction or temporary discontinuation of the drug. Patients may also chew sugarless gum or suck on sugarless candy in order to increase the flow of saliva. Some artificial saliva products may give temporary relief.

Men with prostate enlargement who take trazodone may be especially likely to have problems with urinary

retention. Symptoms include having difficulty starting a urine flow and more difficulty than usual passing urine. In most cases, urinary retention is managed with dose reduction or by switching to another type of antidepressant. In extreme cases, patients may require treatment with bethanechol, a drug that reverses this particular side effect. In rare cases, trazodone has also been known to cause priapism, a prolonged and painful penile erection. People who think they may be experiencing any side effects from this or any other medication should tell their physicians.

Interactions

Trazodone may interact with other drugs, including over-the-counter drugs and supplements. Individuals should inform their healthcare provider of all drugs they are currently taking to avoid the risk of interactions.

Drugs

Because both trazodone and members of the class of antidepressants known as monoamine oxidase inhibitors (MAOIs) may increase serotonin levels in the brain, the combination of these drugs can lead to a serious condition known as serotonin syndrome. Symptoms of serotonin syndrome include a prolonged rapid heart rate, hypertension (high blood pressure), flushing of the skin, hallucinations, tremors, and hyperthermia (increased body temperature). It is dangerous to take trazodone in combination with MAOIs, such as phenelzine (Nardil) or tranylcypromine (Parnate). The same holds true when combining trazodone with an SSRI antidepressant, such as fluoxetine (Prozac), paroxetine, or sertraline. Individuals taking an MAOI should stop the drug and wait at least two weeks before starting therapy with trazodone (and vice versa).

Trazodone may increase the blood pressure-lowering effects in patients who are taking antihypertensive medications. Patients who take these drugs together should have their blood pressure monitored regularly so that their antihypertensive medications can be adjusted if their blood pressure becomes too low.

The sedative effects of trazodone are increased by medications used for other mental disorders such as schizophrenia. The anticholinergic effects of trazodone may be additive with other anticholinergic drugs such as **benztropine**, biperiden, trihexyphenidyl, and antihistamines.

Food and other substances

Individuals taking trazodone should avoid alcohol.

Resources

BOOKS

American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda, MD: American Society of Health-System Pharmacists, 2015.

PERIODICALS

Di Leone, F. G., D. Talevi, and C. Lorio. "Effects of Trazodone on Night Eating Behavior: A Case Report." *Journal of Clinical Psychopharmacology* 35, no. 1 (2015): 109–11.

WEBSITES

AHFS Consumer Medication Information. "Trazodone." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a681038.html> (accessed February 27, 2015).

Micromedex. "Trazodone (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/trazodone-oral-route/before-using/drg-20061280> (accessed February 27, 2015).

Physicians' Desk Reference. "Trazodone." PDR Health. <http://www.pdrhealth.com/drugs/trazodone> (accessed February 27, 2015).

ORGANIZATIONS

National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Revised by Ruth A. Wienclaw, PhD

REVIEWED BY KEVIN GLAZA, RPH

Treanda see **Bendamustine**

Tretinoin (topical)

Definition

Tretinoin is a topical medication derived from retinoic acid. Also known as all-trans retinoic acid (ATRA), it is the carboxylic acid form of vitamin A and is in the drug class known as retinoids.

Purpose

Tretinoin is used primarily as a topical agent for treating skin conditions such as acne vulgaris and keratosis pilaris. Tretinoin is also prescribed for



Retin-A Micro (tretinoin) gel. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

smoothing rough and/or wrinkled skin and helping to lighten dark spots on the skin.

Tretinoin, as all-trans retinoic acid (ATRA), is also an anti-cancer or antineoplastic drug sold under the brand name Vesanoid. It is formulated as a solution or an oral capsule. This type of tretinoin treatment is not discussed in this entry.

Off-label uses

Tretinoin is sometimes used to treat other skin conditions aside from acne. Keratosis follicularis, a skin disorder characterized by small, red bumps, is often treated with tretinoin. Flat warts called verruca plana are also treated with tretinoin cream or gel. In addition, topical tretinoin has been used experimentally to reduce scarring and to treat aging skin.

Description

Topical tretinoin is used for treating various skin problems, primarily mild to moderate acne. Tretinoin creams and gels are applied directly to the affected areas. The drug works by clearing old skin cells from the pores of the skin, which essentially replaces older skin cells with newer skin cells. Tretinoin first irritates the skin, which slows down the process by which the body normally removes skin cells that have been damaged by sun exposure. It then accelerates the growth of new skin

cells. In treating acne, this mechanism of rapid skin cell growth prevents pimples from forming.

The same approach works well to reduce areas of hyperpigmentation (darkened patches of skin) and sun-damaged skin that may be rough or wrinkled. Tretinoin is not intended to treat normal aging of the skin and deep wrinkles will not respond to treatment. Pharmaceutical manufacturers emphasize the importance of using tretinoin in conjunction with a skin-care program that protects the treated skin from more sun damage.

Acne treatment may require several months to effectively clear the skin. Manufacturers claim that dark spots will begin to fade after six to eight weeks of treatment, while wrinkles may require treatment for several months before results are seen. Only a minimal amount of the topical preparation is absorbed into the body.

The application of tretinoin to the skin has the potential for skin irritation. Various newer formulations of tretinoin, such as hydrogels, micronized tretinoin, and propolymers, control the release of tretinoin and may minimize irritation while still providing effective acne treatment.

Tretinoin is available in varying strengths as a cream, gel, or liquid. Gels are prepared in concentrations of 0.01% and 0.025%. Creams are prepared in concentrations of 0.025%, 0.05%, and 0.1%. The liquid form of topical tretinoin is prepared as a 0.05% solution.

U.S. brand names

Topical tretinoin is sold in the United States under the brand name Retin-A.

Canadian brand names

Topical tretinoin is sold in Canada under the brand names Rejuva-A, Retin-A, and Stieva-A.

International brand names

Topical tretinoin is sold internationally under a variety of brand names, the most common being Retin-A.

Origins

Tretinoin was approved for topical use by the FDA in 1971 and has remained the standard treatment for acne.

Recommended dosage

Tretinoin preparations are applied topically to the affected areas of the skin. The physician will determine the appropriate strength for the skin condition being treated and will suggest specific application techniques and frequency of use.

Tretinoin is also available as a 10 mg capsule for oral administration and is used as a chemotherapeutic agent. The oral tretinoin is not used for treating acne or other skin conditions and is not discussed in this article.

Precautions

The topical application of tretinoin may increase sun sensitivity (photosensitivity) in some patients and they may experience sunburn more easily. To reduce the risk of severe sunburn, patients are cautioned to avoid exposing treated areas of the skin to sunlight or ultraviolet lamps. Patients should also inform their physician if they have any unusual reactions to other skin medications or medicines, or any known allergies.

The use of tretinoin for treating acne may cause an initial flare-up of the acne. Patients should be aware of this and inform their physician if the eruption of acne is severe. Otherwise, such flare-ups will subside as the drug begins to work.

Pediatric

Topical tretinoin has only been tested in adults. However, children are not expected to have sun reactions when using this drug, and side effects for older children being treated for acne would be similar to those experienced by adults.

Pregnant or breastfeeding

Topical tretinoin is in the FDA pregnancy category C, meaning that risk to the fetus cannot be ruled out. The effects of topical tretinoin on fetal development have not been investigated. Although only a small amount of topical tretinoin is absorbed into the body, the drug may be hazardous to the fetus. Women should inform their physician if they are planning to become pregnant or are currently pregnant or breastfeeding. Pregnant and breastfeeding women may be advised not to use tretinoin as a topical agent or may use a weaker concentration of the drug. Pregnant or breastfeeding women should not take the oral form of tretinoin.

Side effects

Most side effects of tretinoin are reversible and will disappear after treatment. The most common side effect of tretinoin is local inflammation (inflammation at the site where it is applied). However, this inflammation is predictable because it is actually part of the mechanism by which the drug replaces old skin with new skin cells. The inflammation phase of treatment is usually temporary and disappears entirely when the treatment is discontinued. Patients may also experience mild stinging,

KEY TERMS

Hyperpigmentation—A common, usually harmless condition in which patches of the skin become darker in color. This can be associated with aging and/or deposits of excess melanin, the brown pigment that gives skin its color; “liver spots” as a result of sun exposure, typically appearing on the face or hands, are a common form of hyperpigmentation.

Photosensitivity—An abnormally high sensitivity to sunlight involving immune system activity and manifesting as a skin (cutaneous) reaction that is sometimes described as a sun allergy. Photosensitivity increases the risk of serious sunburn. Certain disease conditions (e.g., systemic lupus erythematosus) and taking certain drugs may cause photosensitivity.

Vesicles—Small, fluid-filled sacs that may develop on the skin or internally.

redness, warmth of the skin, or dryness in the area where tretinoin is applied. Systemic effects from the use of topical tretinoin do not commonly occur.

Tretinoin may occasionally cause severe redness and the development of small, fluid-filled sacs (vesicles) or crusting of the skin surface. If such effects occur, tretinoin cream or gel should not be reapplied and the physician should be notified immediately.

Interactions

The doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

Certain drugs taken orally may increase a patient's sensitivity to sunlight (photosensitivity) and the skin may burn more easily. Phototoxic drugs include antibiotics, antihistamines, antimalarial medications, and certain chemotherapeutic drugs. These drugs include, among others:

- aminocaproic acid
- aprotinin
- chloroquine

- chlortetracycline
- dacarbazine
- demeclocycline
- diphenhydramine
- **doxycycline**
- **hydroxychloroquine**
- lymecycline
- meclocycline
- methacycline
- **methotrexate**
- **minocycline**
- oxytetracycline
- rolitetracycline
- sulfonamides
- **tetracycline**
- **tranexamic acid**
- quinine
- quinolones
- vinblastine

Since tretinoin also increases sun sensitivity in some people, using these drugs may increase or compound the effects of tretinoin and could result in severe sunburn. Certain diabetes drugs such as chlorpropamide and **glyburide**, and nonsteroidal anti-inflammatory drugs such as naproxen or piroxicam, may also be phototoxic. To avoid drug reactions, patients should inform their doctor of any medications being taken at the time tretinoin is being applied to the skin.

Resources

BOOKS

American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda, MD: ASHP, 2015.

PERIODICALS

Baldwin, H. E., et al. "40 Years of Topical Tretinoin Use in Review." *Journal of Drugs in Dermatology* 12, no. 6 (2013): 638–642.

Kircik, L. H. "Evaluating Tretinoin Formulations in the Treatment of Acne." *Journal of Drugs in Dermatology* 13, no. 4 (2014): 466–470.

Malone, V., et al. "Fibroelastolytic Papulosis of the Neck Treated with Topical Tretinoin." *Journal of Dermatology* 41, no. 8 (2014): 758–759.

WEBSITES

MedlinePlus. "Tretinoin Topical." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682437.html> (accessed March 2, 2015).

"Tretinoin Topical." Drugs.com. <http://www.drugs.com/mtm/tretinoin-topical.html> (accessed March 2, 2015).

ORGANIZATIONS

American Society for Clinical Pharmacology and Therapeutics, 528 N Washington Street, Alexandria, VA 22314, (703) 836-6981, info@ascpt.org, <http://www.ascpt.org/>.

L. Lee Culvert

REVIEWED BY JAMES E. WAUN, MD, RPh

Trexail see **Methotrexate**

Triamcinolone

Definition

Triamcinolone acetonide is a type of corticosteroid, which is a type of drug made in a laboratory to closely match a natural hormone produced in the body. Triamcinolone acetonide helps relieve itching and other symptoms of allergic reactions.

Purpose

When a person comes in contact with an allergen, or allergic trigger, the body releases chemicals and the immune system, which normally fights infection, reacts as if the allergen is a threat to the person's health. As a result of the immune system reaction, tender areas of skin or mucous membranes that line the eyes, nose, mouth,



Nasacort Allergy (triamcinolone acetonide). (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

KEY TERMS

Corticosteroid—Also called steroids, these man-made versions of naturally occurring hormones help reduce inflammation in the body. They are not the same as the steroids that are related to male hormones and used by some athletes.

Eczema—Also called atopic dermatitis, eczema is an itchy, red rash that can appear on the body and usually is diagnosed when the person is an infant or young child. Eczema can cause intense itching and discomfort.

Immune system—A system of cells, organs, and tissues throughout the body that help protect the body from infection and maintain health.

Topical—Refers to medicines that are applied to the skin. The medicines are usually contained within lotions, gels, creams, or ointments.

and other areas of the body can become swollen, itchy and irritated. Corticosteroids such as triamcinolone can help ease the swelling, or inflammation, and help calm the immune system.

Description

Triamcinolone comes in a nasal or topical form. The nasal spray is used by individuals with hay fever or other allergies to help ease itching of the nose area, along with a running and stuffy nose and sneezing. The nasal spray comes in a small bottle with an applicator that can be placed just inside the nose to apply sprays of the medicine as directed.

The topical form of triamcinolone comes in a tube filled with a cream or ointment to spread on skin that is itchy, red, dry, swollen, or crusty. Usually, these conditions are caused by allergic reactions, or by skin conditions such as eczema or psoriasis. A special type of the topical form of triamcinolone also may be used to help ease discomfort from sores in the mouth.

U.S. brand names

In the United States, triamcinolone nasal is sold under the brand name of Nasacort. The medicine, which also comes in a spray that lasts for 24 hours, is available without a prescription and in a generic form.

The topical form of triamcinolone is available in the United States under several brand names, including:

- Aristocort
- Kenalog
- Triacet
- Triderm

Recommended dosage

Triamcinolone nasal spray for allergies can be used by adults once a day. Usually, healthcare providers recommend that adults begin treatment with two sprays in each nostril, and reduce the dosage to one spray per nostril once symptoms improve. Children age 6 to 12 should begin treatment with one spray per nostril once a day, and increase to two sprays per nostril once a day only if symptoms have not improved. After allergy symptoms improve, children can reduce dosage to one spray per nostril each day. Children age two to six years old can use one spray per nostril each day only. Adults should supervise the use of nasal triamcinolone in children.

For treating itching and rashes associated with eczema or allergic reactions, healthcare providers usually recommend that adults and children apply a thin layer of topical triamcinolone to the affected area of the skin two to three times a day as needed.

Precautions

It is important to follow directions contained in nasal spray packages to make sure that the sprayer is properly primed, or prepared, before the first use. These directions also explain how to use the sprayer correctly so that triamcinolone works as it should. The sprayer should never be used in the mouth or pointed toward the eyes. The nasal applicator should be wiped clean with a tissue after each use and should never be shared.

Topical triamcinolone can cause toxicity if used over large areas of the body. If a rash is infected, it should be treated with medicines such as antifungals or antivirals.

Pediatric

The safety of triamcinolone nasal spray has not been established in children younger than age two years. It is possible that use of triamcinolone can slow growth rate in some children.

Children are especially vulnerable to the toxic effects of topical triamcinolone. Healthcare providers and parents should spread the medication over the smallest area necessary to improve symptoms.

Geriatric

Healthcare providers usually recommend starting older patients at the lowest dose of nasal triamcinolone possible.

Pregnant or breastfeeding

Triamcinolone is a pregnancy category C drug. It has not been tested for safety or effectiveness in pregnant women and their unborn children. It is not known whether the medicine is passed from a mother to her

infant through breast milk, but tests have shown that some corticosteroids do appear in breast milk. A woman who wants to breastfeed her infant should use caution if on topical or nasal triamcinolone and should discuss its use with her healthcare provider before nursing.

Side effects

Triamcinolone nasal spray can cause some side effects, especially:

- sore throat
- headache
- increasing cough

Some side effects can be more severe and should be reported to a healthcare provider immediately, including:

- fever, sore throat, or other signs of a possible infection
- problems with vision
- frequent or severe nosebleeds

The topical form of triamcinolone also can cause side effects, including:

- changes in skin color
- acne
- burning or itching skin
- drying, blistering, and cracking of skin
- lightening of skin

More severe side effects can occur and should be reported to the healthcare provider immediately. These include:

- wheezing and breathing problems
- severe skin rash
- infection of the skin with redness, swelling, and evidence of pus

Other conditions and allergies

Individuals who have recently had injuries to the nose, nose surgery, or who have an eye infection should talk to their healthcare provider before using nasal triamcinolone.

Interactions

When using triamcinolone, it is important to tell the treating physician about all medications, herbal remedies, and supplements being taken.

Drugs

It is especially important to inform the healthcare provider about any other topical medications or chemotherapy agents being used before applying triamcinolone.

Drugs that affect the immune system can increase side effects or alter how triamcinolone works.

Resources

PERIODICALS

Kelley, Kristin J. "OTC Nasacort Approved." *NEJM Journal Watch* (2013).

Tollefson, Meghan M., and Anna L. Bruckner. "Atopic Dermatitis: Skin-directed Management." *Pediatrics* 134, no. 6 (2014): e1735–e1744.

WEBSITES

Chattem, Inc. "Nasacort Allergy 24 Hour" Nasacort.com. <https://www.nasacort.com/> (accessed February 28, 2015).

MedlinePlus. "Triamcinolone Nasal Spray." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601124.html> (accessed February 28, 2015).

MedlinePlus. "Triamcinolone Topical." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601124.html> (accessed February 28, 2015).

"Nasacort AQ." Rxlist.com. <http://www.rxlist.com/nasacort-aq-drug.htm> (accessed February 28, 2015).

"Triamcinolone Aerosol Solution." Drugs.com. <http://www.drugs.com/cdi/triamcinolone-aerosol-solution.html> (accessed February 28, 2015).

"Triamcinolone Cream." Rxlist.com. <http://www.rxlist.com/triamcinolone-cream-drug.htm> (accessed February 28, 2015).

ORGANIZATIONS

American Academy of Allergy, Asthma & Immunology, 555 E. Wells Street, Suite 1100, Milwaukee, WI 53202-3823, (414) 272-6071, <http://www.aaaai.org/home.aspx>.

American Academy of Dermatology, PO Box 40414, Schaumburg, IL 60168, Fax: (847) 240-1859, (866) 503-7546, <https://www.aad.org/for-the-public>.

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Triazolam

Definition

Triazolam is a hypnotic drug. It is a member of the benzodiazepine family of drugs.

Purpose

Triazolam is used for the short-term (generally seven to ten days) treatment of insomnia. Continued usage for



Triazolam, 0.25 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

more than two to three weeks requires a complete re-evaluation of the person receiving the drug.

Description

Triazolam increases the speed with which people achieve sleep, increases the duration of sleep, and decreases the likelihood of being awakened during sleep. The effect of triazolam decreases after 14 days of continuous use. If it is used for this long, sleep patterns frequently return to those experienced prior to beginning use of triazolam and are sometimes worse. This effect is called rebound insomnia.

U.S. brand name

In the United States, triazolam is sold under the brand name Halcion as well as under its generic name.

Recommended dosage

The recommended dose of triazolam is 0.25 mg before going to bed. People with smaller body masses and older individuals can receive a comparable effect with 0.125 mg of triazolam. The lowest effective dosage of the drug should be used to minimize adverse reactions.

Precautions

Because of problems with rebound insomnia, patients should not take triazolam for more than seven consecutive days. Daytime anxiety may occur after as

KEY TERMS

Benzodiazepines—A group of central nervous system depressants used to relieve anxiety or to induce sleep.

Hypnotic—A medication that causes sleep.

Insomnia—A chronic inability to sleep or to remain asleep throughout the night.

few as ten days of continuous usage. If this occurs, triazolam use should be discontinued.

People using triazolam should exercise caution when driving or using power tools or machinery, due to the drug's sedative effects. People who use triazolam to reduce jet lag on long flights should be aware of a condition sometimes called "traveler's amnesia." This is a condition in which the traveler completes the flight and carries on with normal activities, including driving, but never fully awakens and has no memory of these activities. The period of amnesia may last for a few minutes or a few hours. Traveler's amnesia is most common when the traveler has had too little sleep or has been drinking alcohol.

Pregnant or nursing

Triazolam can cause serious birth defects. Women should not take this medicine if they are pregnant, think they may be pregnant, or are trying to get pregnant.

Side effects

Triazolam has relatively few side effects. Those that have been reported include drowsiness, headache, dizziness, nervousness, a feeling of being light-headed, problems with coordination, nausea, and vomiting.

Less frequent side effects include euphoria, tachycardia, fatigue, confusion, impaired memory, muscle cramping, pain, and depression.

Interactions

Individuals should inform their healthcare provider of all drugs they are taking, including over-the-counter drugs or supplements, before taking triazolam.

Drugs

Triazolam increases the effect of drugs and substances that depress the central nervous system. This class of drugs includes anesthetics, narcotics, sedatives and other sleeping pills, and atropine.

Some drugs increase the effects of triazolam and may also increase the chances of having side effects. These include cimetidine, isoniazid, and **oral contraceptives**.

Food and other substances

Alcohol and grapefruit juice both enhance the effects of triazolam and should be avoided.

Resources

BOOKS

Adams, Michael, and Norman Holland. *Core Concepts in Pharmacology*. 3rd ed. Upper Saddle River, NJ: 2010.

Page, Clive P., et al. *Integrated Pharmacology*. 3rd ed. St. Louis, MO: Elsevier, 2006.

PERIODICALS

Kleykamp, B. A., R. R. Griffiths, and M. Z. Mintzer. "Dose Effects of Triazolam and Alcohol on Cognitive Performance in Healthy Volunteers." *Experimental and Clinical Psychopharmacology* 18, no. 1 (2010): 1–16.

Miyata, A., et al. "The Effects of Acute Treatment with Ramelteon, Triazolam, and Placebo on Driving Performance, Cognitive Function, and Equilibrium Function in Healthy Volunteers." *Psychopharmacology* (December 24, 2014): e-pub ahead of print. <http://dx.doi.org/10.1007/s00213-014-3843-4> (accessed February 27, 2015).

OTHER

U.S. Food and Drug Administration. "Medication Guide: Halcion Tablets." <http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088610.pdf> (accessed February 27, 2015).

WEBSITES

Healthwise. "Triazolam." University of Michigan Health System. <http://www.uofmhealth.org/health-library/d00397a1> (accessed February 27, 2015).

Micromedex. "Triazolam (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/triazolam-oral-route/description/drg-20072203> (accessed February 27, 2015).

National Alliance on Mental Illness. "Insomnia." http://www2.nami.org/Template.cfm?Section=By_Illness&Template=/ContentManagement/ContentDisplay.cfm&ContentID=145368 (accessed February 27, 2015).

National Sleep Foundation. "Compare Different Sleep Aids." <http://sleepfoundation.org/sleep-news/compare-different-sleep-aids> (accessed February 27, 2015).

Physicians' Desk Reference. "Halcion." PDR Health. <http://www.pdrhealth.com/drugs/halcion> (accessed February 27, 2015).

ORGANIZATIONS

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.

National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.

National Sleep Foundation, 1010 N. Glebe Road, Suite 310, Arlington, VA 20221, (703) 243-1697, nsf@sleepfoundation.org, <http://sleepfoundation.org/>.

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Revised by Ruth A. Wienclaw, PhD

REVIEWED BY JAMES E. WAUN, MD, RPH

Tricor see **Fenofibrate**

Trileptal see **Oxcarbazepine**

Trimethoprim/sulfamethoxazole see
Sulfamethoxazole/trimethoprim

Tylenol with codeine see **Acetaminophen/
codeine**



Ultracet see **Tramadol/acetaminophen**

Ultram see **Tramadol**

Ursodiol

Definition

Ursodiol, also known as ursodeoxycholic acid, is an oral drug used to treat cholesterol gallstones, as well as certain other conditions. It is in the drug classes known as gallstone dissolution or solubilizing agents and choleretic agents (drugs that stimulate the liver to release more bile).

Purpose

Ursodiol is approved by the U.S. Food and Drug Administration (FDA) for dissolving gallbladder stones of less than 20 mm (0.8 in.) in diameter in patients who are not candidates for gallstone-removal surgery because of risk or who refuse surgery. It is also approved to prevent gallstone formation in obese patients undergoing very rapid weight loss due to low-calorie diets or bariatric surgery. Gallstones are hard deposits that form in the gallbladder. They can vary in size from a grain of sand to golf ball. Most common gallstones are made of cholesterol, although their formation is not related to the level of cholesterol in the blood. Pigment stones are gallstones made of bilirubin, which cannot be treated with ursodiol. Gallstones are more common in women, Native Americans, Hispanics, and people who are over age 40 or overweight. Gallstones may run in families.

As of early 2015, ursodiol was also the only drug approved by the FDA for the treatment of primary biliary cirrhosis (PBC), a chronic disease characterized by inflammation of the small bile ducts in the liver. Ursodiol is often the first treatment used for PBC, in which

inflammation damages and eventually destroys the ducts. Bile, which consists of bile acids, cholesterol, fats, and fluid, is made in the liver. The bile ducts carry bile from liver cells to the gallbladder for storage and to the small intestine for digestion. When food enters the stomach, the gallbladder contracts, and bile ducts carry bile to the duodenum—the start of the small intestine. Bile helps with the absorption of fats, cholesterol, and fat-soluble vitamins. It also moves cholesterol, toxins, and waste products from the liver to the intestines for removal from the body. When bile ducts are blocked or missing, bile and toxic wastes build up and damage the liver. This can lead to cirrhosis, in which the liver slowly deteriorates and is unable to function properly. Healthy liver tissue is replaced with scar tissue, which further blocks the flow of bile. Ursodiol is a nontoxic bile acid that can replace the blocked bile acids and reduce high levels of bilirubin and liver enzymes in the blood serum. It does not cure PBC, but early treatment reduces the need for an eventual liver transplant and increases survival. Ursodiol treatment later in the disease can slow the progression of liver damage. Studies have found that 13–15 milligrams (mg) of ursodiol per kilogram (kg) of body weight, taken daily for up to four years, improves blood tests for liver function and delays the need for liver transplantation. In some patients, ursodiol appears to bring about PBC remission.

Ursodiol is commonly used to treat other liver conditions involving the blockage or loss of bile ducts, including:

- for sclerosing cholangitis—inflammation, swelling, scarring, and destruction of bile ducts inside and outside the liver
- to correct nutritional deficiencies and promote growth and development of infants and children with Alagille syndrome, a genetic condition characterized by a lack of small bile ducts inside the liver
- to relieve severe skin itching, help correct liver function, and possibly help prevent stillbirth from



Ursodiol, 300 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

intrahepatic cholestasis of pregnancy, a pregnancy-related liver disorder that impedes the flow of bile, causing bile acid to build up in the blood

- to reduce high liver enzymes in some patients with non-alcoholic fatty liver disease—a range of disorders associated with excess fat in the liver
- as an orphan drug for treating cystic fibrosis liver disease

Description

Ursodiol is a nontoxic bile acid that is milder than bile acids normally produced by the body. It is taken up rapidly by the liver and excreted in the bile. Ursodiol that is not absorbed passes into the colon and is excreted in the feces. Ursodiol decreases the production and secretion of cholesterol by the liver, reduces reabsorption of cholesterol by the intestines, and dissolves cholesterol in the bile to prevent it from forming gallstones. Ursodiol can also dissolve small cholesterol stones. The initial gallstone response usually occurs within three to six months, but it may take up to two years or longer of ursodiol treatment, and the gallstones may not dissolve completely or may return within five years after successful treatment. If ultrasound shows that the gallstones have dissolved, the therapy is continued, and gallstone dissolution is confirmed by ultrasound in another 1–3 months. If partial dissolution is not seen after the first 12 months, the treatment is unlikely to succeed. Rarely, a device called a lithotripter that generates shockwaves is used to crush a gallstone into

smaller pieces that are more readily dissolved by ursodiol.

U.S. brand names

U.S. brand names for ursodiol are:

- Actigall
- Urso 250
- Urso Forte

Canadian brand names

Canadian brand names are Urso DS and PMS-Ursodiol C.

International brand names

Generic ursodiol is available internationally as ursodiol or ursodeoxycholic acid. There are many international brand names, of which Ursofalk is the most common. Other more common brand names include:

- Destolit
- Udihep
- Urdox
- Ursa
- Ursacol
- Urso
- Ursobil
- Ursochol
- Ursolic
- Ursosan

Origins

Actigall 300 mg oral capsules were first approved by the FDA in 1987. Urso 250 (250 mg oral tablets) and Urso Forte (500 mg oral tablets) were approved in 1997. Generic ursodiol is available as 300 mg oral capsules and 250 mg and 500 mg oral tablets.

Recommended dosage

Ursodiol dosage is based on the medical condition and the response to treatment:

- gallstone dissolution: 8–10 mg per kilogram (kg, or 2.2 lb.) of body weight per day, divided into two or three doses 8 to 12 hours apart, with a maximum of 300 mg per dose
- gallstone prevention: 300 mg twice a day
- PBC, 13–15 mg/kg/day, divided into two to four doses and taken with food

Doses should be taken at about the same time each day. A missed dose should be taken as soon as possible, but if it is almost time for the next dose, the missed dose

KEY TERMS

Alagille syndrome—An inherited condition in which the liver lacks small bile ducts.

Bile—Fluid secreted by the liver to the gallbladder and duodenum where it helps in the digestion and absorption of fats and removal of toxins and waste products.

Bile acids—Steroid acids, such as ursodiol, that are components of bile.

Biliary atresia—Absence or underdevelopment of bile ducts.

Bilirubin—A reddish-yellow pigment in bile and blood.

Cholestasis—Reduced or failed bile flow.

Cholesterol—A fat-soluble steroid alcohol (sterol) that is found in animal fats and oils and produced in the body from saturated fats and that can form gallstones.

Cirrhosis—Liver damage and destruction that can be caused by blocked bile ducts that allow the buildup of toxic waste.

Cystic fibrosis—An inherited disease that causes mucus accumulation in the airways and blocked bile ducts in the liver.

Gallbladder—The muscular sac that stores bile from the liver.

Gallstones—Hard deposits, usually of cholesterol, that form in the gallbladder or bile ducts.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Orphan drug—A drug for treating rare diseases.

Primary biliary cirrhosis (PBC)—A chronic liver disease characterized by inflammation of the small bile ducts in the liver.

Sclerosing cholangitis—Inflammation, swelling, scarring, and destruction of bile ducts inside and outside the liver.

Ursodeoxycholic acid—Ursodiol.

should be skipped and the regular schedule resumed. Scored 500 mg tablets can be broken in half for the recommended dose: the tablet is placed on a flat surface, with the scored side up, and the thumbs placed close to

the groove; gentle pressure is used to snap the segments apart. The segments should be swallowed with water and without chewing because they have a bitter taste. Segments should be stored separately from whole tablets.

Different brands and strengths of ursodiol have different storage requirements. In general, ursodiol should be stored in the tightly closed container it came in, at room temperature and away from light, excess heat, and moisture (not in the bathroom).

Pediatric

Ursodiol may be used off label (not FDA-approved) in children for certain conditions:

- biliary atresia (underdevelopment or absence of bile ducts): 10–15 mg/kg/day
- cholestasis (reduced or absent bile flow) in infants and children due to parenteral nutrition (nutrition other than through the intestines): 30 mg/kg/day in two or three divided doses
- prevention of cholestasis in newborns: 5 mg/kg/day in four divided doses on the third day of life with initiation of parenteral nutrition; increased to 10 mg/kg/day in four divided doses with initiation of enteral (via the intestines) feedings; increased to 20 mg/kg/day in four divided doses with full enteral feedings
- improving liver metabolism of essential fatty acids with cystic fibrosis: 30 mg/kg/day in two divided doses

Precautions

Some precautions while taking ursodiol include:

- Ursodiol should be used regularly to obtain the most benefit.
- Ursodiol should not be stopped or the dose or frequency increased without consulting the doctor, since this will not increase the benefits and may increase the risk of serious side effects.
- Blood tests for liver function and bilirubin levels and medical tests such as ultrasound will be performed periodically to monitor progress and check for side effects.
- Ursodiol may cause dizziness: patients should not drive, operate machinery, or perform activities that require alertness until they know how the drug affects them.

Pregnant or breastfeeding

Ursodiol is in the FDA pregnancy category B—it may be acceptable during pregnancy but should only be used if clearly needed. Women should contact their doctor if they become pregnant while taking ursodiol. It is not known whether ursodiol passes into breast milk, so caution is advised when breastfeeding.

Other conditions and allergies

Patients should tell their doctor and pharmacist if they are allergic to ursodiol, bile acids, or any other drugs or if they have other allergies. Patients should tell their doctor if they have or have ever had:

- gallbladder/bile duct problems, such as acute cholecystitis, cholangitis, biliary obstruction, gallstone pancreatitis, or biliary-gastrointestinal fistula
- liver disease, such as ascites, variceal bleeding, or hepatic encephalopathy
- pancreatic disease

Side effects

Ursodiol is usually well tolerated. Patients should consult their doctor promptly if any of the following side effects are severe, persistent, or worsening:

- upset stomach or indigestion
- nausea
- vomiting
- diarrhea
- constipation
- dizziness
- back pain
- hair loss
- cough
- sore throat
- runny nose
- muscle and joint pain

The doctor should be called immediately if any of the following rare but serious side effects occur:

- weakness
- swelling of the ankles or feet
- increased thirst or urination or pain on urination
- signs of infection such as fever or persistent sore throat
- easy bleeding or bruising
- cough with fever

Other conditions and allergies

Serious allergic reactions to ursodiol are rare. However, immediate medical attention should be sought for symptoms such as rash, itching or swelling (especially of the face, tongue, or throat), severe dizziness, or trouble breathing.

Interactions

It is very important that the doctor and pharmacist be informed of any and all prescription and nonprescription

medicines, vitamins, minerals, herbal products, and dietary supplements being used. Patients should not start or stop any medications or change dosages without first consulting their doctor or pharmacist. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Drugs

Drugs that may interact with ursodiol include:

- antacids containing aluminum (Amphojel, Gaviscon, Maalox, Mylanta, others)
- cholestyramine (LoCHOLEST, Prevalite, Questran)
- clofibrate (Atromid-S)
- colestipol (Colestid)
- other medications that lower lipid or cholesterol levels
- medications that contain estrogen, including birth control pills

Herbs and supplements

Some vitamins and herbal products may interact with ursodiol.

Food and other substances

Patients should limit their consumption of alcoholic beverages while taking ursodiol.

Resources

PERIODICALS

Lammert, Craig, et al. "Biochemical Response to Ursodeoxycholic Acid Predicts Survival in a North American Cohort of Primary Biliary Cirrhosis Patients." *Journal of Gastroenterology* 49, no. 10 (2014): 1414–20.

WEBSITES

MedlinePlus. "Gallstones." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/ency/article/000273.htm> (accessed February 28, 2015).

Medscape. "Ursodiol (Rx)—Actigall, Ursa Forte." <http://reference.medscape.com/drug/actigall-urso-forse-ursodiol-342072> (accessed February 28, 2015).

National Institute of Diabetes and Digestive and Kidney Diseases. "Gallstones." National Institutes of Health. <http://www.niddk.nih.gov/health-information/health-topics/digestive-diseases/gallstones/Pages/facts.aspx> (accessed February 28, 2015).

National Institute of Diabetes and Digestive and Kidney Diseases. "Primary Biliary Cirrhosis." National Institutes of Health. <http://www.niddk.nih.gov/health-information/health-topics/liver-disease>

/primary-biliary-cirrhosis/Pages/facts.aspx (accessed February 28, 2015).

“Ursodiol.” Drugs.com. <http://www.drugs.com/cdi/ursodiol.html> (accessed February 28, 2015).

ORGANIZATIONS

American College of Gastroenterology, 400 Goldsboro Road, Suite 200, Bethesda, MD 20817, (301) 263-9000, info@acg.gi.org, <http://gi.org/>.

National Institute of Diabetes and Digestive and Kidney Diseases, 9000 Rockville Pike, Bethesda, MD 20892-2560, (301) 496-3583, <http://www.niddk.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY KEVIN GLAZA, RPh



Vaccinations

Definition

Vaccination is the injection of a weakened or dead microbe in a person to stimulate the immune system against the microbe and prevent disease.

Purpose

Vaccines are available against more than 20 infectious diseases, such as influenza, pneumonia, whooping cough, rubella, meningitis, hepatitis B, and shingles.

Vaccines are medicines that contain weakened or dead bacteria or viruses. When individuals are given a vaccine, their immune system responds by producing proteins called antibodies. When these persons are later exposed to live bacteria or viruses of the same kind that were in the vaccine, the antibodies destroy those organisms and prevent them from making these persons sick. Vaccines usually stimulate the cellular immune system as well. In other words, vaccinated individuals become immune to the disease that the organisms normally cause. The process of building up immunity by being given a vaccine is called immunization.

Vaccines are used in several ways. Some, such as the rabies vaccine, are normally given only when people are likely to have been exposed to the virus that causes the disease—for example, through a dog bite. Others are given to travelers planning to visit countries where certain diseases, such as typhoid fever or yellow fever, are common. Vaccines such as the influenza vaccine, also called a flu shot, are especially recommended for specific groups of people who are at high risk of developing influenza or its complications, although everyone is encouraged to get vaccinated against influenza. There are also vaccines that are given to almost everyone, such as the ones that prevent diphtheria, tetanus, polio, and measles.

Children in developed countries are routinely given a series of vaccinations that begin at birth. Given according to a specific schedule, these vaccinations protect against hepatitis B, diphtheria, tetanus, whooping cough, measles, mumps, rubella (German measles), varicella (chickenpox), polio, pneumococcus, *Haemophilus influenzae* type b (Hib disease, a major cause of spinal meningitis) and, in some U.S. states, hepatitis A. This series of vaccinations is recommended by the American Academy of Family Physicians, the American Academy of Pediatrics, and the Centers for Disease Control and Prevention (CDC) and is required in all U.S. states before children can enter school. All states will make exceptions for children who have medical conditions, such as cancer, that prevent them from having vaccinations, and some states also make exceptions for children whose parents object to vaccinations for religious or other reasons.

Additional vaccines are available for preventing rotavirus infection (given to infants), anthrax, cholera, Japanese encephalitis, meningococcal meningitis, plague, tuberculosis, typhoid fever, and yellow fever.

Description

Most vaccines are given as injections, but a few are given by mouth or as a nasal spray.

Some vaccines are combined in one injection, such as the measles-mumps-rubella (MMR) or diphtheria-tetanus-pertussis (DTaP) combinations.

Origins

The first vaccine was developed in 1796 by English physician Edward Jenner, who took a few drops of the fluid seeping from a pustule of a cowpox-infected woman and injected it into a healthy young boy. Six weeks later, Jenner injected the boy with fluid from a smallpox pustule, and the boy did not develop smallpox, a devastating disease that killed over a million people each year in Europe. By the start of the twentieth century,

KEY TERMS

Anthrax—An infectious disease caused by a type of bacterium. The disease can be passed from animals to people and usually is fatal. Symptoms include sores on the skin.

Antibodies—Proteins that are normally produced by specialized white blood cells after stimulation by a foreign substance (antigen) and that act specifically against the antigen in an immune response.

Antigen—Any foreign substance, usually a protein, that stimulates the body's immune system to produce antibodies.

Bacteria—Tiny, single-celled forms of life that cause many diseases and infections.

Cholera—An infection of the small intestine caused by a type of bacterium. The disease is spread by drinking water or eating seafood or other foods that have been contaminated with the feces of infected people. It occurs in parts of Asia, Africa, Latin America, India, and the Middle East. Symptoms include watery diarrhea and exhaustion and are often fatal to young children and the elderly.

Cowpox—A mild disease in cows that is caused by a poxvirus.

Diphtheria—A serious infectious disease that produces a toxin (poison) and an inflammation in the membrane lining of the throat, nose, trachea, and other tissues.

Encephalitis—Inflammation of the brain, usually caused by a virus. The inflammation may interfere with normal brain function and may cause seizures, sleepiness, confusion, personality changes, weakness in one or more parts of the body, and even coma.

Feces—The solid waste that is left after food is digested. Feces form in the intestines and pass out of the body through the anus. Also called stool.

Guillain-Barré syndrome (GBS)—A disease of the nerves with symptoms that include sudden numbness and weakness in the arms and legs, sometimes leading to paralysis. The disease is serious and requires medical treatment, but most people recover completely.

Immune system—The body's natural defenses against disease and infection.

Immunization—Administering a vaccine that stimulates the body to create antibodies to a specific disease (immunity) without causing symptoms of the disease.

Infectious disease—Any disease caused by the invasion of a pathogen that subsequently grows and multiplies in the body.

Inflammation—Pain, redness, swelling, and heat that usually develop in response to injury or illness.

vaccines for smallpox, rabies, diphtheria, typhoid fever, and plague had been developed.

Recommended dosage

The recommended dosage depends on the type of vaccine and may be different for different patients. Dosage is standardized for each specific type of vaccine and usually varies based on the recipient's age. The healthcare professional who gives the vaccine determines the proper dose.

A vaccination health record helps parents and healthcare providers keep track of children's vaccinations. The record should be started when children have their first vaccination and should be updated with each additional vaccination. While most physicians follow the recommended vaccination schedule, parents should understand that some flexibility is allowed; for example,

if a child is sick at the time the vaccination is due. Slight departures will not prevent children from developing immunity, as long as all the vaccinations are given at approximately the right times. The physician is the best person to decide when each vaccination should be given.

Anyone planning a trip to another country should check to find out what vaccinations are needed. Some vaccinations must be given as early as 12 weeks before the trip, so getting this information early is important. Many major hospitals and medical centers have travel clinics that can provide this information.

Recommended schedule

The following is a recommended vaccine schedule based on the guidelines provided by the CDC as of 2015. Individuals should talk to their doctor to make

Influenza—A disease caused by viruses that infect the respiratory tract.

Measles—An acute and highly contagious viral disease that occurs primarily in children and is marked by distinct red spots followed by a rash.

Meningitis—Inflammation of tissues that surround the brain and spinal cord.

Microbe—A microorganism, especially a bacterium, that causes disease.

Mumps—An acute and highly contagious viral illness that usually occurs in childhood.

Pathogen—A disease-causing microorganism.

Plague—A highly infectious disease that can be fatal if not treated promptly. The bacteria that cause plague mainly infect rats, mice, squirrels, and other wild rodents. The disease is passed to people through fleas. Infected people can then spread the disease to other people.

Rabies—A rare but serious disease caused by a virus carried in saliva. It is transmitted when an infected animal bites a person.

Rubella—A contagious viral disease that is milder than typical measles but is damaging to the fetus when it occurs early in pregnancy. Also called German measles.

Seizure—A sudden attack, spasm, or convulsion.

Smallpox—A highly contagious viral disease characterized by fever, weakness, and skin eruption with pustules that form scabs that slough off, leaving scars.

Tuberculosis—An infectious disease that usually affects the lungs but may also affect other parts of the body. Symptoms include fever, weight loss, and coughing up blood.

Typhoid fever—An infectious disease caused by a type of bacterium. People with this disease have a lingering fever and feel depressed and exhausted. Diarrhea and rose-colored spots on the chest and abdomen are other symptoms. The disease is spread through poor sanitation.

Virus—A tiny, disease-causing particle that can reproduce only in living cells.

Whooping cough—An infectious disease, also called pertussis, that is caused by a bacterium and is marked by a convulsive, spasmodic cough, sometimes followed by a shrill intake of breath. This disease is more common in infants and children.

Yellow fever—An infectious disease caused by a virus. The disease, which is spread by mosquitoes, is most common in Central and South America and central Africa. Symptoms include high fever, jaundice (yellow eyes and skin), and dark-colored vomit, a sign of internal bleeding. Yellow fever can be fatal.

sure that this schedule is right for them and to check that they have received all recommended vaccinations.

CHILDHOOD.

- birth: hepatitis B (dose 1)
- 1–2 months: hepatitis B (dose 2)
- 2 months: DTaP (dose 1), Hib (dose 1), polio (dose 1), pneumococcal conjugate (dose 1), rotavirus (dose 1)
- 4 months: DTaP (dose 2), Hib (dose 2), polio (dose 2), pneumococcal conjugate (dose 2), rotavirus (dose 2)
- 6 months: DTaP (dose 3), Hib (dose 3), pneumococcal conjugate (dose 3), rotavirus (dose 3)
- 6 months or older: influenza annually
- 6–18 months: hepatitis B (dose 3), polio (dose 3)
- 12–15 months: Hib (dose 4), pneumococcal conjugate (dose 4), MMR (dose 1), varicella (dose 1)
- 15–18 months: DTaP (dose 4)

- 12–23 months: hepatitis A (dose 1), then 6 months later hepatitis A (dose 2)
- 4–6 years: DTaP (dose 5), polio (dose 4), MMR (dose 2), varicella (dose 2)
- 11 and 12 years: DTaP (repeated every 10 years), meningococcal conjugate vaccine (MCV4), human papillomavirus (HPV) (doses 1, 2, and 3)

ADULTHOOD.

- all adults: influenza vaccine each year; DTaP once, then again every 10 years
- women ages 19–26: HPV vaccine for women (3 doses)
- men ages 19–21: HPV vaccine for men (3 doses)
- adults ages 19–24: MMR (1 or 2 doses)
- adults over age 60: shingles (1 dose)
- adults over age 65: pneumococcal polysaccharide vaccine (PPSV23) (1 dose)

Precautions

Vaccines are not always 100% effective, and there is no way to predict whether a vaccine will fail to provide adequate immunity in any particular person. To be most effective in preventing disease outbreaks, vaccination programs depend on the participation of whole communities. The more people who are vaccinated, the lower everyone's risk of being exposed to a disease. Even people who do not develop immunity through vaccination are safer when their friends, neighbors, children, and coworkers are immunized. In addition to vaccines, handwashing and other forms of hygiene are the most effective means for preventing the spread of infectious diseases.

Like most medical procedures, vaccination has risks as well as substantial benefits. Individuals who receive vaccines should make sure they are fully informed about both the benefits and the risks. Any questions or concerns should be discussed with a physician or other healthcare provider. The CDC offers substantial information on immunizations and vaccinations.

Pregnant or breastfeeding

Certain vaccines are not recommended for use during pregnancy, but some may be given to women at especially high risk of getting a specific disease, such as polio. Vaccines may also be given to pregnant women to prevent medical problems in their babies. For example, vaccinating a pregnant woman with tetanus toxoid can prevent her baby from getting tetanus at birth.

Women should avoid becoming pregnant for three months after receiving the rubella vaccine, measles vaccine, mumps vaccine, or the combined MMR vaccine, as these vaccines may pose risks to the fetus.

Women who are breastfeeding should check with their physician before receiving any vaccine.

Other conditions and allergies

Vaccines may cause problems for people with certain allergies.

- People who are allergic to the antibiotics neomycin or polymyxin B should not receive the rubella vaccine, measles vaccine, mumps vaccine, or the combined MMR vaccine.
- People who are allergic to baker's yeast should not receive the hepatitis B vaccine.
- People who are allergic to antibiotics such as gentamicin sulfate, streptomycin sulfate, or other aminoglycosides should check with their physician before receiving the influenza vaccine, as some influenza vaccines contain small amounts of these drugs.

- People who are allergic to eggs should not receive vaccines grown in the fluids of chick embryos, including those for influenza, measles, and mumps.

In general, people who have had an unusual reaction to a vaccine in the past should inform their physician before taking the same kind of vaccine again. Their physician should also be told about any allergies to foods, medicines, preservatives, or other substances.

People with certain other medical conditions should be cautious about taking vaccines. The influenza vaccine, for example, may reactivate the rare Guillain-Barré syndrome (GBS) in people who have had it before. This vaccine may also worsen illnesses that involve the lungs, such as bronchitis or pneumonia. Vaccines that cause fever as a side effect may trigger seizures in people who have a history of seizures caused by fever.

Side effects

Most side effects from vaccines are minor and easily treated. The most common side effects are pain, redness, and swelling at the site of the injection. Some people may develop a fever or a rash. In rare cases, vaccines may cause severe allergic reactions, swelling of the brain, or seizures. Anyone who has an unusual reaction after receiving a vaccine should contact a physician immediately.

Interactions

Vaccines may interact with other medicines and medical treatments. When this happens, the effects of the vaccine or the other medicine may change, or the risk of side effects may be greater. For example, radiation therapy and cancer drugs may reduce the effectiveness of many vaccines or may increase the chance of side effects. Individuals who plan to receive a vaccine should let the physician know about all other medicines they are taking and should ask whether the possible interactions could interfere with the effects of the vaccine or the other medicines.

Resources

BOOKS

- Espejo, Roman, ed. *Should Vaccinations Be Mandatory?* 1st ed. Detroit: Greenhaven, 2014.
- Morrow, John W., et al, eds. *Vaccinology: Principles and Practice*. Chichester, UK: Wiley-Blackwell, 2012.
- Newton, David E. *Vaccination Controversies: A Reference Handbook*. Santa Barbara, CA: ABC-CLIO, 2013.

Resources

PERIODICALS

- Betsch, Cornelia, and Katharina Sachse. "Debunking Vaccination Myths: Strong Risk Negations Can Increase Perceived Vaccination Risks." *Health Psychology* 32, no. 2 (2013): 146–55.

Gilkey, Melissa B., et al. "Forgone Vaccination during Childhood and Adolescence: Findings of a Statewide Survey of Parents." *Preventive Medicine* 56, nos. 3–4 (2013): 202–6.

Resources

WEBSITES

College of Physicians of Philadelphia. "Top 20 Questions about Vaccination." The History of Vaccines. <http://www.historyofvaccines.org/content/articles/top-20-questions-about-vaccination> (accessed March 10, 2015).

National Center for Immunization and Respiratory Diseases. "Immunization Schedules." Centers for Disease Control and Prevention. <http://www.cdc.gov/vaccines/schedules> (accessed March 10, 2015).

Nemours Foundation. "Frequently Asked Questions about Immunizations." KidsHealth.org. http://kidshealth.org/parent/general/body/fact_myth_immunizations.html (accessed March 10, 2015).

World Health Organization. "What Are Some of the Myths—and Facts—about Vaccination?" <http://www.who.int/features/qa/84/en/> (accessed March 10, 2015).

ORGANIZATIONS

American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, IL 60007-1098, (847) 434-4000, (800) 433-9016, Fax: (847) 434-8000, <http://www.aap.org/>.

Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, Atlanta, GA 30329, (404) 639-3534, (800) CDC-INFO (800-232-4636), TTY: (888) 232-6348, inquiry@cdc.gov, <http://www.cdc.gov/>.

Immunization Action Coalition (IAC), 2550 University Avenue West, Suite 415 North, Saint Paul, MN 55114, (651) 647-9009, Fax: (651) 647-9131, admin@immunize.org, <http://www.immunize.org/>.

National Network for Immunization Information (NNII), 301 University Boulevard, Galveston, TX 77555-0350, (702) 200-0201, Fax: (409) 772-5208, dipineda@utmb.edu, <http://www.immunizationinfo.org/>.

National Vaccine Program Office (NVPO), 200 Independence Avenue, SW, Room 715-H, Washington, DC 20201, (202) 690-5566, nvpo@hhs.gov, <http://www.hhs.gov/nvpo>.

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Valacyclovir

Definition

Valacyclovir is an oral antiviral agent used against herpesvirus infections, including cold sores, genital herpes, shingles (herpes zoster), and chickenpox



Valtrex (valacyclovir), 500 mg. (© Cengage Learning®.)

(varicella). It is in a drug class called purine nucleoside analogs/DNA polymerase inhibitors.

Purpose

Valacyclovir is approved by the U.S. Food and Drug Administration (FDA) for treating and suppressing herpes infections. Valacyclovir does not cure the infection, but it can decrease itching, burning, tingling, tenderness, and pain; help sores heal faster; and prevent new sores from forming.

Specific infections include:

- Herpes labialis—cold sores or fever blisters, also called oral herpes—is usually caused by herpes simplex virus type 1 (HSV-1). HSV-1 is a very common infection of the mouth and surrounding tissues that infects most people in the United States by age 20. Following the initial infection, the virus becomes inactive (dormant) in nerve tissues in the face. Sometimes the virus reactivates, causing small, painful blisters that may be treated with valacyclovir in adults and children ages 12 and older.
- Herpes simplex virus type 2 (HSV-2) causes genital herpes, a sexually transmitted infection that can also spread to the mouth and cause oral herpes. Valacyclovir is approved for the treatment of initial and recurrent episodes of genital herpes in adults with healthy

immune systems (immunocompetent). Episodic therapy can decrease the severity of outbreaks and the duration by hours or a few days but does not reduce the frequency of outbreaks. People with fewer than six outbreaks per year of recurrent genital herpes may be advised to keep a supply of medication for use at the first sign of pain, tingling, or a blister. People with few symptoms of recurrent genital herpes or infrequent outbreaks may not require treatment, especially if they are not at risk for transmitting HSV-2 to an uninfected partner.

- Suppressive therapy is daily low-dose valacyclovir to prevent or decrease the frequency and duration of HSV-2 outbreaks in immunocompetent adults and adults with HIV/AIDS. It may be recommended for people who have at least six outbreaks a year, severe symptoms, or a weakened immune system from HIV/AIDS, immune-suppressing drugs, or other conditions. Some experts recommend periodically suspending suppressive therapy to determine if it is still needed, since valacyclovir can be restarted if outbreaks recur.
- Suppressive therapy is also approved for reducing genital herpes transmission to uninfected sexual partners who have no history of genital herpes or whose blood tests indicate the absence of HSV-1 or HSV-2 antibodies. Suppressive valacyclovir therapy appears to reduce the risk of transmitting HSV-2 by approximately 50%.
- Valacyclovir is used to treat shingles (herpes zoster)—the reactivation of dormant varicella zoster virus (VZV) in people who have had chickenpox (varicella) or the varicella vaccine. Shingles usually affects seniors—about 50% of Americans will have had shingles by age 80. Shingles causes localized itching, blistering rash, and painful nerve inflammation and can sometimes result in painful, long-lasting post-herpetic neuralgia (PHN). Valacyclovir treats shingles symptoms, shortening the illness and decreasing its severity. The earlier valacyclovir is started, the faster the recovery and the lower the likelihood of PHN. Both valacyclovir and the similar drug famciclovir significantly reduce the risk of PHN compared to **acyclovir**, the third antiviral for treating herpesvirus infections. Valacyclovir treatment is especially important for shingles that affects the eyes (herpes zoster ophthalmicus). Although shingles is not contagious, direct contact with sores can transmit VZV to others—usually children—who have not had chickenpox or been immunized against it, causing them to develop chickenpox rather than shingles.
- Valacyclovir is approved for treating chickenpox in children.

Off-label use

Valacyclovir may be prescribed off label for other purposes; for example, it is active against the Epstein-Barr herpesvirus that causes infectious mononucleosis.

Description

Valacyclovir is a “prodrug” derivative of acyclovir that is converted to its active form, acyclovir triphosphate, in the body. Acyclovir is a nucleoside analog that mimics the structure of a purine component of DNA and selectively inhibits the viral DNA polymerase. This prevents the herpesvirus from copying itself (replicating) and spreading. The drug does not significantly affect human DNA polymerase, so side effects are minimized. Valacyclovir is not active against the common herpesvirus cytomegalovirus (CMV) at the approved oral dosages, because CMV does not make the viral enzyme required for converting the drug to acyclovir.

Although valacyclovir is converted to acyclovir, it is about 55% more bioavailable than acyclovir. Both valacyclovir and the drug famciclovir persist longer inside infected cells. For example, 250 milligrams (mg) of valacyclovir four times daily provide about the same antiviral activity as five daily 800 mg doses of oral acyclovir. Three daily 1,000 mg valacyclovir doses have similar activity to intravenous acyclovir injected every eight hours.

Valacyclovir is prescribed as a tablet taken by mouth. The 500 mg caplets are blue, film-coated, unscored, and printed with “VALTREX 500 mg.” The 1 gram (g) caplets are blue, film-coated, partially scored on both sides, and printed with “VALTREX 1 gram.” The 500 mg caplets can be prepared as an oral suspension of 25 mg per milliliter (mL) or 50 mg/mL if swallowing tablets is a problem or for dosage by body weight when treating chickenpox. The drug is stored at room temperature, away from excess heat and moisture (not in the bathroom).

U.S. brand names

Valtrex is the U.S. brand name for valacyclovir.

Canadian brand names

Canadian brand names are:

- Valtrex
- Apo-Valacyclovir
- CO Valacyclovir
- PMS-Valacyclovir

International brand names

There are a large number of international brand names, of which Valtrex is the most common. Other brand names include:

- Valaciclovir Actavis
- Valaciclovir Bluefish
- Valaciclovir Portfarma
- Valaciclovir Sanzoz
- Zelitrex

Origins

Valacyclovir hydrochloride (HCl) was initially approved by the FDA in 1995. Generic 500 mg and 1 g equivalents were first approved in 2007.

Recommended dosage

Recommended adult dosages are:

- cold sores—2 g every 12 hours for one day at earliest symptoms, such as tingling, itching, or burning
- initial episode of genital herpes—1 g twice daily for ten days; most effective within the first 48 hours of signs and symptoms
- recurrent episodes of genital herpes—500 mg twice daily for three days at first sign or symptom
- suppressive genital herpes therapy in immunocompetent patients—1 g once daily; 500 mg once daily for patients with nine or fewer recurrences per year
- suppressive genital herpes therapy in HIV-1-infected patients—500 mg twice daily
- reduction of genital herpes transmission in patients with nine or fewer recurrences in a year—500 mg once daily
- shingles—1 g three times daily for seven days, initiated at first sign or symptom but within 48 hours of onset of rash

Valacyclovir can be taken with or without food. A missed dose should be taken as soon as possible and remaining doses for the day taken at evenly spaced intervals. If it is almost time for the next dose, a missed dose should be skipped.

Pediatric

Cold sores in children aged 12 and older are treated with 2 g every 12 hours for one day at first symptom. Chickenpox in immunocompetent children aged 2 through 17 is treated with 20 mg per kilogram (kg, or 2.2 lb.) of body weight three times daily for five days, not to exceed 1 g three times daily.

Other conditions and allergies

Dosages must be reduced in patients with reduced kidney function.

Precautions

Some precautions while taking valacyclovir include:

- The entire course of valacyclovir must be taken to fully clear the infection even if symptoms disappear.
- Lab tests may be ordered to check the response to valacyclovir.
- Genital intercourse should be avoided when genital herpes lesions are visible, although the virus can be transmitted to sexual partners even in the absence of symptoms.
- The doctor should be notified if symptoms remain after finishing the course of valacyclovir.
- The safety and effectiveness of valacyclovir have not been established for chickenpox in adults.

Pediatric

The safety and effectiveness of valacyclovir have not been established for:

- cold sores in children under 12
- genital herpes or shingles in children under 18
- chickenpox in children under age two
- suppressive therapy in newborns and infants with neonatal HSV infection

Geriatric

A clinical trial found that PHP was longer lasting in valacyclovir-treated patients aged 65 and older when compared with younger patients. Elderly patients also are at risk for acute kidney failure from valacyclovir, even in the absence of previously reduced kidney (renal) function.

Pregnant or breastfeeding

Valacyclovir is in the FDA pregnancy category B—neither valacyclovir nor acyclovir has been well studied in pregnant women, but animal studies have not indicated any harm to the embryo or fetus. Pregnancy registry data indicate that the overall birth defect rate for infants exposed to acyclovir during the first trimester of pregnancy is similar to that for infants in the general population. Nevertheless, valacyclovir should be used during pregnancy only if the potential benefits outweigh potential risks to the fetus.

Acyclovir is excreted in breast milk following oral administration of valacyclovir. However, a maternal dosage of 500 mg of valacyclovir twice daily would expose a nursing infant to less than 2% of the exposure from a standard neonatal dose of 30 mg/kg/day of intravenous acyclovir. Nevertheless, caution should be used in administering valacyclovir to nursing mothers.

KEY TERMS

Acyclovir—An antiviral agent that is formed from valacyclovir in the body.

CD4 count—A measure of the strength of the immune system.

Cold sores—Herpes labialis; fever blisters; itching, burning, or painful lesions, usually in or around the mouth and caused by reactivation of herpes simplex virus type 1.

Cytomegalovirus (CMV)—A common human herpesvirus that is normally not harmful but may cause severe complications if transmitted to a fetus.

Episodic therapy—Antiviral treatment at first sign of a genital herpes outbreak.

Epstein-Barr virus—A herpesvirus that causes infectious mononucleosis.

Famciclovir—An antiviral medication similar to valacyclovir.

Genital herpes—Infection of the genitals with herpes simplex virus type 2.

Herpes simplex virus type 1 (HSV-1)—The virus that is usually responsible for cold sores.

Herpes simplex virus type 2 (HSV-2)—The sexually transmitted virus that causes genital and sometimes oral herpes.

Herpes zoster ophthalmicus—Shingles that affects the eyes.

Immunocompetent—Having a healthy immune system.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Post-herpetic neuralgia (PHN)—Pain that continues or recurs after the shingles rash has healed.

Shingles—Herpes zoster; a blistering rash and nerve pain that primarily affects older adults and is caused by reactivation of the varicella zoster virus that causes chickenpox.

Suppressive therapy—Low-dose antiviral therapy to prevent outbreaks and transmission of genital herpes.

Varicella—Chickenpox; a disease caused by the varicella zoster virus.

Varicella zoster virus (VZV)—Human herpesvirus type 3; the virus that causes chickenpox and remains dormant in the nerves, where its reactivation causes shingles.

Other conditions and allergies

Valacyclovir may need to be used with caution in individuals with certain other conditions or allergies:

- The doctor and pharmacist should be informed of allergies to valacyclovir, any components of the medication, acyclovir (Zovirax), or any other medications.
- The doctor should be informed if the patient has or has ever had kidney or liver disease or immune-system problems, including HIV/AIDS.
- Acute renal failure may occur in patients with kidney disease who receive valacyclovir doses that are higher than recommended for their level of renal function, in patients taking other drugs that are toxic to the kidneys, and in patients who are inadequately hydrated.
- The safety and effectiveness of valacyclovir have not been established for immunocompromised patients other than for the suppression of genital herpes in HIV-1-infected patients with CD4+ cell counts equal to or above 100 cells per cubic millimeter.

- In clinical trials, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome has occurred in patients with advanced HIV-1 disease and in allogeneic bone-marrow transplant and kidney transplant patients administered 8 g per day of valacyclovir.

Side effects

The most common side effects of valacyclovir are headache, nausea, and abdominal pain. The doctor should be notified if any of the following symptoms are severe or persistent:

- headache
- upset stomach
- vomiting
- diarrhea or loose stools
- constipation

Serious adverse central nervous system reactions—such as agitation, hallucinations, confusion, and encephalopathy (brain disorders)—can occur in both adult and

pediatric patients. The doctor also should be notified immediately in case of any of the following side effects:

- rash
- itching
- yellowish skin or eyes
- fever
- blood in the urine

Pediatric

Headache is the only side effect reported in more than 10% of pediatric patients treated with valacyclovir.

Geriatric

Elderly patients are more likely to experience renal or central nervous system side effects.

Other conditions and allergies

Patients with kidney disease who receive higher-than-recommended doses of valacyclovir may have adverse central nervous system reactions.

Interactions

The doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Drugs

Valacyclovir may interact with cimetidine (Tagamet) or probenecid (Benemid).

Herbs and supplements

Some vitamin supplements may interact with valacyclovir. Individuals should consult their healthcare provider before taking any dietary supplements.

Resources

PERIODICALS

- Avalos, Lyndsay A., et al. "The Prevalence and Trends of Antiviral Medication Use During Pregnancy in the US: A Population-Based Study of 664,297 Deliveries in 2001–2007." *Maternal and Child Health Journal* 18, no. 1 (2014): 64–72.
- Henderson, Theodore A. "Valacyclovir Treatment of Chronic Fatigue in Adolescents." *Advances in Mind-Body Medicine* 28, no. 1 (2014): 4–14.
- Seppa, Nathan. "Experimental Herpes Drug Offers Hope." *Science News* 186, no. 8 (2014): 13.

WEBSITES

- Albrecht, Mary A. "Patient Information: Genital Herpes (Beyond the Basics)." UpToDate.com. <http://www.uptodate.com/contents/genital-herpes-beyond-the-basics?view=print> (accessed February 28, 2015).
- GlaxoSmithKline. "Full Prescribing Information." <https://www.gsksource.com/gskprm/htdocs/documents/VALTREX-PI-PIL.PDF> (accessed February 28, 2015).
- MedlinePlus. "Herpes–Oral." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/ency/article/000606.htm> (accessed February 28, 2015).
- Office on Women's Health. "Genital Herpes Fact Sheet." WomensHealth.gov. <http://womenshealth.gov/publications/our-publications/fact-sheet/genital-herpes.html> (accessed February 28, 2015).
- Zachary, Kimon C. "Valacyclovir: An Overview." UpToDate.com. http://www.uptodate.com/contents/valacyclovir-an-overview?source=see_link (accessed February 28, 2015).

ORGANIZATIONS

- National Shingles Foundation, 603 West 115th Street, #371, New York, NY 10025, (212) 222-3390, Fax: (212) 222-8627, Shingles@ShinglesFoundation.org, <http://shinglesfoundation.org/>.
- U.S. Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30329, (800) CDC-INFO (232-4636), cdcinfo@cdc.gov, <http://www.cdc.gov/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY KEVIN GLAZA, RPh

Valium see **Diazepam**

Valproic acid

Definition

Valproic acid is an anticonvulsant (antiseizure) drug.

Purpose

The U.S. Food and Drug Administration (FDA) recognizes valproic acid for the treatment of epilepsy and for mania that occurs with bipolar disorder. Valproic acid is also approved for the prevention of migraine headaches.

Description

Valproic acid is effective in treating a variety of seizure types, which include simple and complex absence seizures, partial seizures, and tonic-clonic seizures (grand



Valproic acid, 250 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

mal seizures). Valproic acid is also effective in treating the manic episodes of patients with bipolar disorder. Patients who have bipolar disorder resulting from a head injury and patients who do not respond to or who cannot tolerate conventional lithium therapy (normally the therapy of choice for bipolar disorder) can be treated with valproic acid. In addition, valproic acid provides a 50% or greater reduction in the frequency of migraine headaches. Valproic acid is also safe and effective in preventing headaches that arise as a side effect of taking a class of drugs known as selective serotonin reuptake inhibitors (SSRIs). SSRIs include **sertraline** (Zoloft), **paroxetine** (Paxil), **fluoxetine** (Prozac), **fluvoxamine** (Luvox), and **citalopram** (Celexa).

Valproic acid comes in 250 milligram (mg) gelatin capsules and in a 250 mg/5 milliliter (mL) syrup.

U.S. brand names

In the United States, valproic acid is also known as valproate and is sold under the brand name Depakene.

Origins

Valproic acid's properties in preventing seizures were first discovered in Europe in 1963. The medication was first used clinically in the United States in 1978.

Recommended dosage

The dosage of valproic acid used to treat epilepsy depends on the type of seizures the patient has. The doses are determined based on the patient's weight.

The initial dose of valproic acid used to treat mania is 750 mg daily. This dose is then reduced to the lowest dose that will achieve the desired effects. Another dosage strategy is based on patient weight. The starting dose is 30 mg per kilogram (kg, or 2.2 lb.) of body weight on each of the first two days, followed by 20 mg per kg of body weight taken daily on days three through ten.

For prevention of migraine headaches, a dose of 250 mg twice daily is beneficial. It may take up to 1,000 mg of valproic acid to control migraine attacks.

Precautions

Valproic acid may cause life-threatening damage to the liver and pancreas. Before starting valproic acid therapy, every patient should have a blood test to assess his or her liver function. The risk that valproic acid will cause liver damage is greatest during the first six months of treatment. Liver function tests should be done once a month during the first three months, then every three to six months for as long as the patient continues to take the drug. Vomiting, lethargy, loss of appetite, and jaundice (yellowing of the skin) may precede signs of liver damage. If a patient develops severe or unusual abdominal pain, this may be a sign of pancreatitis (inflammation of the pancreas). Pancreatitis can occur in both children and adults. It can develop shortly after valproic acid is started or after several years of use.

Pediatric

Patients who are younger than two years old should not take valproic acid. When it is necessary for children under age two to take valproic acid, the drug should be used cautiously and with close physician monitoring.

Pregnant or breastfeeding

Pregnant women or women who are planning to become pregnant should not take valproic acid, as the drug is harmful to the fetus and may cause birth defects, including intellectual developmental disorder.

Side effects

Side effects of valproic acid may include nausea, vomiting, indigestion, and either diarrhea or constipation. Headaches, dizziness, lack of coordination, confusion, fatigue, tremor, drowsiness, and seizures have also been associated with the use of valproic acid. Behavioral changes associated with the drug—including irritability, longer and deeper sleep, hyperactivity, increased sociability, and increased sadness, happiness, or aggression—are seen more often in children than in adults taking valproic acid.

KEY TERMS

Absence seizures—Absence (petit mal) seizures usually begin with a brief loss of consciousness and last between one and ten seconds. People having a petit mal seizure become very quiet and may blink, stare blankly, roll their eyes, or move their lips. When it ends, the individual resumes whatever he or she was doing before the seizure began and may not realize that anything unusual happened.

Epilepsy—A neurological disorder characterized by recurrent seizures. Seizures are caused by a disturbance in the electrical activity in the brain and can lead to loss of consciousness, muscle spasms, rhythmic movements, abnormal sensory experiences, or altered mental states.

Migraine headache—An intense throbbing pain that occurs on one or both sides of the head. The headache is usually accompanied by other symptoms, such as nausea, vomiting, and aversion to light.

Tonic-clonic seizure—This is the most common type of seizure among all age groups and is categorized into several phases beginning with vague symptoms hours or days before an attack. These seizures are sometimes called grand mal seizures.

Less than 1% of patients experience appetite changes. These changes may include either diminished or increased appetite. Skin rash, photosensitivity (acute sensitivity to the sun), hair loss, and other hair changes have also been reported in people using valproic acid.

Interactions

Patients should inform their healthcare provider of all medications they are currently taking, including over-the-counter drugs and supplements, before starting treatment with valproic acid.

Drugs

Using valproic acid with other anticonvulsant drugs, such as phenobarbital, **clonazepam**, and **lamotrigine**, may cause excessive sedation (drowsiness and lack of physical and mental alertness). Valproic acid may diminish the benefits of **phenytoin**, another commonly used anticonvulsant. Severe central nervous system depression has been reported with the use of valproic acid and another anticonvulsant called primidone.

Taking **aspirin** during valproic acid therapy may cause valproic acid levels to increase to toxic (poisonous) levels. Other medications that may cause valproic acid toxicity are the antibiotic **erythromycin** and the antidepressant **amitriptyline**. Drugs that can decrease the effectiveness of valproic acid include **carbamazepine** and cholestyramine.

Herbs and supplements

Ginkgo biloba sold as a supplement may be prepared with a chemical called 4'-O-methylpyridoxine. If this chemical remains in the herbal preparation, it can cause seizures and reduce the effectiveness of valproic acid.

Resources

BOOKS

Lexicomp. *Drug Information Handbook with International Trade Names Index*. 23rd ed. Hudson, OH: Lexi-Comp, 2014.

Sadock, Benjamin J., Virginia A. Sadock, and Pedro Ruiz, eds. *Kaplan and Sadock's Comprehensive Textbook of Psychiatry*. 9th ed. Philadelphia: Lippincott Williams & Wilkins, 2009.

PERIODICALS

Gill, D., et al. "Valproic Acid and Sodium Valproate for Neuropathic Pain and Fibromyalgia." *Cochrane Database of Systematic Reviews* 10, art. no. CD009183 (2011). <http://dx.doi.org/10.1002/14651858.CD009183.pub2> (accessed February 24, 2015).

WEBSITES

AHFS Consumer Medication Information. "Valproic Acid." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682412.html> (accessed February 24, 2015).

American Association for Clinical Chemistry. "Valproic Acid." Lab Tests Online. <http://labtestsonline.org/understanding/analytes/valproic-acid/tab/test/> (accessed February 24, 2015).

Epilepsy Foundation. "Valproic Acid." <http://www.epilepsy.com/medications/valproic-acid> (accessed February 24, 2015).

U.S. Food and Drug Administration. "Depakene (Valproic Acid) Capsules and Oral Solution, Depakote (Divalproex Sodium) Delayed Release and Depakote ER (Extended Release) Tablets, Depakote Sprinkle Capsules (Divalproex Sodium Coated Particles in Capsules), Depacon (Valproate Sodium) Injection." <http://www.fda.gov/safety/medwatch/safetyinformation/ucm360487.htm> (accessed February 24, 2015).

ORGANIZATIONS

Epilepsy Foundation, 8301 Professional Place East, Suite 200, Landover, MD 20785-2353, (800) 332-1000, ContactUs@efa.org, <http://www.epilepsy.com/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Valsartan/amlodipine see **Amlodipine/valsartan**

Valsartan/ hydrochlorothiazide

Definition

Valsartan/hydrochlorothiazide is an oral combination drug for treating hypertension (high blood pressure). Valsartan is in the drug class of angiotensin II receptor blockers (ARBs) or angiotensin II receptor antagonists. **Hydrochlorothiazide** (HCTZ) is a diuretic. The combination drug is in the class known as ARB/HCTZ combos.



Valsartan/hydrochlorothiazide, 160 mg/12.5 mg.
(© Cengage Learning®.)

Purpose

Valsartan/HCTZ is used to treat hypertension. It helps control high blood pressure but does not cure it. High blood pressure is very common, and untreated hypertension can damage the heart, blood vessels, brain, kidneys, and other organs. Lowering high blood pressure helps prevent heart disease, heart attacks, heart failure, strokes, kidney failure, loss of vision, and other problems. Valsartan/HCTZ is not used for initial treatment of hypertension; however, it is used to treat heart failure, in which the heart is unable to pump adequate blood to the body. Lifestyle modifications—including reducing dietary fats and salt, maintaining a healthy weight, exercising at least 30 minutes most days, not smoking, using alcohol only in moderation, and reducing stress—may increase the effectiveness of valsartan/HCTZ.

Description

Valsartan and other ARBs or angiotensin II receptor antagonists interfere with the renin-angiotensin-aldosterone system (RAAS)—a signaling pathway that controls blood pressure. Angiotensin II is a peptide hormone that is a powerful vasoconstrictor for narrowing blood vessels throughout the body, thereby raising blood pressure. Angiotensin II also stimulates the secretion of aldosterone by the adrenal gland. Aldosterone causes the kidneys to retain more water and sodium and to excrete more potassium, thereby increasing total blood volume and blood pressure. By blocking the binding of angiotensin II to its type 1 receptors, valsartan blocks the vasoconstriction and aldosterone-secreting effects of angiotensin II to relax blood vessels and lower blood pressure, enabling the blood to flow more readily and the heart to work more efficiently.

HCTZ is a thiazide diuretic, or “water pill,” and a sulfonamide that increases urine production and inhibits sodium reabsorption by the kidneys. This helps remove excess water, sodium, potassium, and hydrogen ions from the body.

Valsartan/HCTZ is a tablet taken by mouth. The drug is stored at room temperature away from light and moisture (not in the bathroom).

Valsartan/HCTZ is available in the following strengths:

- 80 milligrams (mg) valsartan/12.5 mg HCTZ
- 160 mg valsartan/12.5 mg HCTZ
- 320 mg valsartan/12.5 mg HCTZ
- 160 mg valsartan/25 mg HCTZ
- 320 mg valsartan/25 mg HCTZ

KEY TERMS

Aldosterone—A steroid hormone produced by the adrenal cortex that regulates salt and water balance in the body.

Angiotensin II—A peptide hormone that narrows blood vessels (vasoconstriction), especially in the kidneys, and raises blood pressure.

Angiotensin II receptor blocker (ARB)—Angiotensin II receptor antagonist; a blood pressure-lowering drug, such as valsartan, that blocks angiotensin II binding to its receptors.

Angiotensin-converting enzyme (ACE) inhibitor—A blood pressure-lowering drug that inhibits the enzyme that converts angiotensin I to active angiotensin II.

Antagonist—A drug, such as valsartan, that blocks the action of a substance by binding to its receptors.

Dehydration—Abnormal depletion of body fluids, as from vomiting, diarrhea, or a diuretic.

Diuretic—“Water pill”; a medication, such as hydrochlorothiazide, that increases urine excretion and removes water and salt from the body, which helps lower blood pressure.

Electrolytes—Ions, such as potassium, calcium, sodium, and chloride, that are dissolved in bodily fluids such as blood and that regulate or affect most metabolic processes.

Hydrochlorothiazide (HCTZ)—A sulfonamide diuretic that is combined with valsartan in blood-pressure-lowering combination drugs.

Hyperkalemia—High blood potassium.

Hypertension—High blood pressure.

Hypokalemia—Low blood potassium.

Hypotension—Low blood pressure.

Orthostatic hypotension—Postural hypotension; a drop in blood pressure that causes faintness or dizziness upon standing.

Receptor—A molecule, usually a protein, inside or on the surface of a cell, that binds to a specific substance, such as angiotensin II, to initiate specific activities.

Renin-angiotensin-aldosterone system (RAAS)—A signaling pathway that regulates blood pressure and is disrupted by valsartan.

Sulfonamides—A common class of medications that includes hydrochlorothiazide and sulfa drugs.

U.S. brand names

The U.S. brand name for valsartan/hydrochlorothiazide is Diovan HCT.

Canadian brand names

The Canadian brand name for valsartan/hydrochlorothiazide is Diovan HCT.

International brand names

Internationally, valsartan/hydrochlorothiazide is sold under the brand name Diovan HCT.

Origins

Diovan HCT was originally approved by the U.S. Food and Drug Administration (FDA) in 1998. Various generic forms of valsartan/hydrochlorothiazide have been available since 2012. Valsartan/HCTZ is also available in a combination medication with **amlodipine** (Exforge HCT).

Recommended dosage

Valsartan/HCTZ dosage depends on the condition being treated and the response to treatment. The recommended initial dosage for hypertension is one tablet per day of 80–160 mg valsartan/12.5–25 mg HCTZ. This may be increased after one to two weeks, based on response, to a maximum of 320 mg valsartan/25 mg HCTZ daily. Valsartan/HCTZ is taken with or without food at about the same time each day. If it causes increased urination, it is best to take it at least four hours before bedtime to prevent having to get up in the night to urinate. Valsartan/HCTZ must be taken at least four hours before or at least four to six hours after taking bile-acid-binding resins such as cholestyramine or colestipol for lowering cholesterol. A missed dose should be taken as soon as possible, unless it is almost time for the next dose, in which case the dose should be skipped and the regular dosing schedule resumed.

Precautions

- Valsartan/HCTZ should be taken regularly for the most benefit.
- Patients should check their blood pressure regularly.
- Patients should contact their doctor if their blood pressure or other condition does not improve or worsens.
- Valsartan/HCTZ can cause dizziness; patients should not drive, operate machinery, or perform any activity that requires alertness until they know that they can perform the activity safely.

- HCTZ, in particular, may cause dizziness, light-headedness, or fainting when rising too quickly from lying down, especially when first taking the drug. Patients should rise from bed slowly, resting their feet on the floor for a few minutes before standing.
- Severe sweating, diarrhea, or vomiting increase the risk of light-headedness and fainting due to a drop in blood pressure or dehydration (excess water loss). Such conditions should be reported to the doctor. Patients should drink plenty of fluids to prevent dehydration unless directed otherwise by their doctor.
- HCTZ can increase sun sensitivity. Patients should avoid unnecessary or prolonged sun exposure, sun-lamps, and tanning booths and wear sunscreen, sunglasses, and protective clothing outdoors.
- Laboratory or medical tests, such as serum electrolytes and kidney function, should be performed periodically to check for responses and side effects. HCTZ can cause low potassium levels (hypokalemia) and low sodium levels (hyponatremia).
- HCTZ may decrease calcium excretion in the urine.
- Valsartan/HCTZ can interfere with some laboratory tests, including parathyroid function tests, and may cause false results, so all doctors and laboratory personnel should be informed of valsartan/HCTZ use.
- Patients should inform their doctor and dentist of valsartan/HCTZ use (and all prescription and nonprescription drugs and herbal products) before having any type of surgery.
- Acute transient myopia (nearsightedness) and acute angle-closure glaucoma have been reported, especially in patients with a history of sulfonamide or penicillin allergies.
- HCTZ may cause excess uric acid in the blood (hyperuricemia) or precipitate gout.
- HCTZ may affect glucose tolerance and raise serum cholesterol and triglyceride levels.

Pediatric

The safety and effectiveness of valsartan/HCTZ have not been established for pediatric patients.

Geriatric

Valsartan/HCTZ should be used with caution in geriatric patients because of the risk of dizziness or fainting upon standing (orthostatic hypotension).

Pregnant or breastfeeding

Valsartan/HCTZ carries a boxed warning to discontinue use immediately if pregnancy occurs. Drugs, such

as valsartan, that affect the RAAS can cause fetal injury or death. Valsartan/HCTZ is in the FDA pregnancy category C for the first trimester and in the FDA pregnancy category D for the second and third trimesters. Women should use reliable methods of birth control while taking valsartan. It is unknown whether valsartan passes into breast milk, but HCTZ does. Women should either discontinue the drug or refrain from breastfeeding.

Other conditions and allergies

Valsartan/HCTZ should not be used by patients taking aliskiren for diabetes or who have:

- hypersensitivity or allergies to valsartan, hydrochlorothiazide, or sulfonamide antibiotics
- defective urination (anuria)
- severe kidney impairment with creatinine clearance below 30 milliliters (mL) per minute
- bilateral renal artery stenosis (narrowing)

Valsartan/HCTZ should be used with caution in patients with diabetes. Blood sugar levels should be checked regularly, and diabetes medications, exercise programs, or diet may need adjusting. The drug should also be used with caution in patients with:

- autonomic dysfunction that increases the risk of orthostatic hypotension
- severe liver impairment
- renal artery stenosis
- low magnesium levels (hypomagnesemia), which can cause hypokalemia that is difficult to treat

Before taking valsartan/HCTZ, patients should provide their doctor with a complete medical history, including:

- any allergies to medications or other substances
- gout
- kidney disease
- bile duct blockage, as from gallstones, tumors, or injury
- liver disease
- heart disease
- lupus
- dehydration
- asthma
- high cholesterol

Side effects

Dizziness or light-headedness are common as the body first adjusts to valsartan/HCTZ. Patients should contact their doctor immediately if these effects persist or

worsen or if any of the following uncommon but serious side effects occur:

- fainting
- decreased vision
- eye pain
- symptoms of high potassium levels (hyperkalemia), such as muscle weakness or slow or irregular heartbeat
- unusual change in the amount of urine, other than the normal increase when first starting a diuretic
- swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs
- hoarseness
- difficulty breathing or swallowing
- unexplained weight gain

Other possible side effects include:

- hypotension
- fatigue
- anemia (low red blood cell count)
- prolonged loss of appetite (anorexia)
- confusion
- digestive distress, including stomach pain, nausea, or diarrhea
- skin disorders
- headache
- inflammation of blood or lymph vessels (vasculitis)
- blurred vision
- cough
- frequent urination
- hair loss
- symptoms of high uric acid in the blood or low magnesium levels
- kidney impairment or failure
- elevated liver enzymes or hepatitis (rare)
- decreased blood platelets for clotting (rare)

Geriatric

Older adults may be more sensitive to valsartan/HCTZ side effects, especially dizziness and changes in the amount of urine.

Other conditions and allergies

Very serious allergic reactions to valsartan/HCTZ are rare. However, signs of a serious allergic reaction that require immediate medical assistance include:

- rash
- itching or swelling, especially of the face, tongue, or throat

- severe dizziness
- trouble breathing

Interactions

The doctor and pharmacist should be informed of all prescription and nonprescription medicines, vitamins, minerals, herbs, and dietary supplements being used. Patients should not start, stop, or change dosages of any medicines without their doctor's approval. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of emergency.

Drugs

Patients should check the labels on all medications—such as cough-and-cold products, diet aids, and nonsteroidal anti-inflammatory drugs (NSAIDs) such as **ibuprofen** and **naproxen**—because they may contain ingredients that can raise blood pressure or worsen heart failure. Other drugs that can interact with valsartan/HCTZ include:

- **aspirin** and other NSAIDs
- drugs that can increase blood potassium levels, including potassium-sparing diuretics such as **amiloride**, **spironolactone**, and **triamterene**; angiotensin-converting enzyme (ACE) inhibitors such as **benazepril** and **lisinopril**; and **oral contraceptives** containing **drospirenone**
- other RAAS-blocking drugs such as ACE inhibitors or other ARBs
- other diuretics
- other medications for treating high blood pressure or heart problems
- **aliskiren**
- **barbiturates** such as **phenobarbital** and **secobarbital**
- **cholestyramine**
- **colestipol**
- **corticosteroids** such as **betamethasone**, **budesonide**, **cortisone**, **dexamethasone**, **fludrocortisone**, **hydrocortisone**, **methylprednisolone**, **prednisolone**, **prednisone**, and **triamcinolone**
- **corticotropin**
- selective COX-2 inhibitors such as **celecoxib**
- **cyclosporine**
- **dofetilide**
- **insulin** and oral diabetes medications
- **lithium**
- **pain medications**
- **rifampin**
- **ritonavir**

Herbs and supplements

Potassium supplements may interact with valsartan/HCTZ.

Food and other substances

Patients should follow prescribed low-salt or low-sodium diets but should not use salt substitutes containing potassium without consulting their doctor. Patients may be instructed to eat potassium-rich foods, such as bananas, prunes, raisins, and orange juice. Alcoholic beverages should be limited while taking valsartan/HCTZ.

Resources

PERIODICALS

Bays, Harold, Dingliang Zhu, and Helmut Schumacher.

"Single-Pill Combination of Telmisartan and Hydrochlorothiazide: Studies and Pooled Analyses of Earlier Hypertension Treatment." *High Blood Pressure & Cardiovascular Prevention* 21, no. 2 (2014): 119–26.

"Drugs to Treat Hypertension." *Journal of Psychosocial Nursing & Mental Health Services* 52, no. 2 (2014): 11–12.

"Drugs to Treat Hypertension." *Journal of Psychosocial Nursing & Mental Health Services* 53, no. 2 (2015): 21–22.

WEBSITES

MedlinePlus. "Hydrochlorothiazide." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682571.html> (accessed March 10, 2015).

MedlinePlus. "Valsartan." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a697015.html> (accessed March 10, 2015).

U.S. Food and Drug Administration. "High Blood Pressure—Medicines to Help You." FDA.gov. <http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118594.htm> (accessed March 10, 2015).

"Valsartan/Hydrochlorothiazide (Rx)." Medscape.com. <http://reference.medscape.com/drug/diovan-hct-valsartan-hydrochlorothiazide-342341#91> (accessed March 10, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Valtrex see **Valacyclovir**

Vardenafil

Definition

Vardenafil hydrochloride is an oral drug for treating erectile dysfunction (ED). It is an impotence agent in the phosphodiesterase-5 (PDE5) inhibitor drug family.

Purpose

When used as directed, vardenafil and other PDE5 inhibitors are safe and effective for treating ED, which is the consistent inability to achieve or maintain an erection. ED affects an estimated 15–30 million men in the United States and about 70% of men ages 70 and older. PDE5 inhibitors such as vardenafil have success rates of 70%–80%, although results vary with the individual. Vardenafil is effective within 30–60 minutes, and its effects last for four to five hours. With sexual stimulation, men with ED should be able to achieve an erection sufficient for sexual satisfaction within this time period. Vardenafil may be prescribed for other purposes.

Description

When men become sexually aroused, nitric oxide (NO) is released from specialized cells. NO causes the formation of cyclic guanosine monophosphate (cGMP), which dilates the blood vessels of the penis and relaxes the penile muscles, allowing increased blood flow and erection. Compression of the dilated blood vessels against the firm outer lining of the penis prevents the blood from escaping and perpetuates the erection. PDE5 is an enzyme produced in the lungs and elsewhere in the body that causes the breakdown of cGMP and returns the penis to its flaccid state. Vardenafil and other PDE5



Levitra (vardenafil), 10 mg. (U.S. National Library of Medicine, Pillbox)

inhibitors decrease PDE5 activity so that more cGMP is available to achieve and maintain an erection.

Vardenafil is very similar to **sildenafil** (Viagra) in its chemical structure and effects. Its chemical structure differs from the drug **tadalafil** (Cialis), which lasts much longer than vardenafil and can also be taken on a once-daily basis without regard to the timing of sexual activity.

U.S. brand names

The U.S. brand names for vardenafil hydrochloride are Levitra for conventional tablets and Staxyn for orally disintegrating tablets.

Canadian and international brand names

Vardenafil is marketed as Levitra in Canada and most other countries. Other brand names include:

- Vardenafil GMP
- Fiable
- Barafil
- Vivanza
- Yaila

Origins

Levitra (vardenafil hydrochloride) was first approved by the U.S. Food and Drug Administration (FDA) in 2003 as 2.5, 5, 10, and 20 milligram (mg) film-coated oral tablets. Staxyn was approved as orally disintegrating 10 mg tablets in 2010. Generic vardenafil hydrochloride manufactured by Teva Pharmaceuticals was approved in 2012 as 2.5 mg, 5 mg, 10 mg, and 20 mg tablets.

Recommended dosage

The usual initial dosage of vardenafil is 10 mg about 60 minutes before sexual activity. The dosage may be increased to 20 mg or decreased to 5 mg depending on effectiveness and side effects. The maximum dose is 20 mg once in 24 hours. Dosages of rapidly disintegrating tablets cannot be adjusted, so doses other than 10 mg require regular tablets. The orally disintegrating tablets provide a higher systemic (body-wide) dose and so are not interchangeable with 10 mg regular tablets. Vardenafil should not be taken more than once every 24 hours. It should be stored at room temperature and away from excess heat and moisture (not in the bathroom).

The blisterpack for rapidly disintegrating tablets should be examined for defects before taking the first dose. The package includes directions for removing the tablets. The tablets should not be pushed through the foil. After removal from the package, the tablet should be immediately placed on the tongue and the mouth closed.

KEY TERMS

Alpha-blockers—Drugs for treating high blood pressure and other conditions.

Angina—Chest pain that occurs when diseased blood vessels restrict the flow of blood to the heart.

Cyclic guanosine monophosphate (cGMP)—A second messenger in the body that, among many other functions, enables the achievement and maintenance of penile erections; vardenafil slows its breakdown.

Cytochrome P450 3A4 (CYP3A4) inhibitors—Substances, such as a drug or grapefruit juice, that inhibit a liver enzyme that is required to metabolize and detoxify drugs such as vardenafil.

Erectile dysfunction (ED)—Impotence; the consistent inability to achieve or maintain a penile erection.

Levitra—The brand name of vardenafil tablets.

Nitric oxide (NO)—A regulator of various bodily processes, including penile erection.

Phosphodiesterase-5 (PDE5)—An enzyme that interferes with penile erections by breaking down cGMP; inhibited by vardenafil.

Ritonavir—An antiviral drug that inhibits cytochrome P450 and can prevent drugs such as vardenafil from being properly metabolized.

Staxyn—The brand name for vardenafil rapidly dissolving oral tablets.

The tablet will dissolve quickly. It should not be taken with water or other liquid.

Geriatric

The initial dose for patients 65 and older is 5 mg as needed, but no more than once in 24 hours.

Other conditions and allergies

No dose adjustment is necessary for mild liver dysfunction. For moderate dysfunction, the dose is 5 mg no more than once per day, with a maximum dose of 10 mg. Vardenafil should not be used by patients with severe liver dysfunction.

The initial vardenafil dosage for patients on stable alpha-blocker therapy is 5 mg no more than once daily. Vardenafil should not be initiated with orally disintegrating tablets, although patients on alpha-blockers may be switched to orally disintegrating tablets if they have

previously used the regular tablets. Alpha-blockers and vardenafil should be taken at least four hours apart.

For patients taking cytochrome P450 3A4 inhibitors:

- with ritonavir, no more than 2.5 mg vardenafil in a 72-hour period
- with indinavir, saquinavir, atazanavir, **clarithromycin**, or 400 mg daily of **ketoconazole** or itraconazole, no more than 2.5 mg in a 24-hour period
- with **erythromycin** or 200 mg daily of ketoconazole or itraconazole, no more than 5 mg in a 24-hour period

Precautions

Some precautions while taking vardenafil include:

- Vardenafil does not cure ED, increase sexual desire, or prevent pregnancy or the spread of sexually transmitted diseases.
- Sexual stimulation is necessary for vardenafil response.
- PDE5 inhibitors cannot treat ED occurring after radiation therapy for prostate cancer.
- Sexual activity can strain the heart; if chest pain occurs, patients should refrain from further activity and seek immediate medical attention.
- All healthcare providers should be informed of vardenafil usage, especially before any surgery, including dental surgery.
- Patients requiring emergency treatment for a heart problem must tell medical personnel of their last use of vardenafil.
- Vardenafil may cause postural hypotension (low blood pressure on standing up).
- Vardenafil should be stopped and medical attention sought in case of sudden loss of vision in one or both eyes or decrease or loss of hearing.
- The doctor should be informed if vardenafil is not effective or if side effects occur.
- Symptoms of vardenafil overdose include back or muscle pain and blurred vision.
- Disreputable online pharmacies may offer illegal generic vardenafil that is potentially unsafe.

Pediatric

Vardenafil is not intended for use in pediatric patients.

Pregnant or breastfeeding

Vardenafil is only for men. Women should not take vardenafil, especially if they are pregnant, could become pregnant, or are breastfeeding.

Other conditions and allergies

Patients with heart disease or low blood pressure should have a thorough examination before being prescribed vardenafil. Patients taking nitroglycerine or other organic nitrates cannot take vardenafil. Vardenafil and other ED drugs are less effective in men with damaged arteries or nerves from prostate surgery, diabetes, or cardiovascular disease.

Vardenafil should not be used by patients undergoing kidney dialysis.

Patients should tell their doctor and pharmacist if they are allergic to vardenafil or any other medications. They should tell their doctors if they smoke, have ever been advised to refrain from sexual activity for medical reasons, or have or have ever had:

- an erection lasting more than four hours
- a condition that affects the shape of the penis, such as angulation, cavernosal fibrosis, or Peyronie's disease
- diabetes
- high cholesterol
- high or low blood pressure
- irregular heartbeat
- heart attack
- angina
- stroke
- stomach or intestinal ulcers
- bleeding disorders
- blood cell disorders such as sickle cell disease, multiple myeloma, or leukemia
- seizures
- liver, kidney, or heart disease
- long QT syndrome or retinitis pigmentosa or family members with these conditions
- severe vision loss, especially vision loss caused by a blockage of blood flow
- phenylketonuria, since rapidly disintegrating vardenafil tablets are sweetened with aspartame, which is a source of phenylalanine
- fructose intolerance, since rapidly disintegrating vardenafil tablets are sweetened with sorbitol

Side effects

The most common side effects of vardenafil and other ED drugs are, in order of decreasing frequency:

- headache
- flushing
- upset stomach
- nasal congestion

- urinary tract infections
- vision problems, especially blue-tinged vision
- diarrhea
- dizziness
- rash

The doctor should be consulted if any of the following symptoms are severe or persistent:

- headache
- upset stomach
- heartburn
- flushing
- stuffy or runny nose
- flulike symptoms

Serious side effects that require immediate medical attention include:

- an erection lasting longer than four hours
- blurred vision
- changes in color vision, such as a blue tinge, indistinguishable blues and greens, or poor night vision
- sudden severe vision loss
- dizziness
- ringing in the ears
- sudden decrease or loss of hearing, usually in one ear, which may be permanent
- swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs
- hoarseness
- difficulty breathing or swallowing
- fainting
- hives
- rash

Interactions

The doctor and pharmacist should be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Drugs

Many drugs can interact with vardenafil. Vardenafil cannot be taken with nitrates for heart conditions because they can cause a dangerous drop in blood pressure. Nitrates come in many forms and include isosorbide dinitrate (Isordil), **isosorbide mononitrate** (Imdur, ISMO), and **nitroglycerin** (Nitro-BID, Nitro-Dur, Nitroquick, Nitrostat, and others). Vardenafil cannot be used by people

taking street drugs containing nitrates, such as amyl nitrate or butyl nitrate (“poppers”). Many men take alpha-blockers for urinary symptoms, and these can lower blood pressure. Alpha-blockers include alfuzosin (Uroxatral), doxazosin (Cardura), prazosin (Minipress), **tamsulosin** (Flomax), and terazosin (Hytrin). Tamsulosin has less effect on blood pressure than other alpha-blockers.

Other drugs that may require changing dosages or monitoring for side effects include:

- amiodarone (Cordarone, Pacerone)
- antifungals such as **fluconazole** (Diflucan), itraconazole (Sporanox), and ketoconazole (Nizoral)
- clarithromycin (Biaxin)
- disopyramide (Norpace)
- erythromycin (E.E.S., E-Mycin, Erythrocin)
- **haloperidol** (Haldol)
- HIV protease inhibitors including atazanavir (Reyataz), indinavir (Crixivan), ritonavir (Norvir, in Kaletra), and saquinavir (Fortovase, Invirase)
- medications for high blood pressure or irregular heartbeat
- other medications or treatments for ED
- **methadone** (Dolophine)
- **moxifloxacin** (Avelox)
- pimozide (Orap)
- procainamide (Procanbid, Pronestyl)
- quinidine (Quinidex)
- **sotalol** (Betapace)
- thioridazine
- verapamil (Calan, Covera, Isoptin, Verelan)

Herbs and supplements

The herbal supplement St. John’s wort can interact with vardenafil.

Food and other substances

Vardenafil is not well absorbed if taken after a meal. Patients should ask their doctor about consuming grapefruit or grapefruit juice while taking vardenafil.

Resources

PERIODICALS

“ED Drugs after Cancer Treatment Don’t Protect Erectile Function.” *Harvard Men’s Health Watch* 18, no. 12 (2014): 8.

Hartmann, Uwe, Jens Ulrich Hanisch, and Andreas Mattern. “The Real-Life Perception of Efficacy, Attitude, Satisfaction and Safety of Vardenafil Therapy (REPEAT): A Prospective, Non-Interventional, Observational Study.” *Aging Male* 17, no. 2 (2014): 117–24.

WEBSITES

- MedlinePlus. "Vardenafil." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a603035.html> (accessed February 28, 2015).
- National Kidney and Urologic Diseases Information Clearinghouse. "What I Need to Know about Erectile Dysfunction." National Institutes of Health. http://kidney.niddk.nih.gov/KUDiseases/pubs/ED_EZ/index.aspx#vardenafil (accessed February 28, 2015).
- Spark, Richard F. "What Is Men's Endocrine Health?" American Association of Clinical Endocrinologists. <http://www.empoweryourhealth.org/mens-endocrine-health> (accessed February 28, 2015).
- U.S. Food and Drug Administration. "Hidden Risks of Erectile Dysfunction 'Treatments' Sold Online." <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048386.htm> (accessed February 28, 2015).
- "Vardenafil Dosage." Drugs.com. <http://www.drugs.com/dosage/vardenafil.html> (accessed February 28, 2015).

ORGANIZATIONS

- American Association of Clinical Endocrinologists, 245 Riverside Avenue, Suite 200, Jacksonville, FL 32202. contact@empoweryourhealth.org, <http://www.empoweryourhealth.org/>.
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 9000 Rockville Pike, Bethesda, MD 20892-2560, (301) 496-3583, <http://www.niddk.nih.gov/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY JAMES E. WAUN, MD, RPH

Varenicline

Definition

Varenicline is an oral medication for helping smokers quit. It is in the drug class of smoking-cessation aids.

Purpose

Quitting smoking can lower the risk of lung disease, heart disease, and certain types of cancer. Varenicline, **bupropion**, and nicotine-replacement therapy (NRT) are first-line treatments for helping reduce nicotine withdrawal symptoms and the urge to smoke. Varenicline is considered the most effective smoking-cessation drug, with a six-month success rate of about 35%, compared with less than 30% for other treatments, including NRT and behavioral therapies. A study published in 2014



Chantix (varenicline), 0.5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

found that English smokers who used medication (varenicline, bupropion, or NRT) in combination with specialist behavioral counseling were almost three times more likely to have quit smoking after six months than participants who did not use medication or counseling. Another 2014 study reported that varenicline in combination with NRT was more effective than varenicline alone for tobacco abstinence at the end of 12 weeks of treatment and at three months after the end of treatment. Finally, a 2014 Canadian study reported that both standard and extended courses of varenicline were significantly cost-effective compared with other smoking-cessation interventions and could provide significant healthcare savings.

About half of smokers who seek treatment for quitting have a history of depression, and depressed smokers are known to have a harder time quitting and high relapse rates. A 2013 study reported that varenicline may help some smokers with depression quit, without worsening depression or anxiety. Furthermore, the results of an 18-month-long clinical trial reported in 2014 that varenicline helped outpatients with schizophrenia and bipolar disorder abstain from smoking. This is important because severe psychiatric disorders increase susceptibility to tobacco addiction and make it harder to quit. Although treatment and prevention have cut smoking by nearly 50% in the general population, smoking prevalence among people with psychiatric illnesses has

remained about the same. The U.S. Substance Abuse and Mental Health Services Administration (SAMHSA) estimates that 53% of adults with serious mental disorders smoke, compared with 18% of adults in the overall population, and tobacco-related illnesses are the primary reason that people with mental disorders die, on average, 25 years sooner than people in the general population.

Off-label use

Varenicline may be prescribed for other purposes. For example, a study by the National Institute on Alcohol Abuse and Alcoholism found that varenicline significantly reduced alcohol cravings and consumption in alcohol-dependent adults.

Description

Varenicline is a molecule that is similar in structure to nicotine and binds to alpha-4 beta-2 nicotinic acetylcholine receptors (nAChR) in the brain. Cigarette smoking saturates these receptors, and varenicline competitively competes with nicotine for binding to the receptors. Varenicline is both a partial antagonist and a partial agonist of alpha-4 beta-2 nAChR. As a partial antagonist, it blocks the pleasant effects of nicotine on the brain. Even if people do not stop smoking or start again after quitting, smoking is less pleasurable while taking varenicline. As a partial agonist, varenicline mimics the effects of nicotine. Nicotine binding to alpha-4 beta-2 nAChR stimulates the production of high levels of dopamine in the brain. Varenicline binding stimulates moderate levels of dopamine—32%–60% of the dopamine response to nicotine—to counteract nicotine cravings and withdrawal symptoms. It is this combination of antagonistic and agonistic activities that makes varenicline effective. Varenicline also binds with moderate affinity to serotonin receptors, which may account for the nausea that can occur with the drug.

U.S. brand names

The U.S. brand name for varenicline is Chantix. The Canadian and international brand name is Champix.

Origins

Varenicline is the first alpha-4 beta-2 nAChR partial agonist for smoking cessation. It was developed based on cytisine, a nicotine substitute derived from laburnum seeds that has been widely used for many years as a smoking-cessation aid in Central and Eastern Europe. Varenicline tartrate, as Chantix, was approved by the U.S. Food and Drug Administration (FDA) in 2006.

KEY TERMS

Alpha-4 beta-2 nicotinic acetylcholine receptors (nAChR)—Nicotine receptors in the brain that bind varenicline.

Agonist—A drug, such as varenicline, that binds to a receptor, such as a nicotine receptor, and has activity similar to the binding of the endogenous substance (nicotine).

Antagonist—A drug, such as varenicline, that blocks the action of a substance, such as nicotine, by binding to its receptor.

Boxed warning—A warning label required by the U.S. Food and Drug Administration (FDA) for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

Bupropion—Zyban; Wellbutrin; an antidepressant and smoking-cessation medication.

Chantix—The brand name for varenicline.

Cytisine—A plant alkaloid that binds nicotinic acetylcholine receptors and has been widely used as a smoking-cessation aid in Eastern Europe.

Dopamine—A neurotransmitter in the brain that is stimulated by nicotine and varenicline.

Nicotine replacement therapy (NRT)—Over-the-counter and prescription products that supply low doses of nicotine as smoking-cessation aids.

Off-label use—The use of a prescription medication to treat conditions outside the indications approved by the FDA. It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

Receptor—A molecule, usually a protein, inside or on the surface of a cell, that binds a specific substance to initiate a series of events.

Serotonin—A neurotransmitter and strong vasoconstrictor that is found primarily in the brain and blood and that binds varenicline.

Varenicline is available as 0.5 milligram (mg) white oral tablets and 1 mg blue tablets. The tablets are stored at room temperature, in the tightly closed container they are supplied in and away from excess heat and moisture (not in the bathroom).

Recommended dosage

The recommended dosage of varenicline is 0.5 mg once daily for three days, followed by 0.5 mg every 12 hours for four days, followed by 1 mg every 12 hours for 11 weeks. Patients who have successfully quit smoking after 12 weeks can continue to take varenicline for another 12 weeks, at 1 mg every 12 hours, to help prevent relapse. There are two ways to quit smoking with varenicline: patients can choose a quit date and start taking varenicline seven days before that date, or patients can start taking varenicline and then pick a quit date between 8 and 35 days after starting treatment. It can take several weeks for varenicline to exert its full benefit, and both methods enable it to build up in the body before attempting to quit. If patients smoke after their quit day, they should continue to take varenicline and try not to smoke. Side effects may require a temporary or permanent dose reduction.

Varenicline is taken with a full 8 ounce (240 milliliters) glass of water after a meal. When taking it twice daily, one dose should be taken in the morning and the other in the evening, at about the same times each day. A missed dose should be taken as soon as possible, unless it is almost time for the next dose, in which case the dose should be skipped and the regular schedule resumed.

Other conditions and allergies

Patients with severe kidney impairment should start at 0.5 mg once daily. This may be increased to 0.5 mg every 12 hours. Dosage should not exceed 0.5 mg once daily for patients with end-stage renal disease on hemodialysis.

Precautions

Varenicline comes with a boxed warning due to the risk of psychiatric effects:

- Some people have experienced behavioral changes, hostility, agitation, depression, and suicidal thoughts while taking varenicline. Although nicotine withdrawal—with or without medication—can cause changes in mental health, some people have experienced these symptoms while taking varenicline and continuing to smoke. These symptoms have developed when first taking varenicline, after several weeks on the drug, or after stopping the drug. Symptoms have occurred in patients with no history of mental illness, and worsening symptoms have occurred in patients with a mental illness.
- Patients should tell their doctors if they have ever had depression, bipolar disorder, schizophrenia, or other mental illness.

- Patients should stop taking varenicline and call their doctor immediately if they experience suicidal thoughts or actions, new or worsening depression, anxiety, panic attacks, agitation, restlessness, angry or violent behavior, dangerous actions, mania, abnormal thoughts or sensations, hallucinations, paranoia, confusion, or any other sudden or unusual changes in behavior, thoughts, or mood.
- Family members or caregivers should be aware of these serious symptoms, so that they can call the doctor if patients are unable to seek help on their own.
- Patients with such symptoms should be closely monitored until symptoms resolve.

Other precautions concerning varenicline include:

- The drug may cause drowsiness, dizziness, difficulty concentrating, or loss of consciousness. Patients should not drive, operate machinery, or perform other activities that require alertness until they know how the drug affects them. There have been reports of traffic accidents and injuries in people taking varenicline.
- The doctor should be informed of any other smoking-cessation treatments being used.
- Varenicline is more likely to be effective if patients receive information and support for smoking cessation.
- Varenicline has been linked to increased risk of heart attack, stroke, and other serious heart or blood vessel problems. However, a 2014 review concluded that varenicline and other smoking cessation aids are less of a cardiovascular risk than continuing to smoke.

Pediatric

Varenicline should not be used by children under age 18.

Pregnant or breastfeeding

Varenicline is in the FDA pregnancy category C—it is not known whether it poses harm to the fetus but should be used during pregnancy only if benefits outweigh risks. Women should contact their doctor if they become pregnant while taking varenicline. It is not known whether varenicline passes into breast milk, but it should not be used while breastfeeding.

Other conditions and allergies

Patients should tell their doctor and pharmacist if they are allergic to varenicline or any other medications. Patients should tell their doctor if they drink alcohol and if they have:

- ever had depression or other mental health problems
- experienced symptoms in previous attempts to quit smoking

- kidney, heart, or blood vessel problems
- a history of seizures
- any other medical conditions

Cardiovascular symptoms have occurred primarily in people with pre-existing cardiovascular conditions. Symptoms that require stopping varenicline and getting emergency medical assistance include:

- chest discomfort that lasts more than a few minutes or goes away and returns
- shortness of breath, sweating, nausea, vomiting, or light-headedness associated with chest discomfort
- discomfort or pain in one or both arms, back, neck, jaw, or stomach
- leg pain while walking
- sudden weakness or numbness in an arm or leg, especially on one side of the body
- difficulty moving an arm or leg
- slow or difficult speech

Symptoms of a severe allergic reaction to varenicline include:

- swelling of the face, throat, tongue, lips, gums, eyes, neck, hands, arms, feet, ankles, or lower legs
- hoarseness
- difficulty swallowing or breathing
- rash
- swollen, red, peeling, or blistering skin
- mouth blisters

Side effects

Varenicline is well tolerated by most people, and adverse effects are uncommon. The most common side effects include:

- nausea
- vomiting
- constipation
- gas
- trouble sleeping or vivid, unusual, or strange dreams or nightmares

Patients should inform their doctors if any of the above or following side effects are severe or persistent:

- headaches
- sleepiness
- bad taste in the mouth
- heartburn
- increased or decreased appetite

Patients should stop taking varenicline and call their doctor immediately if mental health problems occur or worsen or if they have a seizure. Most seizures have occurred during the first month of treatment. Symptoms of nicotine withdrawal, with or without varenicline, include:

- urge to smoke
- trouble sleeping
- depression
- irritability
- frustration
- anger
- anxiety
- difficulty concentrating
- restlessness
- decreased heart rate
- increased appetite or weight gain
- suicidal thoughts

Interactions

The doctor and pharmacist should be informed of all prescription and over-the-counter medications, vitamins, minerals, and herbal and dietary supplements being taken by the patient, as well as any new medicines added during treatment. Patients should bring a list of all of these to all medical appointments and carry the list in case of emergency. It may be necessary to change dosages of other medications once a patient stops smoking.

Drugs

Varenicline should not be used in combination with other smoking cessation medications, including bupropion and nicotine patches, gums, inhalers, nasal sprays, or lozenges. Using varenicline with a nicotine patch may cause more frequent nausea, vomiting, headache, dizziness, upset stomach, and tiredness. Other drugs that may interact with varenicline include anticoagulants (blood thinners) such as **warfarin**, insulin, and theophylline.

Food and other substances

Patients should decrease their alcohol consumption until they know how varenicline affects alcohol tolerance. When combining alcohol with varenicline, some people have experienced:

- increased intoxication
- unusual and sometimes aggressive behavior
- no memory of events

Resources

BOOKS

- Cobb, N. K., D. Mays, and A. L. Graham. "Sentiment Analysis to Determine the Impact of Online Messages on Smokers' Choices to Use Varenicline." *Cancer Prevention and Control in the Changing Communication Landscape*, edited by the Behavioral Research Program of the National Cancer Institute Division of Cancer Control and Population Sciences and the Health Communication and Informatics Research Branch. Cary, NC: Oxford University Press, 2013.
- Stahl, Stephen M. *Stahl's Essential Psychopharmacology: Prescriber's Guide*. 5th ed. New York: Cambridge University, 2014.

PERIODICALS

- Anthenelli, R. M., et al. "Effects of Varenicline on Smoking Cessation in Adults with Stably Treated Current or Past Major Depression. A Randomized Trial." *Annals of Internal Medicine* 159, no. 6 (2013): 390–400.
- Hartmann-Boyce, Jamie, et al. "Efficacy of Interventions to Combat Tobacco Addiction: Cochrane Update of 2013 Reviews." *Addiction* 109, no. 9 (2014): 1414–25.
- Koegelenberg, Coenraad F. N., et al. "Efficacy of Varenicline Combined with Nicotine Replacement Therapy vs. Varenicline Alone for Smoking Cessation: A Randomized Clinical Trial." *Journal of the American Medical Association* 312, no. 2 (2014): 155–61.
- Kotz, Daniel, Jamie Brown, and Robert West. "Prospective Cohort Study of the Effectiveness of Smoking Cessation Treatments Used in the 'Real World.'" *Mayo Clinic Proceedings* 89, no. 10 (2014): 1360–67.
- Kotz, Daniel, Jamie Brown, and Robert West. "'Real World' Effectiveness of Smoking Cessation Treatments: A Population Study." *Addiction* 109, no. 3 (2014): 491–99.
- Rowland, Kate. "Review: Nicotine Replacement Therapy Increases CVD Events; Bupropion and Varenicline Do Not." *Annals of Internal Medicine* 160, no. 8 (2014): JC2.
- Wartburg, M., V. Raymond, and P. E. Paradis. "The Long-Term Cost-Effectiveness of Varenicline (12-Week Standard Course + 12-Week Extended Course) vs. Other Smoking Cessation Strategies in Canada." *International Journal of Clinical Practice* 68, no. 5 (2014): 639–46.

WEBSITES

- American Cancer Society. "Guide to Quitting Smoking." <http://www.cancer.org/acs/groups/cid/documents/webcontent/002971-pdf.pdf> (accessed February 28, 2015).
- HealthDay News. "Two-Pronged Program Looks Best for Helping Smokers Quit." <http://consumer.healthday.com/general-health-information-16/prescription-drug-news-551/combo-program-best-for-helping-smokers-quit-692538.html> (accessed February 28, 2015).
- MedlinePlus. "Smoking Cessation Medications." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/ency/article/007439.htm> (accessed February 28, 2015).
- MedlinePlus. "Varenicline." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a606024.html> (accessed February 28, 2015).

- Sarlin, Eric. "Varenicline Helps People with Mental Illness Maintain Abstinence from Smoking." DrugAbuse.gov. <http://www.drugabuse.gov/news-events/nida-notes/2014/11/varenicline-helps-people-mental-illness-maintain-abstinence-smoking> (accessed February 28, 2015).
- Smokefree Women. "Medication Guide." <http://women.smokefree.gov/medication-guide.aspx> (accessed February 28, 2015).
- Pfizer Labs. "Medication Guide Chantix (Varenicline) Tablets." U.S. Food and Drug Administration. <http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088569.pdf> (accessed February 28, 2015).
- U.S. Food and Drug Administration. "Smoking—Medicines to Help You Quit." <http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118667.htm> (accessed February 28, 2015).

ORGANIZATIONS

- American Cancer Society, 250 Williams Street NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org/>.
- National Institute on Drug Abuse, Office of Science Policy and Communications, Public Information and Liaison Branch, 6001 Executive Boulevard, Room 5213, MSC 9561, Bethesda, MD 20892-9561, (301) 443-1124, <http://www.drugabuse.gov/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY KEVIN GLAZA, RPH

Vasotec see **Enalapril**

Venlafaxine

Definition

Venlafaxine is an antidepressant. It belongs to a class of drugs called serotonin and norepinephrine reuptake inhibitors (SNRIs).

Purpose

Venlafaxine is used to treat depression and generalized anxiety disorder. It has also been used to treat obsessive-compulsive disorder and irritable bowel syndrome.

Description

Venlafaxine has actions common to both the cyclic antidepressants, such as **imipramine** (Tofranil) and



Effexor XR (venlafaxine), 75 mg. (© Cengage Learning®.)

amitriptyline (Elavil), and the selective serotonin reuptake inhibitors (SSRIs), such as **fluoxetine** (Prozac), **sertraline** (Zoloft), and **paroxetine** (Paxil). When a nerve cell is triggered, it releases a neurotransmitter that carries the nerve impulse across a gap to the next nerve cell. The neurotransmitter is then reabsorbed by the releasing cell. It is believed that venlafaxine works by slowing the reabsorption of the neurotransmitters norepinephrine and serotonin, thus increasing their levels in the brain. Low levels of these neurotransmitters are thought to play a role in depression and certain other mental disorders.

The therapeutic effects of venlafaxine, like other antidepressants, appear slowly. Maximum benefit often is not evident for at least two weeks after starting the drug. People taking venlafaxine should be aware of this and continue taking the drug as directed even if they do not see immediate improvement.

Venlafaxine is available in 25, 37.5, 50, 75, and 100 milligram (mg) rapid-release tablets and 75 mg and 150 mg extended-release capsules.

U.S. brand names

Venlafaxine is available in the United States under the brand names of Effexor and Effexor XR.

Recommended dosage

The usual recommended initial dosage of venlafaxine is 75 mg daily taken as two or three equal doses. The dosage may be increased in 75 mg increments every four days as needed until symptoms of depression or anxiety resolve. Most dosages range between 150 mg and 225 mg daily, although in severe situations 375 mg per day may be needed. Once patients are stabilized using the rapid-acting tablets, they may be converted over to the appropriate dose of extended-release capsules.

Other conditions and allergies

Venlafaxine is broken down by the liver and eliminated from the body by the kidneys. As a result, the dosage of venlafaxine must be lowered in people with liver or kidney disease. In people with liver disease, the daily dosage of venlafaxine normally should be cut in half. In patients with kidney disease, the daily dosage of venlafaxine should be reduced by 25%–50%, depending upon the extent of kidney damage. When stopping venlafaxine, the dosage should be reduced gradually over a period of at least two weeks before the drug is totally stopped.

Precautions

Patients taking venlafaxine should be monitored closely for insomnia, anxiety, mania, significant weight loss, seizures, and thoughts of suicide. Children and adults up to age 24 are at increased risk for developing suicidal thoughts and behaviors when taking an antidepressant drug, including venlafaxine. Patients of any age who are taking antidepressants should be monitored for signs of worsening depression or changes in behavior.

Until individuals understand the effects that venlafaxine may have, they should avoid driving, operating dangerous machinery, or participating in hazardous activities. Alcohol should not be used while taking venlafaxine. Before discontinuing venlafaxine, patients should consult a physician. Dosage should be tapered, rather than halted abruptly; otherwise, patients may experience antidepressant discontinuation syndrome, which usually results in withdrawal symptoms shortly after discontinuation.

Caution should be exercised when prescribing venlafaxine to patients over age 60 and to children.

Pregnant or breastfeeding

Care should be taken to weigh the risks and benefits of this drug in women who are or wish to become

KEY TERMS

Depression—A mental state characterized by excessive sadness. Other symptoms include altered sleep patterns, thoughts of suicide, difficulty concentrating, agitation, lack of energy, and loss of enjoyment in activities that are usually pleasurable.

Generalized anxiety disorder—A general form of fear that can dominate a person's life.

Insomnia—A sleep disorder characterized by waking in the middle of the night and having difficulty returning to sleep or waking too early in the morning.

Mania—An elevated or euphoric mood or irritable state that is characteristic of bipolar disorder.

Narrow-angle glaucoma—An eye disorder caused by a buildup of fluid pressure inside the eyeball due to an abnormally small angle between the iris (the colored portion of the eye) and the cornea (the transparent front part of the eye).

Neurotransmitter—One of a group of chemicals secreted by a nerve cell (neuron) to carry a chemical message to another nerve cell, often as a way of transmitting a nerve impulse. Examples of neurotransmitters include acetylcholine, dopamine, serotonin, and norepinephrine.

Norepinephrine—A chemical messenger in the brain thought to play a role in mood regulation.

Obsessive-compulsive disorder—A disorder in which affected individuals have an obsession (such as a fear of contamination or thoughts they do not like to have and cannot control) and feel compelled to perform certain acts to neutralize the obsession (such as repeated hand-washing).

Pregnancy category C—No adequate human or animal studies, or adverse fetal effects in animal studies but no available human data.

Seizure—A convulsion, or uncontrolled discharge of nerve cells that may spread to other cells throughout the brain.

Serotonin—A chemical messenger in the brain thought to play a role in mood regulation.

Serotonin syndrome—A condition characterized by at least three of the following symptoms: diarrhea, fever, extreme perspiration, mood or behavior changes, overactive reflexes, fast heart rate, restlessness, shivering, or shaking. The condition occurs when there is too much serotonin in the body.

pregnant, as well as in breastfeeding mothers. The U.S. Food and Drug Administration (FDA) has categorized venlafaxine as a pregnancy category C drug. It should be taken during pregnancy only when benefits outweigh risks. Venlafaxine has been found in breast milk, but its effects, if any, on infants are not known.

Other conditions and allergies

Caution should also be exercised when prescribing venlafaxine to patients with impaired liver or kidney function, individuals with bipolar disorder or a history of seizures, people with diabetes, persons with narrow-angle glaucoma, and individuals expressing ideas of committing suicide. People with diabetes should monitor their blood or urine sugar more carefully, since venlafaxine may affect blood sugar.

Side effects

More common side effects associated with venlafaxine include decreased sexual drive, restlessness, difficulty sitting still, skin rash, hives, and itching. Less common

side effects include fever or chills and pain in joints or muscles.

Rare side effects include pain or enlargement of breasts or abnormal milk production in women, seizures, fast heart rate, irregular heartbeat, red or purple spots on the skin, low blood sugar and its symptoms (anxiety, chills, cold sweats, confusion, difficulty concentrating, drowsiness, excess hunger, rapid heart rate, headache, shakiness or unsteadiness, severe fatigue), low blood sodium and its symptoms (including confusion, seizures, drowsiness, dry mouth, severe thirst, decreased energy), serotonin syndrome (characterized by at least three of the following symptoms: diarrhea, fever, sweatiness, mood or behavior changes, overactive reflexes, fast heart rate, restlessness, shivering or shaking), excitability, agitation, irritability, pressured talking, difficulty breathing, and odd body or facial movements.

Interactions

Venlafaxine interacts with a long list of other medications. Individuals starting this drug should review the other medications they are taking with their physician

and pharmacist for possible interactions. Patients should always inform all of their healthcare providers, including dentists, that they are taking venlafaxine.

Drugs

Dangerously high blood pressure has resulted from the combination of antidepressants, such as venlafaxine, and members of another class of antidepressants known as monoamine oxidase inhibitors (MAOIs). Because of this, venlafaxine should never be taken in combination with MAOIs. Patients taking any MAOIs—for example, phenelzine (Nardil) or tranylcypromine (Parnate)—should stop taking the MAOI and wait at least 14 days before starting venlafaxine or any other antidepressant. When stopping treatment with venlafaxine, patients should wait five weeks before taking an MAOI.

Some other drugs—such as **trazodone** (Desyrel), **sibutramine** (Meridia), and **sumatriptan** (Imitrex)—also interact with venlafaxine and cause a syndrome known as neuroleptic malignant syndrome, characterized by irritability, muscle stiffness, shivering, muscle spasms, and altered consciousness.

The sedative effects (drowsiness or lack of mental clarity) of venlafaxine are increased by other central nervous system depressants such as sedatives, sleeping medications, or other medications used for mental disorders such as schizophrenia. Patients taking blood thinners, including **aspirin**, are at risk for increased bleeding when taking venlafaxine.

Food and other substances

Alcohol increases the sedative effects of venlafaxine.

Resources

BOOKS

Sadock, Benjamin, J., et al. *Kaplan & Sadock's Pocket Handbook of Psychiatric Drug Treatment*. 6th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2014.

Wegmann, Joseph. *Psychopharmacology: Straight Talk on Mental Health Medications*. 2nd ed. Eau Claire: PPM, 2012.

Resources

PERIODICALS

Mitchell, Ann M., et al. "Antidepressant Use in Children, Adolescents, and Young Adults: 10 Years after the Food and Drug Administration Black Box Warning." *Journal for Nurse Practitioners* 10, no. 3 (2014): 149–56.

Park, Susie H., and Risa Ishino. "Liver Injury Associated with Antidepressants." *Current Drug Safety* 8, no. 3 (2013): 207–23.

Resources

WEBSITES

MedlinePlus. "Venlafaxine." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a694020.html> (accessed February 28, 2015).

Micromedex. "Venlafaxine (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/venlafaxine-oral-route/description/drg-20067379> (accessed February 28, 2015).

Uddin, Rae. "Drug Side Effects of Effexor." Livestrong.com. <http://www.livestrong.com/article/88988-drug-side-effects-effexor> (accessed February 28, 2015).

ORGANIZATIONS

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, 888-35-PSYCH (77924), apa@psych.org, <http://www.psych.org/>.

Depression and Bipolar Support Alliance, 55 E. Jackson Boulevard, Suite 490, Chicago, IL 60604, (312) 642-0049, (800) 826-3632, Fax: (312) 642-7243, <http://www.dbsalliance.org/>.

Mental Health America, 2000 North Beauregard Street, 6th Floor, Alexandria, VA 22311, (703) 684-7722, (800) 969-6642, Fax: (703) 684-5968, <http://www.nmha.org/>.

National Institute of Mental Health, 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 443-4513, TTY (301) 443-8431, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nimh.nih.gov, <http://www.nimh.nih.gov/>.

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Ventolin see **Albuterol**

Verapamil SR

Definition

Verapamil SR is a sustained-release oral drug for treating high blood pressure (hypertension), angina (chest pain), and irregular heartbeat (arrhythmia or dysrhythmia). It is in the drug classes of calcium channel blockers (CCBs) and group IV antidysrhythmics (antiarrhythmics).



Verapamil hydrochloride ER (extended release), 100 mg.
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Purpose

Verapamil SR helps control—but does not cure—hypertension and angina. Blood pressure that is slightly above normal may be controllable with lifestyle changes such as diet, weight control, limiting alcohol, and quitting smoking or with diuretics; however, a CCB such as verapamil may be necessary for people with both high blood pressure and angina or who are at high risk for a heart attack or stroke. Verapamil may be used alone, but it is often used in combination with other drugs such as diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, or angiotensin receptor blockers (ARBs). It is not unusual for patients to take two or more drugs to control hypertension. Verapamil SR is also used alone or with other medications to prevent and treat an irregular heartbeat.

Verapamil SR may be used to treat other cardiovascular problems. It is sometimes used to treat cluster headaches and bipolar disorder or to prevent and treat migraines and vertigo caused by migraines. Cardiovascular and other problems may also be treated with immediate-release or intravenous (IV) verapamil.

Description

Verapamil is a non-dihydropyridine CCB and a coronary vasodilator. It works by inhibiting the influx of extracellular calcium ions across the membranes of heart

muscle cells and smooth muscle cells of the blood vessels (without affecting calcium concentrations in the blood serum). This inhibits heart and vascular smooth muscle contraction, which relaxes (dilates) the main coronary and systemic arteries. Dilation enables the blood to flow more easily, lowering blood pressure, and eases strain on the heart muscle. It also increases blood and oxygen to the heart and slows the conduction of electrical impulses in the heart, which decreases the force of contractions and slows the heart rate to prevent and control chest pain from angina. Although verapamil is less effective than beta-blockers for slowing heart rate, it is a safe and effective alternative to beta-blockers and is effective for variant (vasospastic) angina.

The antihypertensive effects of oral verapamil are usually evident within the first week, although it may take several weeks for full benefits to be realized. Patients may need to try more than one CCB to find what works best.

Verapamil SR tablets or capsules are usually taken once or twice a day, compared with three to four times a day for regular verapamil tablets. The medication is stored in the tightly closed container that it came in, at room temperature and away from excess heat and moisture (not in the bathroom).

U.S. brand names

U.S. brand names for verapamil SR include:

- Calan SR
- Covera-HS
- Verelan PM

Canadian brand names

Canadian brand names for verapamil SR include Covera-HS and Isoptin SR.

International brand names

Verapamil SR is available in many countries under various brand and generic names. More common brand names include:

- Isoprin SR
- Isoptin retard
- Veramex retard
- Verasal Retard
- Verogalid ER
- Veroptinstada retard

Origins

Verapamil hydrochloride (Calan) tablets were originally approved by the U.S. Food and Drug Administration (FDA) in 1984. Calan SR extended release was

approved in 1986 as 120 and 240 milligram (mg) tablets. Covera-HS 180 mg and 240 mg extended-release tablets were approved in 1996. Verelan 120 mg, 180 mg, 240 mg, and 360 mg extended-release capsules were approved in 1990. Verelan PM 100 mg, 200 mg, and 300 mg extended-release capsules were approved in 1998. There are various extended-release generic forms of verapamil available in multiple strengths, as well as combination medications containing extended-release verapamil and trandolapril.

Recommended dosage

Verapamil SR is taken at about the same time every day, in the morning or at bedtime. It is usually initiated at a low dose—and a lower dose for patients of small stature—and may be gradually increased. For example, the initial dose of extended-release Covera-HS for angina is 180 mg at bedtime, with a maintenance dose of 180–540 mg at bedtime. For hypertension:

- The Calan SR or Isoptin SR dosage is 120–180 mg once daily in the morning with food. Depending on weekly evaluations of blood pressure response and safety, the dose may be increased to 240 mg per day and then to 360 mg per day, as either 180 mg every 12 hours or 240 mg in the morning and 120 mg in the evening.
- The initial Covera-HS dose is 120–180 mg per day at bedtime, which may be increased to 240 mg per day and then increased by 120 mg per day at weekly intervals, not to exceed 480 mg daily.
- The initial sustained-release Verelan dosage is 120–240 mg once daily in the morning. To obtain the desired response, the dose may be increased to 240 mg daily, with additional increases of 120 mg per day at weekly intervals, not to exceed 480 mg per day. Safety and effectiveness should be evaluated about 24 hours after a dose.
- The initial Verelan PM dose is 100–200 mg per day at bedtime. It may be increased by 100 mg per day at weekly intervals as needed, not to exceed 400 mg per day.

For idiopathic hypertrophic subaortic stenosis, cluster headache, bipolar disorder, or migraine prevention, the usual initial dose of sustained-release tablets or capsules is 240 mg once daily at bedtime. The initial dose of Covera-HS is 180 mg once daily. Dosage may be adjusted at weekly intervals for maintenance.

Extended-release tablets and capsules are swallowed whole—not chewed or crushed. Some tablets can be split in half, but this varies with the verapamil product. Patients who cannot swallow extended-release capsules may carefully open the capsule and sprinkle

KEY TERMS

Angina—Chest pain that occurs when diseased blood vessels restrict the flow of blood to the heart.

Arrhythmia—Abnormality in the force or timing of the heartbeat.

Beta-blocker—A drug that slows heart rate and lowers blood pressure by blocking beta-receptors for the hormones adrenaline (epinephrine) and norepinephrine.

Calcium channel blocker (CCB)—A drug, such as verapamil, that lowers blood pressure and reduces heart rate by blocking the entry of calcium ions into smooth muscle cells.

Diuretic—“Water pill”; a medication that increases urine excretion and removes water and salt from the body, which helps lower blood pressure.

Dysrhythmia—Disordered rhythm in the electrical activity of the heart.

Hypertension—High blood pressure.

Sustained release (SR)—A dosage form that releases a drug slowly over an extended period of time.

the entire contents over a spoonful of applesauce that is not hot and can be swallowed immediately without chewing. This is followed by a glass of cool water to ensure that all the medication is swallowed. This mixture cannot be stored. A missed dose should be taken as soon as possible unless it is almost time for the next dose, in which case the dose should be skipped and the regular schedule resumed.

Geriatric

Geriatric patients generally take the lowest initial dose, which is subsequently adjusted based on clinical response. For angina, the initial dose of Covera-HS is 180 mg at bedtime, with a maintenance dose of 180–540 mg at bedtime. For hypertension, the initial dose of Covera-HS for hypertension is 120 mg per day at bedtime. The initial dose of Calan SR, Isoptin SR, and Verelan is 120 mg in the morning. The initial dose of Verelan PM is 100 mg per day at bedtime.

Other conditions and allergies

For liver cirrhosis, the verapamil dose should be reduced by 20%–50%. For renal (kidney) impairment, the Verelan PM manufacturer recommends an initial dose of 100 mg at bedtime. If creatinine clearance is less than

10 milliliters (mL) per minute, the dose should be reduced by 25%–50%. Creatinine is a waste material that is filtered out of the body by the kidneys; measuring the amount of creatinine in a patient's urine helps determine kidney function.

Precautions

Some precautions while taking verapamil include:

- Blood pressure should be checked regularly, and lab tests may be ordered to monitor response to verapamil.
- Patients should tell their doctor and dentist that they are taking verapamil before having any type of surgery.
- Patients should not stop taking verapamil without talking to their doctor.
- An empty tablet shell from extended-release tablets such as Covera-HS may be noticed in the stool—this does not mean that the full dose of medication was not delivered.
- Because verapamil decreases the force of heart contractions and slows the conduction of electrical impulses, it can depress cardiac function by significantly slowing heart rate and impairing electrical conduction in the heart (heart block), worsening heart failure.
- Symptoms of verapamil overdose can include dizziness; blurred vision; slow, fast, or irregular heartbeat; seizures; confusion; or difficulty swallowing or breathing.

Pediatric

Verapamil is used in pediatric patients only for IV treatment of supraventricular tachycardia.

Pregnant or breastfeeding

Verapamil is in the FDA pregnancy category C—it should be used with caution during pregnancy and only if benefits outweigh risks. Women should contact their doctor if they become pregnant while taking verapamil. Verapamil passes into breast milk, with the nursing infant receiving less than 0.01%–0.1% of the mother's dose. Although the manufacturer suggests not breastfeeding while taking verapamil, the American Academy of Pediatrics considers the drug compatible with nursing.

Other conditions and allergies

Patients should tell their doctor and pharmacist if they are allergic to verapamil or any other medications. Verapamil should not be used or should be used with caution in patients with heart conditions such as sick

sinus syndrome or atrioventricular block. It should be used with caution in patients with kidney impairment, and such patients should have electrocardiogram (ECG) monitoring. Patients should tell their doctor if they have or have ever had:

- heart, liver, or kidney disease
- heart failure
- a narrowing or blockage of the digestive system or any other condition that causes slow movement of food through the system
- muscular dystrophy
- myasthenia gravis (a weakening of certain muscles)

Side effects

Side effects of CCBs, including verapamil, include dizziness, flushing, constipation, headaches, and swollen gums or ankles. CCBs can also cause diarrhea, nausea, and fatigue. Rarely, CCBs cause the heart to slow down too much. Constipation is the major side effect of verapamil, affecting more than 25% of patients. Swelling of the extremities (peripheral edema) is uncommon with verapamil.

Patients should contact their doctor if any of the following side effects are severe or persistent:

- constipation
- heartburn
- dizziness or light-headedness
- headache

Patients should call their doctor immediately if any of the following potentially serious side effects occur:

- swelling of the hands, feet, ankles, or lower legs
- difficulty breathing or swallowing
- slow heartbeat
- fainting
- blurred vision
- rash
- nausea
- extreme tiredness
- unusual bleeding or bruising
- lack of energy
- loss of appetite
- pain in the upper-right stomach
- yellowing of the skin or eyes
- flulike symptoms
- fever

Interactions

The doctor and pharmacist should be informed of all prescription and nonprescription medicines, vitamins, minerals, herbs, and dietary supplements being used or planning to be used by the patient. Patients should bring a list of all medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Drugs

A large number of drugs—in addition to those listed—may interact with verapamil. Verapamil is not usually used in combination with beta-blockers—such as **atenolol** (Tenormin), **metoprolol** (Lopressor, Toprol XL), nadolol (Corgard), **propranolol** (Inderal), and timolol (Betimol, Istalol, Timoptic, in Cosopt)—because together the drugs can markedly slow the heart rate. Drugs that may require changing doses or carefully monitoring for side effects include:

- alpha-blockers such as prazosin (Minipress)
- antifungals such as itraconazole (Sporanox) and **ketoconazole** (Nizoral)
- **aspirin**
- **carbamazepine** (Tegretol)
- cimetidine (Tagamet)
- **clarithromycin** (Biaxin, in Prevpac)
- **cyclosporine** (Neoral, Sandimmune)
- **digoxin** (Lanoxin, Lanoxicaps)
- disopyramide (Norpac)
- diuretics
- **erythromycin** (E.E.S., E-Mycin, Erythrocin)
- flecainide (Tambocor)
- certain HIV protease inhibitors such as indinavir (Crixivan), nelfinavir (Viracept), and ritonavir (Norvir, in Kaletra)
- quinidine (Quinaglute, Quinidex)
- lithium (Eskalith, Lithobid)
- other high blood pressure medications
- nefazodone
- phenobarbital
- **pioglitazone** (Actos, in Duetact)
- **rifampin** (Rifadin, Rimactane)
- telithromycin (Ketek)
- theophylline (Theolair, Uniphyll)

Herbs and supplements

The herbal product St. John's wort may interact with verapamil.

Food and other substances

Patients should discuss with their doctors the safe use of alcohol while taking verapamil, because the drug may make alcohol effects longer lasting and more severe. Patients should also talk to their doctors about eating grapefruit or drinking grapefruit juice while taking verapamil.

Resources

BOOKS

Lederman, Robert J. *Tarascon Internal Medicine & Critical Care Pocket Book*. 5th ed. Burlington, MA: Jones & Bartlett Learning, 2013.

Smith, Howard S., Marco Pappagallo, and Stephen M. Stahl. *Essential Pain Pharmacology: The Prescriber's Guide*. New York: Cambridge University Press, 2012.

OTHER

"Treating High Blood Pressure: Is a Calcium Channel Blocker Drug Right for You?" *Consumer Reports*. http://www.consumerreports.org/health/resources/pdf/best-buy-drugs/2pager_CCBs.pdf (accessed February 28, 2015).

WEBSITES

Aroesty, Julian M., and Joseph P. Kannam. "Patient Information: Medications for Angina (Beyond the Basics)." UpToDate.com. <http://www.uptodate.com/contents/medications-for-angina-beyond-the-basics?view=print> (accessed February 28, 2015).

MedlinePlus. "Verapamil." National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a684030.html> (accessed February 28, 2015).

Medscape. "Verapamil (Rx)." Reference.medscape.com. <http://reference.medscape.com/drug/calan-sr-isoptin-sr-verapamil-342380> (accessed February 28, 2015).

U.S. Food and Drug Administration. "High Blood Pressure—Medicines to Help You." <http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118594.htm> (accessed February 28, 2015).

"Verapamil Dosage." Drugs.com. <http://www.drugs.com/dosage/verapamil.html> (accessed February 28, 2015).

ORGANIZATIONS

American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1 (242-8721), <http://www.heart.org/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, (888) INFO-FDA (463-6332), <http://www.fda.gov/>.

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Vermox see **Mebendazole**

Vesicare see **Solifenacin**

Viagra see **Sildenafil**

Vibramycin see **Doxycycline**

Vicodin see **Hydrocodone/
acetaminophen**

Vicoprofen see **Hydrocodone/ibuprofen**

Victoza see **Liraglutide**

Vigamox see **Moxifloxacin**

Vistaril see **Hydroxyzine**

Voltaren see **Diclofenac**

Vyvanse see **Lisdexamfetamine**

W

Warfarin

Definition

Warfarin is a vitamin K antagonist that belongs to the family of drugs called anticoagulants. Anticoagulants are also referred to as blood thinners, although they do not actually thin the blood.

Purpose

Warfarin is used to decrease the clotting ability of the blood and to help prevent harmful clots from forming in the blood vessels. It is in a class of medications called anticoagulants. Warfarin is prescribed to treat or prevent

venous thrombosis (swelling and blood clot in a vein), pulmonary embolism (blood clot in the lung), and thromboembolic disease, and it is also used in people with certain types of irregular heartbeat, with replacement or mechanical heart valves, or who have suffered a heart attack.

When used as an anticoagulant to treat irregular heartbeat, following a heart attack, and in long-term maintenance of heart valves, warfarin can prevent further complications by decreasing the clotting of the blood, which improves blood perfusion, and by preventing existing clots from growing larger.

One of the most common hematological complications is disordered coagulation. Cancer patients make up one group of people with a high incidence of thromboembolic disease. Thromboembolic disease may represent only one of many complications in cancer patients. Thromboembolic disease includes superficial and deep vein thrombosis, pulmonary embolism, thrombosis of venous access devices, arterial thrombosis, and embolism. The cancer itself or cancer treatments may induce coagulation. For example, **tamoxifen**, a drug prescribed to treat breast cancer, increases the chance of developing pulmonary embolism or deep vein thrombosis.

Cancer and its treatment can affect all three causes of thromboembolic disease: the alteration of blood flow, damage to the cells in blood vessels (endothelial cells), and enhancement of procoagulants (precursors, such as fibrinogen or prothrombin, that mediate coagulation). Cancer can impact blood flow by affecting blood vessels close to the tumor. In addition, tumors cause angiogenesis, which may create complexes of blood vessels with a disordered appearance and flow (varying in magnitude and direction). Chemotherapy or tumors may directly damage endothelial cells. Procoagulants may be secreted into the bloodstream by cancer cells or can be increased on the surface of cancer cells. Warfarin is prescribed to manage these conditions.



Coumadin (warfarin), 2 mg. (© Cengage Learning®.)

KEY TERMS

Angiogenesis—The formation of new blood vessels that occurs naturally under certain circumstances, for example, in the healing of a cut.

Anticoagulant—A medication that prevents the formation of new blood clots and keeps existing blood clots from growing larger.

Arterial thrombosis—A condition characterized by a blood clot in an artery.

Blood clot—A clump of blood that forms in or around a vessel as a result of coagulation. The formation of blood clots when the body has been cut is essential because without blood clots to stop the bleeding, a person would bleed to death from a relatively small wound.

Coagulation—The blood's natural tendency to clump and stick.

Embolism—An obstruction in a blood vessel due to a blood clot or other foreign matter that gets stuck while traveling through the bloodstream.

Embolus—A blood clot, gas bubble, piece of tumor tissue, or other foreign matter that moves through the bloodstream from its site of origin to obstruct a blood vessel.

Endothelial cells—The cells lining the inside of blood vessels.

Fibrinolytics—Agents that decompose fibrin, a protein produced in the clotting process.

Pulmonary embolism—A blockage of the pulmonary artery by foreign matter such as a blood clot.

Thromboembolic disease—A condition in which a blood vessel is obstructed by an embolus carried in the bloodstream from the site of formation.

Thrombosis—A condition in which a clot develops in a blood vessel.

Vein thrombosis—A condition characterized by a blood clot in a vein.

Description

Warfarin will not dissolve an existing blood clot, but it may prevent it from getting larger. When warfarin is taken orally, it is absorbed quickly from the gastrointestinal tract. It reaches a maximal plasma concentration in 90 minutes and stays in the bloodstream for 36–42 hours. Warfarin circulates in the bloodstream attached to plasma proteins—in particular, a protein called albumin. The response or effects of a warfarin dose vary from person to person.

Whether anticoagulants like warfarin may also improve cancer survival rates independent of their effect on thromboembolism has been investigated. There is suggestive evidence that warfarin may actually enhance cancer survival rates. Animal studies show that warfarin and other agents such as heparin, fibrinolytics, and even antiplatelet agents inhibit tumor growth and metastasis.

U.S. brand names

The brand name of warfarin in the United States is Coumadin.

Recommended dosage

A doctor may prescribe a dosage based on laboratory blood tests that determine a patient's clotting time. This blood test (called prothrombin time, or PT, and international normalized ratio, or INR) is conducted usually weekly or monthly, as suggested by a physician, and should always be done at the same time of day. Based on the clotting time, the doctor determines the initial dose and whether the dose should be adjusted. Warfarin is normally prescribed to be taken once a day, and it should be taken at the same time every day.

Standard dosing is started at 2–5 milligrams (mg) per day, titrated according to the PT and INR lab results, up to a maximum of 10 mg per day.

Warfarin is available in both oral and injectable forms.

Pediatric

Pediatric use must be determined by the doctor.

Precautions

Following certain precautions when taking warfarin may reduce the risk of side effects and improve the effectiveness of the medication. The rate of blood clotting is affected by illness, diet, medication changes, and physical activities. If an individual has other medical problems, this may affect the use of warfarin. Of particular importance are bleeding ulcers, heavy menstrual periods, infections, high blood pressure, and liver or kidney problems. The doctor should be informed of any changes in these conditions so dose alterations can be made, if necessary. If a patient using warfarin is scheduled for surgery or dental work, the doctor or dentist should be informed that the patient is taking this medication. Warfarin should not be prescribed if an allergic reaction has occurred in the past. Anyone taking warfarin should exercise extra care not to get cut and not to sustain injuries that can result in bruising or bleeding.

In addition, patients taking warfarin should watch their intake of vitamin K, since too much vitamin K

may alter the way in which warfarin works. The amount of foods high in vitamin K (such as broccoli, spinach, and turnip greens) eaten each week should be kept stable. Grapefruit juice should be avoided because it may intensify the effects of this medication. Alcohol should also be avoided while taking warfarin because it interferes with warfarin's effectiveness.

In order to determine a safe and effective dose, regular blood tests to check PT and INR should be done while taking this medicine. Individuals taking warfarin frequently require dose adjustments.

Pediatric

The doctor should determine if warfarin benefits are applicable in each case and will also identify specific precautions, if applicable.

Pregnant or breastfeeding

In studies in animals or pregnant women, warfarin has been demonstrated to have positive evidence of fetal abnormalities. This drug should not be used in women who are or may become pregnant because the risk clearly outweighs any possible benefit. In breastfeeding women, warfarin has been demonstrated to cause minimal risk to the infant. The doctor should evaluate the benefit of warfarin in each case.

Geriatric

No specific precautions have been identified in the elderly population other than regular monitoring of the PT and INR according to doctor recommendations.

Side effects

The most common complication of long-term warfarin therapy is bleeding. The intensity of anticoagulant therapy, age, kidney function, and unidentified diseases of the gastrointestinal and genitourinary tracts all directly influence the risk of bleeding. Patients taking warfarin should be aware of the signs and symptoms that may indicate a bleeding problem. These signs and symptoms include:

- bleeding from the gums or nose
- red or black bowel movements
- coughing up blood (hemoptysis)
- heavy bleeding from cuts or wounds that will not stop
- unusually heavy menstrual bleeding
- blood in the urine
- easy bruising or purple spots on the skin
- severe headache

The patient should inform a doctor immediately if any of these symptoms are present.

Other side effects that may occur with warfarin treatment include:

- mild stomach cramps
- upset stomach
- hair loss (alopecia)
- poor appetite (anorexia)
- cough or hoarseness
- fever or chills
- skin rash, hives, or itching
- painful or difficult urination

The occurrence of any of these side effects should also be reported to the doctor.

Interactions

Some medications should not be combined. The patient should check with the doctor monitoring the warfarin treatment before taking any new medication, including over-the-counter medication or medication prescribed by another doctor.

Warfarin should be carefully cross-checked by a pharmacist and the doctor. Many drugs do interact with warfarin and can cause decreased effectiveness, increased action of the drug, or other adverse interactions.

Examples of common prescription medications that should be evaluated prior to adding warfarin to the medication regimen include but are not limited to:

- **azithromycin**, **amoxicillin**, cefepime, and some other antibiotic medications
- **omeprazole**, **plaquenil**, **citalopram**, **sertaline**, and other frequently prescribed medications
- **cisplatin**, **tamoxifen**, and other cancer treatment medications

Among over-the-counter medications and dietary supplements that may alter the way warfarin works are:

- nonprescription medications such as **aspirin** or nonsteroidal anti-inflammatory drugs (e.g., **ibuprofen**)
- cough or cold remedies
- herbal products and nutritional supplements
- products containing vitamin K

Studies have shown that warfarin along with cranberry juice can have dangerous side effects. The volume of the case studies included glasses of cranberry juice daily, not gallons. This drug-food interaction was shown to cause an increased risk of bleeding. This risk prompted the United Kingdom's

Committee on Safety of Medicines and the Medicines and Healthcare Products Regulatory Agency to warn patients taking warfarin to limit consumption of cranberry juice or avoid it altogether. According to Dr. Jacqui Bainbridge of the University of Colorado, Denver, a cranberry juice/warfarin interaction is biologically plausible, stating “Warfarin is metabolized chiefly by cytochrome P-450 in the liver, and the antioxidant flavonoids contained in the juice are known to inhibit the enzyme pathway.” Limited consumption is advised. In addition, because vitamin K is found in an abundance of food sources, dietary education while taking warfarin is recommended.

Resources

WEBSITES

Mayo Clinic staff. “Warfarin.” MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/warfarin-oral-route/description/drg-20070945> (accessed on February 28, 2015).

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Welchol see **Colesevelam**

Wellbutrin see **Bupropion**

X-Z

Xanax see **Alprazolam**

Xarelto see **Rivaroxaban**

Xopenex see **Levalbuterol**

Zanaflex see **Tizanidine**

Zantac see **Ranitidine**

Zestril see **Lisinopril**

Zetia see **Ezetimibe**

Zidovudine/lamivudine see **Lamivudine/
zidovudine**

Ziprasidone

Definition

Ziprasidone is an atypical antipsychotic drug used to treat schizophrenia. It is also used to treat acute manic or mixed episodes associated with bipolar disorder.

Purpose

Ziprasidone is in a class of drugs called antipsychotics. It is used to control symptoms of schizophrenia or for acute symptoms associated with bipolar disorder. It may also be used in conjunction with lithium or valproate (Depakote) as maintenance treatment for bipolar disorder. Ziprasidone is one of the newer antipsychotic drugs (often called atypical antipsychotics), which are less likely to cause significant adverse side effects than conventional antipsychotic medications.

Description

In people with schizophrenia or bipolar disorder, chemical systems in the brain are out of balance. Mental well-being is partially related to maintaining a balance

between naturally occurring chemicals called neurotransmitters. Ziprasidone is thought to modify the actions of several neurotransmitters and restore appropriate function to the chemical systems.

U.S. brand names

Ziprasidone is available with a prescription under the brand name Geodon.

Origins

The U.S. Food and Drug Administration (FDA) approved ziprasidone for treatment of schizophrenia in 2001, for treatment of acute manic or mixed episodes associated with bipolar disorder in 2004, and as maintenance treatment of bipolar disorder in 2009.

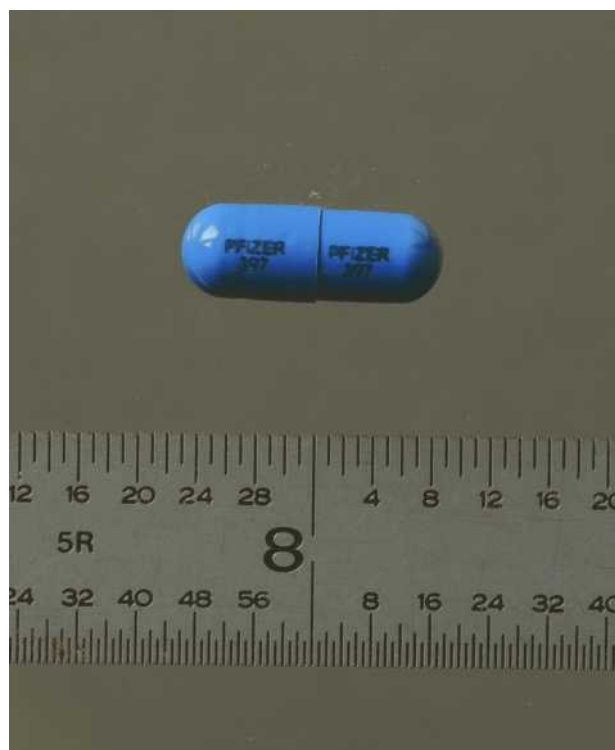
Recommended dosage

The dosage of ziprasidone varies widely from one individual to another. A common initial dosage is 20 milligrams (mg) of ziprasidone taken twice daily. The dosage is gradually increased until symptoms of schizophrenia subside. Dosages of up to 100 mg may be taken twice daily. Dosing for treatment of bipolar disorder generally ranges from 40–80 mg twice daily. Ziprasidone should be taken with food.

For acute treatment of agitation in schizophrenia, ziprasidone may be administered intramuscularly (as an injection) at a dose of 10–40 mg (maximum) per day.

Precautions

Ziprasidone may lower blood pressure to dangerously low levels, possibly causing a person to faint. It may also increase the risk of seizures and may raise body temperatures to dangerously high levels. People who exercise strenuously, those exposed to extreme heat, individuals taking drugs with anticholinergic effects (including many common antidepressants), and persons prone to dehydration should use the drug cautiously and be alert to dehydration-related side effects.



Geodon (ziprasidone), 40 mg. (© Cengage Learning®.)

Because there is a high incidence of suicide in all patients with psychotic illnesses, people using ziprasidone should be observed carefully for signs of suicidal behavior.

In June 2008, the FDA announced a requirement for manufacturers of ziprasidone (and other antipsychotic drugs) to issue a warning label regarding the adverse effects of using ziprasidone to treat behavioral problems in older individuals with dementia-related psychosis, including death. Studies showed that older adults with dementia taking antipsychotics such as ziprasidone were at increased risk of having a stroke or mini-stroke during treatment and, in some cases, had an increased chance of death during treatment, though the reason for the finding was unclear. The use of ziprasidone in treating older adults with dementia-related psychosis is not approved by the FDA.

Geriatric

Elderly persons with increased risk of developing pneumonia should be carefully monitored while taking ziprasidone.

Pregnant or breastfeeding

Women who are pregnant or breastfeeding should not take ziprasidone, as it may harm the fetus. Some

newborns born to mothers who had taken ziprasidone during pregnancy exhibited withdrawal symptoms, including respiratory problems and tremor.

Other conditions and allergies

Ziprasidone should not be taken by people with a history of irregular or prolonged heart rhythms (long QT syndrome), those with heart failure, or individuals who have recently had a heart attack. People with a history of heart disease should discuss the risks and benefits of treatment with their doctor before starting ziprasidone. It should not be taken by people who have slow heartbeats or low levels of potassium or magnesium in their blood. People taking medication to regulate their blood pressure should have their blood pressure monitored and their treatment modified as needed. Individuals with a history of seizures, even seizures brought on by drug or alcohol abuse, should use ziprasidone cautiously and with close physician supervision.

Side effects

The most common reason that ziprasidone is stopped is the development of a rash. Another common side effect is drowsiness. This side effect is usually worse when starting the drug and becomes less severe with continued use. People performing tasks that require mental alertness, such as driving or operating machinery, should refrain from doing so until they see how the drug affects them. Other side effects that may occur are abnormal, involuntary twitching (5%) and respiratory disorders (8%). Nausea, constipation, indigestion, and dizziness due to low blood pressure occur in more than 5% of people taking ziprasidone.

Other, less common side effects include rapid heartbeat, low blood pressure, agitation, tremor, confusion, amnesia, dry mouth, increased salivation, joint pains, and abnormal vision.

The incidence of some adverse effects, such as low blood pressure, loss of appetite, abnormal involuntary movements, sleepiness, tremor, cold symptoms, rash, abnormal vision, dry mouth, or increased salivation, appears to increase at higher dosages.

People taking ziprasidone should alert their healthcare provider immediately if they develop a rash or hives, since this could indicate a potentially serious adverse reaction. Patients should also notify their healthcare provider right away if they experience any abnormal involuntary muscle movements. People who think they may be experiencing side effects from this or any other medication should tell their physicians.

KEY TERMS

Antipsychotic—A drug used to treat serious mental disorders that cause hallucinations or delusions, such as schizophrenia or psychosis.

Bipolar disorder—A mood disorder marked by alternating episodes of extremely low mood (depression) and exuberant highs (mania); formerly known as manic-depressive disorder.

Dementia—A disease characterized by the progressive deterioration of intellectual functions, such as memory, reasoning, and language. Other symptoms include changes in personality, deterioration in personal grooming, and disorientation.

Mania—An elevated or euphoric mood or irritable state that is characteristic of bipolar disorder. Mania is characterized by mental and physical hyperactivity, disorganization of behavior, and inappropriate elevation of mood.

Neurotransmitter—One of a group of chemicals secreted by a nerve cell (neuron) to carry a chemical message to another nerve cell, often as a way of transmitting a nerve impulse. Examples of neurotransmitters include acetylcholine, dopamine, serotonin, and norepinephrine.

Schizophrenia—A major mental illness marked by psychotic symptoms, including hallucinations, delusions, and severe disruptions in thinking.

Withdrawal symptoms—A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

Interactions

Ziprasidone interacts with many other drugs, and patients should let their physician know of all the other medications they are taking before starting treatment with ziprasidone.

Drugs

Ziprasidone may produce irregular heart rhythms and other cardiac problems when used with other drugs, including quinidine, dofetilide, pimozide, **sotalol**, **erythromycin**, thioridazine, **moxifloxacin**, and sparfloxacin; these drugs should not be taken in combination with ziprasidone.

Drugs that cause drowsiness, such as antidepressants, antihistamines, and some pain relievers may increase the sedative effects of ziprasidone. Individuals taking **zolpidem** (Ambien, Ambien CR) concomitantly

with ziprasidone should be monitored for central nervous system effects such as respiratory depression and should avoid activities requiring mental alertness and motor coordination.

Other drugs taken in combination with ziprasidone may alter the effects of ziprasidone. Drugs such as **carbamazepine**, used to treat seizures, increase liver metabolism and may cause ziprasidone to be less effective. In contrast, drugs such as **ketoconazole**, used to treat fungal infections, slow liver metabolism and may increase negative side effects associated with ziprasidone. Ziprasidone may also decrease the effects of drugs used to treat Parkinson's disease, such as levodopa.

Food and other substances

Alcohol may increase the sedative effects of ziprasidone and should be avoided.

Resources

BOOKS

- Albers, Lawrence J., Rhoda K. Hahn, and Christopher Reist. *Handbook of Psychiatric Drugs*. Laguna Hills, CA: Current Clinical Strategies Publishing, 2010.
- American Society of Health-System Pharmacists. *AHFS Drug Information 2015*. Bethesda: American Society of Health-System Pharmacists, 2015.
- Graham, George. *The Disordered Mind: An Introduction to Philosophy of Mind and Mental Illness*. New York: Routledge, 2010.
- Holland, Leland Norman, and Michael Patrick Adams. *Core Concepts in Pharmacology*. 3rd ed. New York: Prentice Hall, 2011.
- North, Carol, and Sean Yutzy. *Goodwin and Guze's Psychiatric Diagnosis*. New York: Oxford University Press, 2010.
- Preston, John D., John H. O'Neal, and Mary C. Talaga. *Handbook of Clinical Psychopharmacology for Therapists*. 7th ed. Oakland, CA: New Harbinger Publications, 2013.

PERIODICALS

- Jeon, H. J., et al. "Psychomotor Symptoms and Treatment Outcomes of Ziprasidone Monotherapy in Patients with Major Depressive Disorder: A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Sequential Parallel Comparison Trial." *International Clinical Psychopharmacology* 29, no. 6 (2014): 332–38.
- Jung, W. Y., et al. "Open Prospective Study of Ziprasidone in Patients with Schizophrenia with Depressive Symptoms: A Multicenter Study." *Psychiatry and Clinical Neurosciences* 69, no. 1 (2015): 43–48.
- Mandrioli, R., M. Protti, and L. Mercolini. "Evaluation of the Pharmacokinetics, Safety and Clinical Efficacy of Ziprasidone for the Treatment of Schizophrenia and Bipolar Disorder." *Expert Opinion on Drug Metabolism & Toxicology* 11, no. 1 (2015): 149–74.

WEBSITES

- AHFS Consumer Medication Information. "Ziprasidone." American Society of Health-System Pharmacists. Available from: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699062.html> (accessed February 27, 2015).
- National Alliance on Mental Illness. "Geodon® (Ziprasidone)." http://www2.nami.org/Template.cfm?Section=About_Medications&Template=/TaggedPage/TaggedPageDisplay.cfm&TPLID=51&ContentID=20821 (accessed February 27, 2015).
- U.S. Food and Drug Administration. "FDA Drug Safety Communication: FDA Reporting Mental Health Drug Ziprasidone (Geodon) Associated with Rare but Potentially Fatal Skin Reactions." <http://www.fda.gov/Drugs/DrugSafety/ucm426391.htm> (accessed February 27, 2015).

ORGANIZATIONS

- American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, (703) 907-7300, apa@psych.org, <http://www.psych.org/>.
- National Alliance on Mental Illness, 3803 N. Fairfax Drive, Suite 100, Arlington, VA 22203, (703) 524-7600, (800) 950-NAMI (6264), Fax: (703) 524-9094, <http://www.nami.org/>.
- National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (301) 433-4513, (866) 615-6464, Fax: (301) 443-4279, TTY: (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

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Zithromax see **Azithromycin**Zocor see **Simvastatin**Zofran see **Ondansetron**

Zoledronic acid

Definition

Zoledronic acid is in a class of drugs called bisphosphonates that are used to treat and prevent osteoporosis.

Purpose

Zoledronic acid can inhibit, or help control, a process called osteoclastic bone resorption. Normally,



Zoledronic acid. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

old bone is removed throughout a person's lifetime, which is called resorption. When people are younger, the skeleton adds new bone, in a process called formation, at a faster rate than old bone is removed. As a result, the bones grow and strengthen. As people age, however, bone loss eventually begins to outpace bone formation. The most rapid bone loss for women occurs after they reach menopause, but men also lose bone as they become very old. Certain risk factors such as smoking, a diet low in calcium and vitamin D, and some diseases and conditions can speed up bone loss.

When more bone is removed than formed, the bones become weak, thin, and brittle. Zoledronic acid can slow down the resorption process in women who are postmenopausal, in elderly men with osteoporosis, and in people who have Paget disease of the bone.

Description

Zoledronic acid is available only by prescription and usually is given to a patient by a doctor or other healthcare provider. The medicine comes in liquid form that is injected into the patient's vein. The medicine is infused over a period of about 15 minutes. Patients receive the medicine annually or less often, depending on the reason for its use.

U.S. brand names

In the United States, zoledronic acid for use in treating osteoporosis and Paget disease of the bone is

KEY TERMS

Bisphosphonates—A class of drugs that binds to the minerals in bone tissue and lessens the amount of bone loss associated with Paget disease and osteoporosis.

Menopause—The end of a woman's menstrual periods, when a woman no longer can conceive a child.

Osteoclast—Large cells associated with bone resorption, or removal, and normally helping to allow new bone to form.

Osteoporosis—The excessive loss of calcium from the bones, causing the bones to become fragile and break easily. Postmenopausal women are especially vulnerable to this condition because estrogen, a hormone that protects bones against calcium loss, decreases drastically after menopause.

Paget disease of the bone—A rare, chronic bone condition that causes some bones in the affected person to soften.

sold as Reclast. Another injectable form of the medication is sold as Zometa, but this form is designed for uses related to cancer.

Recommended dosage

To treat osteoporosis in men or in postmenopausal women, zoledronic acid is infused once a year through an intravenous (IV) line at a dose of 5 milligrams (mg) for at least 15 minutes. After administering the drug, the healthcare provider flushes the line with normal saline. Postmenopausal women who are receiving the medicine to prevent osteoporosis receive the zoledronic acid infusion at the same dose over at least 15 minutes, but only every two years.

For people with Paget disease of the bone, 5 mg of zoledronic acid should be injected in the same manner one time only, and patients should take supplemental calcium and vitamin D.

Patients usually are instructed to drink at least two glasses of water before receiving their injection.

Precautions

Some people have allergic reactions to zoledronic acid, so it is important to notify the doctor of any known allergies before receiving the drug. People should not

take both forms of zoledronic acid (Reclast and Zometa), so it is important to inform the doctor of any medications being used. Anyone who has a condition called hypocalcemia, or low calcium levels, should have the condition treated before receiving zoledronic acid. Anyone who is dehydrated or who has kidney disease should not receive zoledronic acid because the drug can affect kidney function. The drug should always be infused slowly, over at least 15 minutes.

Pediatric

Studies using zoledronic acid in children with a rare bone disease called osteogenesis imperfecta showed that the drug's benefits were not significant enough to justify the negative side effects the medicine caused in the children. Zoledronic acid should not be used in children.

Geriatric

Older people are more likely to have problems with kidney function. Seniors and their doctors should take special care to ensure that there are no problems with the kidneys before administering zoledronic acid.

Pregnant or breastfeeding

Zoledronic acid is a pregnancy category D medication, which means it should not be used while a woman is pregnant. Studies of bisphosphonates in animals suggest that the drugs could harm a fetus. There are no studies of the drug's use in nursing mothers, but doctors do not recommend use of zoledronic acid if a woman chooses to breastfeed.

Other conditions and allergies

There have been some reports that people who have sensitivity to aspirin have had tightened airways when using zoledronic acid.

Side effects

There are several side effects that people who have zoledronic acid may experience, including:

- swelling, redness, itching, or pain at the injection site
- swelling, itching, or redness around the eyes
- stomach pain
- nausea, vomiting, constipation, or diarrhea
- heartburn
- depression or problems sleeping
- sores or white patches in the mouth

More severe side effects may indicate a severe reaction and a reason to call the doctor immediately. Among these are:

- swelling of the face, lips, eyes, throat, lower legs, or hands
- hives or a rash
- trouble breathing or swallowing
- pain in the chest
- irregular heartbeat
- muscle spasms or cramps
- painful gums, loose teeth, or a heavy feeling in the jaw

Interactions

A person should never take more than one type of zoledronic acid at a time.

Drugs

Certain antibiotics called aminoglycosides, including amikacin (Amikin) and paromomycin (Humatin) can interact with zoledronic acid. Special caution is indicated for anyone using **aspirin** and other nonsteroidal anti-inflammatory drugs (NSAIDs) such as **ibuprofen** or naproxen. Patients should inform their doctors if they take diuretics (water pills), along with any other medications or herbal supplements or vitamins.

Food and other substances

It is important to drink plenty of water, at least two full glasses, or other liquid a few hours before receiving a zoledronic acid injection.

Resources

PERIODICALS

- Boonen, Steven, and E. Orwoll. "Fracture Risk and Zoledronic Acid Therapy in Men with Osteoporosis." *New England Journal of Medicine* 367, no. 18 (2012): 1714–23.
- Kaufman, A. J., B. Lapauw, and S. Goemaere. "Current and Future Treatments of Osteoporosis in Men." *Best Practice and Research: Clinical Endocrinology and Metabolism* 28, no. 6 (2014): 871–84.

WEBSITES

- U.S. Food and Drug Administration. "Reclast (Zoledronic Acid) Injection." <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM241522.pdf> (accessed February 28, 2015).

WEBSITES

- American College of Rheumatology. "Reclast (Zoledronic Acid)." [Rheumatology.org. https://www.rheumatology.org/practice/clinical/drugsafety/reclast.asp](http://www.rheumatology.org/practice/clinical/drugsafety/reclast.asp) (accessed February 28, 2015).
- MedlinePlus. "Zoledronic Acid Injection." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a605023.html> (accessed February 28, 2015).

ORGANIZATIONS

National Osteoporosis Foundation, 1150 17th Street, Suite 850 Washington, DC 20036, (202) 223-2237, (800) 231-4222, info@nof.org, <http://nof.org/>.

NIH Osteoporosis and Related Bone Diseases National Resource Center, 2 AMS Circle, Bethesda, MD 20892-3676, (202) 223-0344, Fax: (202) 293-2356, (800) 624-2663, TTY: (202) 466-4315, NIHBoneInfo@mail.nih.gov, <http://www.bones.nih.gov/>.

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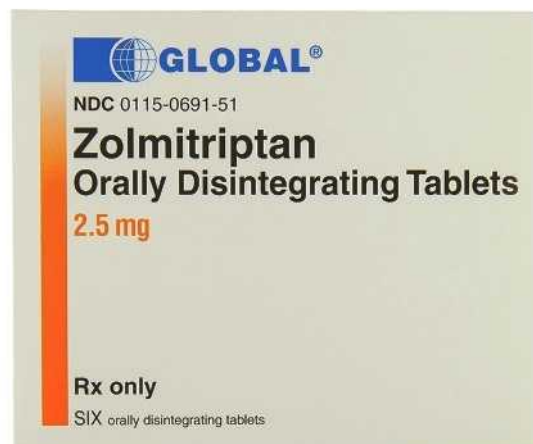
Zolmitriptan

Definition

Zolmitriptan is an oral medication or nasal spray used to treat the symptoms of migraine headaches in adults. It is classified as an antimigraine agent in the drug family known as selective serotonin receptor agonists (SSRAs) or triptans.

Purpose

Zolmitriptan is used to treat the symptoms of migraine headaches, which are severe, throbbing headaches that may be accompanied by nausea and sensitivity



Zolmitriptan, 2.5 mg. (Reprinted with permission. Copyright 1974–2015 Truven Health Analytics Inc. All rights reserved.)

to light and sound. Zolmitriptan is used for migraines with and without auras—visual symptoms such as flashing lights and wavy lines that accompany or precede some migraines. Zolmitriptan can only treat a headache that has already started—it cannot prevent migraines or reduce their frequency. Although zolmitriptan may be prescribed for other purposes, it is only used for headaches that have been unequivocally diagnosed as migraines. It cannot be used to treat cluster headaches.

Description

Migraine headaches are thought to be caused by the widening (dilating) of cranial blood vessels, which exerts pressure on the brain. Migraines are associated with low levels of the neurotransmitter serotonin (5-hydroxytryptamine, or 5-HT), which constricts blood vessels. Zolmitriptan binds to specific serotonin receptors, called 5-HT_{1B/1D} receptors, located on blood vessels in the brain and sensory nerves leading to the brain. Zolmitriptan is a selective 5-HT_{1B/1D} receptor “agonist,” because it binds with high affinity to these receptors and exerts the same effects as serotonin binding to the receptors, acting as a powerful vasoconstrictor that narrows the widened blood vessels. This reduces pressure on the brain and blocks the transmission of pain signals and the release of inflammatory neuropeptides that cause pain and other migraine symptoms. Zolmitriptan completely eliminates migraine headaches in many people and often relieves accompanying symptoms, such as nausea, vomiting, and sensitivity to light and sound. For other people, zolmitriptan lessens headache pain, enabling them to resume their normal activities.

U.S. brand names

Zolmitriptan is marketed in the United States under the brand names Zomig, Zomig-ZMT (orally disintegrating tablets; ODT), and Zomig Nasal Spray.

Canadian brand names

Zolmitriptan is marketed in Canada as Zomig.

International brand names

The most common international brand names are Zomig and Zomig Rapimelt. It is marketed as AscoTop in Germany, Zomigoro in France, and Zomigon in Greece and Argentina.

Origins

Zolmitriptan is a synthesized derivative of tryptamine. It is a white powder that readily dissolves in water. Zomig 2.5 and 5 milligram (mg) oral tablets were first approved by the U.S. Food and Drug Administration

KEY TERMS

5-HT_{1B/1D} receptors—Serotonin receptors in blood vessels in the brain that bind zolmitriptan.

Agonist—A drug, such as zolmitriptan, that binds to a receptor and mimics the effects of the endogenous receptor-binding substance.

Aura—Visual and other sensory disturbances that can precede the onset of a migraine headache.

Cluster headache—Severe pain in one eye or temple.

Migraine—A common primary headache characterized by debilitating neurological symptoms, especially severe throbbing pain on one or both sides of the head, lasting for several hours or more.

Monoamine oxidase inhibitors (MAOIs)—A class of antidepressants that can interact with zolmitriptan.

Neurotransmitter—A chemical that carries nerve impulses from one nerve cell to another across a synapse or from a nerve cell to a muscle cell.

Receptor—A protein inside or on the surface of a cell that binds a specific substance.

Selective serotonin receptor agonists (SSRAs)—Drugs that bind to specific serotonin receptors, mimicking the effects of serotonin binding.

Selective serotonin reuptake inhibitors (SSRIs)—A class of antidepressants that increase levels of serotonin in the brain by preventing its reuptake by nerve cell endings.

Serotonin—5-Hydroxytryptamine (5-HT); a neurotransmitter in the brain and blood; low levels are associated with various disorders, including migraines and depression.

Serotonin and norepinephrine reuptake inhibitors (SNRIs)—A class of antidepressants that increase the levels of the neurotransmitters serotonin and norepinephrine by preventing their reuptake.

Triptans—A class of drugs that bind to serotonin receptors and mimic the action of serotonin; believed to treat migraine headaches by constricting cranial blood vessels, inhibiting inflammatory neuropeptides, and blocking the transmission of pain signals.

Zomig—The common brand name for zolmitriptan.

Zomig-ZMT—The brand name for zolmitriptan orally disintegrating tablets.

(FDA) in 1997. Zomig-ZMT 2.5 mg and 5 mg orally disintegrating tablets were approved in 2001. Zomig 2.5 mg and 5 mg nasal sprays were approved in 2003. Generic oral and orally disintegrating zolmitriptan tablets were first approved in 2014.

Recommended dosage

Zolmitriptan is typically used at the first sign of a migraine headache. If symptoms improve after the initial dose but the migraine is not resolved or returns two or more hours later, a second dose may be used. However, a second dose should not be used without consulting the doctor. The recommended oral dosage of zolmitriptan is 1.25–2.5 mg. The 2.5 mg tablets may be broken with the fingers along the line on the tablet for a 1.25 mg dose. Orally disintegrating tablets cannot be broken. The maximum single dose is 5 mg. The maximum dose in a 24-hour period is 10 mg. It has been reported that there is little added benefit from 5 mg compared with 2.5 mg, and adverse effects are generally increased with 5 mg. The intranasal dose is 2.5–5 mg sprayed once into one nostril, with a maximum single dose of 5 mg and a maximum dose of 10 mg in a 24-hour period.

Orally disintegrating tablets must be kept in their blister packs until use. The package is opened, and the foil is peeled back with dry hands. Pushing the tablet through the foil may damage it. The tablet is immediately placed on the tongue, dissolved without chewing, and swallowed with saliva.

The nasal spray is used as follows:

- The nose is blown gently.
- The protective cap is removed from the sprayer.
- The sprayer is held between the thumb and fingers without pressing the plunger.
- One nostril is blocked with the other hand by pressing firmly on the side of the nose.
- The tip of the sprayer is inserted into the other nostril as far as is comfortable, and the head is tilted back slightly.
- The plunger is pressed firmly with the thumb while breathing in gently through the nose.
- The tip is removed while keeping the head slightly tilted back.
- The patient breathes gently through the mouth for five to ten seconds.
- The single-dose sprayer is discarded in the trash.

Other conditions and allergies

Patients with liver dysfunction should take only one dose of 1.25 mg oral zolmitriptan.

Precautions

Some precautions while taking zolmitriptan include:

- Patients should keep diaries of headache occurrences and zolmitriptan use.
- Zolmitriptan is used only for clearly diagnosed migraine headaches. It should not be used to treat hemiplegic or basilar migraines or other types of headaches such as cluster headaches.
- The first dose of zolmitriptan may be administered in a medical facility so that the patient can be monitored for serious reactions.
- Zolmitriptan or any other headache medicine should not be used for more than ten days in a month. The doctor should be notified if zolmitriptan is needed to treat more than three headaches in a month or if headaches do not improve or if they occur more frequently with zolmitriptan.
- Zolmitriptan must not be taken within 24 hours of taking another SSRA or an ergot-type medication.
- Zolmitriptan must not be taken within two weeks of taking a monoamine oxidase inhibitor (MAOI).
- Zolmitriptan can cause drowsiness. Patients should not drive or operate machinery until they know how zolmitriptan affects them.
- Extreme drowsiness is a symptom of zolmitriptan overdose.

Pediatric

The safety and effectiveness of zolmitriptan have not been established in patients under age 18.

Pregnant or breastfeeding

Zolmitriptan is in the FDA pregnancy category C—it is not known whether it poses harm to the fetus, but animal studies have found evidence of embryo death and fetal abnormalities. Furthermore, the manufacturer lists miscarriage as a rare adverse effect. Zolmitriptan should be used during pregnancy only if the benefits outweigh potential risks to the fetus. Women should use an effective method of birth control while using zolmitriptan.

Studies with rats have indicated that high levels of zolmitriptan are excreted in breast milk. Although there have been no studies on zolmitriptan in human milk, many drugs are excreted in breast milk. Thus, caution is advised for the use of zolmitriptan by breastfeeding women.

Other conditions and allergies

The doctor and pharmacist should be informed of allergies to zolmitriptan, any of the ingredients in

zolmitriptan, or any other medications. People with phenylketonuria (PKU) should be aware that orally disintegrating zolmitriptan tablets contain aspartame, which forms phenylalanine in the body. Zolmitriptan may not be appropriate for people who have or have ever had:

- heart disease
- a heart attack
- angina (chest pain)
- irregular heartbeat
- a stroke or “mini-stroke” (transient ischemic attack)
- circulation problems such as varicose veins, blood clots in the legs, Raynaud’s disease, or ischemic bowel disease
- high blood pressure
- high cholesterol
- diabetes
- seizures
- liver or kidney disease

Caution should be used in prescribing zolmitriptan to people who smoke or are overweight and to postmenopausal women. The doctor should be informed of any family members who have had heart disease or stroke. Because significant blood pressure elevation has been reported in some patients with moderate to severe liver dysfunction, such patients should have regular blood pressure monitoring, in addition to receiving a lower zolmitriptan dosage.

Side effects

The doctor should be contacted if the following symptoms are severe or persistent:

- drowsiness
- dizziness or faintness
- nausea
- feeling warm or cold
- heartburn
- sweating

The doctor should be notified if the following additional side effects of zolmitriptan nasal spray are severe or persistent:

- sore or irritated nose
- sensitive skin, especially around the nose
- dry mouth
- unusual taste in the mouth
- nausea
- tiredness
- dizziness

- weakness
- burning or tingling

Serious side effects that require immediately calling the doctor or getting emergency medical attention are:

- tightness, pain, pressure, or heaviness in the chest, throat, neck, or jaw
- difficulty breathing or swallowing
- slow or difficult speech
- weakness or numbness in an arm or leg
- rapid, pounding, or irregular heartbeat
- bloody diarrhea
- sudden or severe stomach pain
- paleness or blue color to the fingers and toes
- shortness of breath
- swelling of the face, eyes, lips, tongue, or throat
- pain, burning, or tingling in the hands or feet
- rash
- hoarseness
- hives
- faintness
- cold sweat
- vision problems
- vomiting
- sudden weight loss

Interactions

It is very important that the doctor and pharmacist be informed of any and all prescription and nonprescription medicines, herbs, vitamins, minerals, and dietary supplements being used by the patient. Patients should bring a list of all such medications and supplements to all medical appointments and carry the list with them in case of an emergency.

Drugs

Zolmitriptan must not be taken if:

- another SSRA—such as **almotriptan** (Axert), eletriptan (Relpax), frovatriptan (Frova), naratriptan (Amerge), **rizatriptan** (Maxalt), or **sumatriptan** (Imitrex, Treximet)—has been taken in the past 24 hours
- an ergot-type medication—such as bromocriptine (Parlodel), cabergoline, dihydroergotamine (D.H.E. 45, Migranal), ergoloid mesylates (Hydergine), ergonovine (Ergotrate), ergotamine (Cafergot, Ergomar, Wigraine), methylergonovine (Methergine), methysergide (Sansert), or pergolide (Permax)—has been taken in the past 24 hours

- an MAOI—such as isocarboxazid (Marplan), phenelzine (Nardil), or tranylcypromine (Parnate)—has been taken in the past two weeks

Other drugs that can interact with zolmitriptan include:

- acetaminophen (Tylenol)
- **aspirin** and other nonsteroidal anti-inflammatory drugs (NSAIDs), such as **ibuprofen** (Advil, Motrin) and naproxen (Aleve, Naprosyn)
- cimetidine (Tagamet)
- **oral contraceptives**
- **propranolol**
- selective serotonin reuptake inhibitors (SSRIs), such as citalopram (Celexa), **escitalopram** (Lexapro), **fluoxetine** (Prozac, Sarafem, Symbyax), **fluvoxamine**, **paroxetine** (Paxil), and **sertraline** (Zoloft)
- serotonin and norepinephrine reuptake inhibitors (SNRIs), such as desvenlafaxine (Pristiq), **duloxetine** (Cymbalta), sibutramine (Meridia), and **venlafaxine** (Effexor)
- other antidepressants, such as **amitriptyline** (Elavil), amoxapine (Asendin), clomipramine (Anafranil), **desipramine** (Norpramin), doxepin (Adapin, Sinequan), **imipramine** (Tofranil), **nortriptyline** (Aventyl, Pamelor), protriptyline (Vivactil), or trimipramine (Surmontil)

Resources

BOOKS

Smith, Howard S., Marco Pappagallo, and Stephen M. Stahl. *Essential Pain Pharmacology: The Prescriber's Guide*. New York: Cambridge University, 2012.

PERIODICALS

Pringsheim, Tamara, and Werner J. Becker. "Triptans for Symptomatic Treatment of Migraine Headache." *British Medical Journal* 348, no. 7953 (2014): 35.

OTHER

"Triptans: What You Should Know." *Consumer Reports*. http://www.consumerreports.org/health/resources/pdf/best-buy-drugs/BBD_Triptans_Summary.pdf (accessed February 28, 2015).

WEBSITES

Mayo Clinic staff. "Zolmitriptan (Oral Route)." MayoClinic.org. <http://www.mayoclinic.org/drugs-supplements/zolmitriptan-oral-route/description/drg-20066780> (accessed February 28, 2015).

MedlinePlus. "Zolmitriptan." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601129.html> (accessed February 28, 2015).

MedlinePlus. "Zolmitriptan Nasal." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a605046.html> (accessed February 28, 2015).

National Institute of Neurological Disorders and Stroke. "Pain: Hope Through Research." National Institutes of Health. http://www.ninds.nih.gov/disorders/chronic_pain/detail_chronic_pain.htm (accessed February 28, 2015).

"Zolmitriptan." Drugs.com. <http://www.drugs.com/cdi/zolmitriptan.html> (accessed February 28, 2015).

ORGANIZATIONS

American Headache Society, 19 Mantua Road, Mount Royal, NJ 08061, (856) 423-0043, Fax: (856) 423-0082, ahshq@talley.com, <http://www.americanheadache-society.org/>.

National Institute of Neurological Disorders and Stroke, NIH Neurological Institute, PO Box 5801, Bethesda, MD 20824, (301) 496-5751, (800) 496-5751, <http://www.ninds.nih.gov/>.

U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Margaret Alic, PhD

REVIEWED BY KEVIN GLAZA, RPH

Zoloft see **Sertraline**

Zolpidem

Definition

Zolpidem is classified as a hypnotic drug. These drugs help people sleep.

Purpose

Zolpidem is a drug used to treat insomnia. Zolpidem is especially helpful for people who have trouble falling asleep. However, once individuals have fallen asleep, zolpidem also helps them continue to sleep restfully. Zolpidem should be used only for short periods, approximately seven to ten days. If sleeping pills are needed for a longer period, an evaluation by a physician is recommended to determine if another medical condition is responsible for the insomnia.

Description

Although the way zolpidem helps people sleep is not entirely understood, it is believed to mimic a chemical in the brain called gamma-aminobutyric acid (GABA) that naturally helps to facilitate sleep. Zolpidem is a central



Ambien (zolpidem), 5 mg. (© Cengage Learning®.)

nervous system depressant, which means that it slows down the nervous system. Unlike some sleeping pills, zolpidem does not usually interfere with the quality of sleep or leave the user feeling sedated in the morning. As a result, most people using zolpidem awake feeling refreshed.

Zolpidem is available as an immediate-release tablet, an extended-release tablet, a sublingual tablet (a tablet that is dissolved under the tongue), and an oral spray.

U.S. brand names

Zolpidem is sold under a variety of brand names, including Ambien CR (extended release), Zolpimist, Edluar, and Invermezzo. In 2007, the U.S. Food and Drug Administration (FDA) approved the first generic version of Ambien and provided approval for its generic manufacture by 13 companies in the United States.

Tablet forms of zolpidem have come in a variety of shapes and colors. A 5-milligram (mg) tablet of Ambien is a pink, capsule-shaped pill with “AMB 5” stamped on the front and the numbers 5401 stamped on the back. A 10 mg tablet of Ambien is a white, capsule-shaped pill with “AMB 10” stamped on the front and the numbers 5421 stamped on the back. Ambien CR is a small, round, blue or pink pill with “A~” stamped on the front. Generic forms of the drug come in a variety of shapes and colors.

Recommended dosage

The usual dose of zolpidem in adults is 5–10 mg. For healthy adults, 10 mg is commonly recommended. However, people taking other drugs that cause drowsiness or people who have severe health problems, especially liver disease, normally should take a lower dose, usually 5 mg. Zolpidem should be taken immediately before bedtime and only if the individual can count on getting seven or eight hours of uninterrupted sleep. It usually takes only about 30 minutes for the sleep-inducing actions of zolpidem to be felt. Unlike some sleeping pills, the sleep-facilitating effects appear to last six to eight hours.

If zolpidem is taken with a meal, it will take longer to work. For the fastest sleep onset, it should be taken on an empty stomach. The maximum dose for one day is 10 mg. People who miss a dose of zolpidem should skip the missed dose and take the next dose at the regularly scheduled time. Under no circumstances should a person take more than 10 mg in one day. Zolpidem should be taken exactly as directed and only for as long as determined by the prescribing physician.

Sublingual zolpidem is often prescribed to help individuals who wake up in the middle of the night and who are unable to return to sleep. When it is prescribed for this purpose, a single dose of 1.75 mg for women or 3.5 mg for men is generally prescribed to be taken upon awaking, if the person is able to sleep for at least four more hours. Usage should not exceed one dose of zolpidem per night.

Geriatric

Adults over age 65 generally take 5 mg of zolpidem.

Other conditions and allergies

The dosage of zolpidem may need to be adjusted in individuals with kidney impairment. For individuals with impaired liver function, a lower dose of zolpidem (5 mg of the immediate-release formulation) is generally the maximum recommended, since the drug is removed more slowly from the bloodstream.

Precautions

Zolpidem should not be used before driving, operating machinery, or performing activities that require mental alertness.

If zolpidem is needed for more than ten days, patients should be re-evaluated by a physician to determine if another disorder is causing their difficulty in sleeping. When zolpidem or other sleeping pills are used every night for more than a few weeks, they begin to lose their effectiveness, and people may become

dependent upon them to fall asleep. Zolpidem can be habit forming when taken over a long period. People using zolpidem should not stop taking the drug suddenly but should gradually reduce the dose over a few days before quitting, even if zolpidem has been used only for a short time.

Geriatric

Many experts question the practice of prescribing zolpidem, or any form of hypnotic sedative, to elderly individuals. In 2014, the *New York Times* reported that Ambien use was the cause of about 20% of visits to the emergency room by individuals over age 65. Elderly individuals may have a prolonged negative effect from zolpidem that lasts not only through the night but also into the next morning. In many cases, individuals were brought to the emergency room because of confusion, difficulty in being awakened, or excessive sleepiness. As liver function deteriorates with age, it becomes more difficult for the body to rid itself of drugs, including zolpidem. The after-effects of zolpidem can include drowsiness, confusion, headache, and other unpleasant lingering side effects. Daytime drowsiness may cause people, especially the elderly, to be less coordinated and more susceptible to falls.

Pregnant or breastfeeding

Zolpidem is categorized as a class C drug in pregnancy, meaning that it should only be used with caution and if the benefits outweigh the risks. Some cases of severe respiratory distress have been reported in infants born to mothers who had used zolpidem near the end of their pregnancies.

Other conditions and allergies

Zolpidem should be used with close physician supervision in people with liver disease. The drug should be used cautiously in individuals with respiratory distress or respiratory issues such as sleep apnea, because studies have shown that zolpidem may worsen these and related issues.

People with a history of drug abuse, psychiatric disorders, or depression should be carefully monitored when using zolpidem, since the drug may worsen symptoms of some psychiatric disorders.

Side effects

Some sleeping pills such as zolpidem can cause aggressiveness, agitation, hallucinations, amnesia (partial or complete loss of memory), rapid heartbeat, and chest pains. These side effects are rare, but patients or their caregivers should call their physician immediately if such

KEY TERMS

Antidepressant—A medication used to treat the symptoms of depression.

Antihistamine—A medication used to alleviate allergy or cold symptoms such as runny nose, itching, hives, watering eyes, or sneezing.

Antipsychotic—A medication used to treat psychotic symptoms of schizophrenia such as hallucinations, delusions, and delirium. May be used to treat symptoms in other disorders as well.

Gamma-aminobutyric acid (GABA)—A neurotransmitter that helps to lower or reduce the level of excitement in the nerves, leading to muscle relaxation, calmness, sleep, and the prevention of seizures.

Hypnotic—A medication that causes sleep.

Insomnia—A sleep disorder characterized by inability to either fall asleep or stay asleep.

side effects occur. Other serious side effects include anaphylaxis (severe allergic reaction) and angioedema (swelling similar to hives).

Some patients taking sleep medications have engaged in sleep-related behaviors, including eating, talking, and even driving while asleep, with no recollection of the events. Side effects that are more common include headache, nausea, muscle aches, and drowsiness. Although drowsiness is desired when trying to fall asleep, a few people continue to feel drowsy the next day. Other, less common side effects include anxiety, confusion, dizziness, and stomach upset.

Interactions

Individuals should inform the healthcare provider of all other drugs they are currently taking, including over-the-counter drugs and supplements, before taking zolpidem.

Drugs

Any drug that causes drowsiness may lead to substantially decreased mental alertness and impaired motor skills when taken with zolpidem. Some examples include antidepressants such as **imipramine** (Tofranil) or **paroxetine** (Paxil), antipsychotics such as thioridazine, and antihistamines (commonly found in allergy and cold medications).

The effectiveness of zolpidem may be reduced if taken with rifampin (Rifadin, Rimactane), an antibiotic that is commonly used to treat tuberculosis infections.

Food and other substances

Alcohol increases the sedative effects of zolpidem and should be avoided.

Resources

BOOKS

- Berry, Richard B., and Mary H. Wagner. *Sleep Medicine Pearls*. 3rd ed. Philadelphia: Elsevier/Saunders, 2015.
- Stahl, Stephen M. *Stahl's Essential Psychopharmacology: Prescriber's Guide*. 5th ed. New York: Cambridge University Press, 2014.

PERIODICALS

- Farkas, Ronald H., Ellis F. Unger, and Robert Temple. "Zolpidem and Driving Impairment—Identifying Persons at Risk." *New England Journal of Medicine* 369, no. 8 (2013): 689–91.
- Fy, Lin, et al. "Retrospective Population Cohort Study on Hip Fracture Risk Associated with Zolpidem Medication." *Sleep* 37, no. 4 (2014): 673–79.
- Roth, Thomas, et al. "Novel Sublingual Low-Dose Zolpidem Tablet Reduces Latency to Sleep Onset Following Spontaneous Middle-of-the-Night Awakening in Insomnia in a Randomized, Double-Blind, Placebo-Controlled, Outpatient Study." *Sleep* 36, no. 2 (2013): 189–96.

WEBSITES

- Mayo Clinic staff. "Prescription Sleeping Pills: What's Right for You?" MayoClinic.org. <http://www.mayoclinic.org/diseases-conditions/insomnia/in-depth/sleeping-pills/art-20043959> (accessed February 28, 2015).
- MedlinePlus. "Zolpidem." U.S. National Library of Medicine, National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a693025.html> (accessed February 28, 2015).

U.S. Food and Drug Administration. "Questions and Answers: Risk of Next-Morning Impairment after use of Insomnia Drugs; FDA Requires Lower Recommended Doses for Certain Drugs Containing Zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist)." <http://www.fda.gov/Drugs/DrugSafety/ucm334041.htm> (accessed February 28, 2015).

ORGANIZATIONS

- American Academy of Sleep Medicine, 2510 North Frontage Road, Darien, IL 60561, (630) 737-9700, Fax: (630) 737-9790, inquiries@aasmnet.org, <http://www.aasmnet.org/>.
- National Center on Sleep Disorders Research, 6701 Rockledge Drive, Bethesda, MD 20892, (301) 435-0199, Fax: (301) 480-3451, twery@nih.gov, <http://www.nhlbi.nih.gov/about/ncsdr/index.htm>.
- National Sleep Foundation, 1010 N. Glebe Road, Suite 310, Arlington, VA 20221, (703) 243-1697, nsf@sleepfoundation.org, <http://sleepfoundation.org/>.
- U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) INFO-FDA (463-6992), <http://www.fda.gov/>.

Tish Davidson, AM

REVIEWED BY JAMES E. WAUN, MD, RPh

Zomig see **Zolmitriptan**

Zovirax see **Acyclovir**

Z-Pak see **Azithromycin**

Zyban see **Bupropion**

Zyloprim see **Allopurinol**

Zyprexa see **Olanzapine**

Zyrtec see **Cetirizine**

Zyvox see **Linezolid**

QUESTIONS TO ASK YOUR PHARMACIST

How can I protect myself from being overmedicated, from taking duplicate medications, and from possible drug interactions? Keep a list with you of all of the medications and supplements that you take on a regular (or even occasional) basis, and show it to the physicians and pharmacists who provide services for you.

What can you do to help me take medications effectively and safely? Ask that every prescription label state the purpose for which the medication is being used (e.g. for sleep, blood pressure, anxiety.)

Can you help me find lower-cost alternatives to this medication? In some instances, your pharmacist can offer suggestions for alternative, lower-cost drugs that you can then discuss with your healthcare provider.

I take several medicines. Does it matter what time of day I take them? Your pharmacist can help you schedule when to take your medications. With some medicines, it does not matter when you take them, but others must be taken in the morning, on an empty stomach, before meals, with food, or at bedtime.

What should I do if I forget to take a dose of medication, or if I accidentally take two doses the same day? Call your pharmacist or healthcare provider. It may be dangerous to take an extra dose of some medicines and not so for others. For some medications, it is okay to miss an occasional dose; for others, it is not. Your pharmacist can advise you what to do.

I take several medications. How can I keep them straight? Pharmacies sell several types of plastic medication boxes to help organize drugs. Some arrange drugs by time of day, by the week, or by the month. Some pharmacies will even fill the boxes for you.

How do I dispose of extra, unwanted medications? Medicines should be incinerated, not flushed down the toilet or put in the trash. Local authorities—e.g. health departments—can advise you where and when unwanted medicines can be dropped off.

Can unwanted medicines that are sealed or in unopened containers be donated for use by others?

Excess drugs that are not outdated can sometimes be used by charitable organizations like the American Red Cross.

How can I know if a drug is outdated? Prescription containers have dates on the labels that state the drug's expiration date. Over-the-counter medications have an outdate stamped on them—usually on the label or an end flap.

Are there dangers in using outdated drugs? Outdated drugs have lost some of their potency and will not be as effective. Some, such as aspirin, can undergo chemical changes and become more toxic.

How should drugs be stored? Ask your pharmacist, or refer to the consumer information sheets provided with new prescriptions, for storage instructions. Package labels should have storage information on them. Some drugs must be refrigerated; others must be kept frozen. All others should be kept away from extremely warm temperatures.

Where can I get additional, reliable information on my medications or my health condition(s)? Your pharmacist may be able to direct you to additional sources of information on your condition and on drug safety.

What are medication guides? Medication guides are information sheets about individual drugs that the U.S. Food and Drug Administration (FDA) has determined are necessary to help patients use their medications safely and effectively. They are available for several hundred drugs and are considered part of a drug's label; many can be obtained online.

Are consumer information sheets, given with new prescriptions, the same as medication guides? No. Consumer information sheets provide more general precautions and warnings and explain how to store and use medications.

Are generic drugs as safe and effective as brand-name drugs? Both generic and brand-name drugs are required by the FDA to contain the same concentration and purity of active ingredient.

Why I can take some brands or generics, and not others? Though all drugs are required to have equal purity and potency, manufacturers formulate their products differently into capsules, pills, or liquids. That can explain the difference in taste or effects.

Are prescription drugs and herbal products regulated and monitored the same way? No. There are vast and important differences between how the FDA monitors and regulates prescription drugs and herbal products.

Can foods or nutritional products like vitamins have effects on prescription drugs? Yes. The effects can take place in the stomach or intestinal tract or in the liver, which processes all substances equally. The effects can be profound.

What precautions should I take while starting on a new medicine? Talk with your pharmacist about how the drug may effect you—how you might feel, whether

alcohol increases the drug's effects, and if you should restrict activities like driving or using machinery until you have adjusted to the drug's effects. It is wise to use caution until you determine how a new drug affects you.

Can I cut or crush this medicine and take it with applesauce, or open the capsule and sprinkle the contents on food? The form of some drugs can be changed to facilitate taking them. Your pharmacist can help you with your specific medication.

How can I tell if what I am feeling is caused by an adverse/side effect of a drug or a drug interaction? Unfortunately, there is no way to know for sure. Some adverse effects and interactions occur immediately. Some develop gradually over time. If you take several drugs and are developing new symptoms, it would be wise to talk with your pharmacist about the possibility of adverse effects or interactions.

LIST OF CONFUSED DRUG NAMES

Institute for Safe Medication Practice's (ISMP) List of *Confused Drug Names*

This list of confused drug names, which includes look-alike and sound-alike name pairs, consists of those name pairs that have been published in the *ISMP Medication Safety Alert!*® and the *ISMP Medication Safety Alert!*® Community/Ambulatory Care Edition. Events involving these medications were reported to ISMP through either the ISMP National Medication Errors Reporting Program (ISMP MERP) or ISMP National Vaccine Errors Reporting Program (ISMP VERP). We hope you will use this list to determine which medications require special safeguards to reduce the risk of errors. This may include strategies such as: using both the brand and generic names on prescriptions and labels; including the purpose of the medication on prescriptions; configuring computer selection screens to prevent look-alike names from appearing consecutively; and changing the appearance of look-alike product names to draw attention to their dissimilarities. Both the FDA-approved and the ISMP-recommended tall man (mixed case) letters have been included in the list below.

Updated February 2015

Drug Name	Confused Drug Name	Drug Name	Confused Drug Name
Abelcet	amphotericin B	Afrin (saline)	Afrin (oxymetazoline)
Accupril	Aciphex	Aggrastat	argatroban
aceta ZOLAMIDE	aceto HEXAMIDE	Aldara	Alora
acetic acid for irrigation	glacial acetic acid	Alkeran	Leukeran
aceto HEXAMIDE	aceta ZOLAMIDE	Alkeran	Myleran
Aciphex	Accupril	Allegra (fexofenadine)	Allegra Anti-Itch Cream (diphenhydramine/allantoin)
Aciphex	Aricept	Allegra	Viagra
Activase	Cathflo Activase	Allegra Anti-Itch Cream (diphenhydramine/allantoin)	Allegra (fexofenadine)
Activase	TNKase	Alora	Aldara
Actonel	Actos	ALPRAZolam	LORazepam
Actos	Actonel	Altacor	Advicor
Adacel (Tdap)	Daptacel (DTaP)	amantadine	amiodarone
Adderall	Inderal	Amaryl	Reminyl
Adderall	Adderall XR	Ambisome	amphotericin B
Adderall XR	Adderall	Amicar	Omacor
ado-trastuzumab emtansine	trastuzumab	Amikin	Kineret
Advair	Advicor	a MILoride	am LODIPine
Advicor	Advair	amiodarone	amantadine
Advicor	Altacor	am LODIPine	a MILoride
Afrin (oxymetazoline)	Afrin (saline)	amphotericin B	Abelcet

Note: Brand names always start with an uppercase letter. Some brand names incorporate tall man letters in initial characters and may not be readily recognized as brand names. Brand name products appear in black; generic/other products appear in red.

Institute for Safe Medication Practice's (ISMP) List of *Confused Drug Names* [CONTINUED]

Drug Name	Confused Drug Name	Drug Name	Confused Drug Name
amphotericin B	Ambisome	Axert	Antivert
Anacin	Anacin-3	azaCITIDine	azaTHIOprine
Anacin-3	Anacin	azaTHIOprine	azaCITIDine
antacid	Atacand	Azilect	Aricept
Anticoagulant Citrate Dextrose Solution Formula A	Anticoagulant Sodium Citrate Solution	B & O (belladonna and opium)	Beano
Anticoagulant Sodium Citrate Solution	Anticoagulant Citrate Dextrose Solution Formula A	BabyBIG	HBIG (hepatitis B immune globulin)
Antivert	Axert	Bayhep-B	Bayrab
Anzemet	Avandamet	Bayhep-B	Bayrho-D
Apidra	Spiriva	Bayrab	Bayhep-B
Apresoline	Priscoline	Bayrab	Bayrho-D
argatroban	Aggrastat	Bayrho-D	Bayhep-B
argatroban	Orgaran	Bayrho-D	Bayrab
Aricept	Aciphex	Beano	B & O (belladonna and opium)
Aricept	Azilect	Benadryl	benazepril
ARIPIprazole	proton pump inhibitors	benazepril	Benadryl
ARIPIprazole	RABEprazole	Benicar	Mevacor
Arista AH (absorbable hemostatic agent)	Arixtra	Betadine (with providone-iodine)	Betadine (without providone-iodine)
Arixtra	Arista AH (absorbable hemostatic agent)	Betadine (without providone-iodine)	Betadine (with providone-iodine)
Asacol	Os-Cal	Bextra	Zetia
Atacand	antacid	Bicillin C-R	Bicillin L-A
atomoxetine	atorvastatin	Bicillin L-A	Bicillin C-R
atorvastatin	atomoxetine	Bicitra	Polycitra
Atrovent	Natru-Vent	Bidex	Videx
Avandamet	Anzemet	Brethine	Methergine
Avandia	Prandin	Bio-T-Gel	T-Gel
Avandia	Coumadin	Brevibloc	Brevital
AVINza	INVanz	Brevital	Brevibloc
AVINza	Evista	Brilinta	Brintellix

Institute for Safe Medication Practice's (ISMP) List of *Confused Drug Names* [CONTINUED]

Drug Name	Confused Drug Name	Drug Name	Confused Drug Name
Brintellix	Brilinta	chlorpro MAZINE	chlordiazep OXIDE
bu PROP ion	bus PIR one	chlorpro MAZINE	chlorpro PAMIDE
bus PIR one	bu PROP ion	chlorpro PAMIDE	chlorpro MAZINE
Capadex [non-US product]	Kapidex	Cidex	Cedax
Capex	Kapidex	CIS platin	CARBO platin
Carac	Kuric	Claritin (loratadine)	Claritin Eye (ketotifen fumarate)
captopril	carvedilol	Claritin-D	Claritin-D 24
car BAM azepine	OX carbazepine	Claritin-D 24	Claritin-D
CARBO platin	CIS platin	Claritin Eye (ketotifen fumarate)	Claritin (loratadine)
Cardene	Cardizem	Clindesse	Clindets
Cardizem	Cardene	Clindets	Clindesse
Cardura	Coumadin	clobazam	clonazep PAM
carvedilol	captopril	clomi PHENE	clomi PRAMINE
Casodex	Kapidex	clomi PRAMINE	clomi PHENE
Cathflo Activase	Activase	clonazep PAM	clobazam
Cedax	Cidex	clonazep PAM	clo NID ine
ce FAZ olin	cef TRIA Xone	clonazep PAM	LOR azepam
cef TRIA Xone	ce FAZ olin	clo NID ine	clonazep PAM
Cele BREX	Cele XA	clo NID ine	Klono PIN
Cele BREX	Cerebyx	Clozaril	Colazal
Cele XA	Zy PREXA	coagulation factor IX (recombinant)	factor IX complex, vapor heated
Cele XA	Cele BREX	codeine	Lodine
Cele XA	Cerebyx	Colace	Cozaar
Cerebyx	Cele BREX	Colazal	Clozaril
Cerebyx	Cele XA	colchicine	Cortrosyn
cetirizine	sertraline	Comvax	Recombivax HB
cetirizine	stavudine	Cortrosyn	colchicine
chlordiazep OXIDE	chlorpro MAZINE	Coumadin	Avandia

Institute for Safe Medication Practice's (ISMP) List of *Confused Drug Names* [CONTINUED]

Drug Name	Confused Drug Name	Drug Name	Confused Drug Name
Coumadin	Cardura	Diabinese	Diamox
Covaryx HS	Covera HS	Diabeta	Zebeta
Covera HS	Covaryx HS	Diamox	Diabinese
Cozaar	Colace	Diflucan	Diprivan
Cozaar	Zocor	Dilacor XR	Pilocar
cyclophosphamide	cyclo SPORINE	Dilaudid	Dilaudid-5
cyclo SERINE	cyclo SPORINE	Dilaudid-5	Dilaudid
cyclo SPORINE	cyclophosphamide	dimenhy DRINATE	diphenhydr AMINE
cyclo SPORINE	cyclo SERINE	diphenhydr AMINE	dimenhy DRINATE
Cymbalta	Symbyax	Dioval	Diovan
DACTIN omycin	DAPTO mycin	Diovan	Dioval
Daptacel (DTaP)	Adacel (Tdap)	Diovan	Zyban
DAPTO mycin	DACTIN omycin	Diovan	Darvon
Darvocet	Percocet	Diprivan	Diflucan
Darvon	Diovan	Diprivan	Ditropan
DAUNO rubicin	DAUNO rubicin citrate liposomal	disopyramide	desipramine
DAUNO rubicin	DOXO rubicin	Ditropan	Diprivan
DAUNO rubicin	IDA rubicin	DOBUT amine	DOP amine
DAUNO rubicin citrate liposomal	DAUNO rubicin	DOP amine	DOBUT amine
Denavir	indinavir	Doribax	Zovirax
Depakote	Depakote ER	Doxil	Paxil
Depakote ER	Depakote	DOXO rubicin	DAUNO rubicin
Depo-Medrol	Solu- MEDROL	DOXO rubicin	DOXO rubicin liposomal
Depo-Provera	Depo-subQ provera 104	DOXO rubicin	IDA rubicin
Depo-subQ provera 104	Depo-Provera	DOXO rubicin liposomal	DOXO rubicin
desipramine	disopyramide	Dulcolax (bisacodyl)	Dulcolax (docusate sodium)
Desyrel	SERO quel	Dulcolax (docusate sodium)	Dulcolax (bisacodyl)
dexmethylphenidate	methadone	DULO xetine	FLU xetine

Institute for Safe Medication Practice's (ISMP) List of *Confused Drug Names* [CONTINUED]

Drug Name	Confused Drug Name	Drug Name	Confused Drug Name
Durasal	Durezol	Farxiga	Fetzima
Durezol	Durasal	Fastin (phentermine)	Fastin (dietary supplement)
Duricef	Ultracet	Fastin (dietary supplement)	Fastin (phentermine)
Dynacin	Dynacirc	Femara	Femhrt
Dynacirc	Dynacin	Femhrt	Femara
edetate calcium disodium	edetate disodium	fentaNYL	SUFentanil
edetate disodium	edetate calcium disodium	Fetzima	Farxiga
Effexor	Effexor XR	Fioricet	Fiorinal
Effexor XR	Enablex	Fiorinal	Fioricet
Effexor XR	Effexor	flavoxATE	fluvoxamine
Enablex	Effexor XR	Flonase	Flovent
Enbrel	Levbid	Floranex	Florinef
Engerix-B adult	Engerix-B pediatric/adolescent	Florastor	Florinef
Engerix-B pediatric/adolescent	Engerix-B adult	Florinef	Floranex
Enjuvia	Januvia	Florinef	Florastor
ePHEDrine	EPINEPHrine	Flovent	Flonase
EPINEPHrine	ePHEDrine	flumazenil	influenza virus vaccine
epirubicin	eribulin	FLUoxetine	PARoxetine
eribulin	epirubicin	FLUoxetine	DULoxetine
Estratest	Estratest HS	FLUoxetine	Loxitane
Estratest HS	Estratest	fluvoxamine	flavoxATE
ethambutol	Ethmozine	Focalgin B	Focalin
ethavirine [non-US name]	etravirine	Focalin	Focalgin B
Ethmozine	ethambutol	Folex	Foltx
etravirine	ethavirine [non-US name]	folic acid	folinic acid (leucovorin calcium)
Evista	AVINza	folinic acid (leucovorin calcium)	folic acid
factor IX complex, vapor heated	coagulation factor IX (recombinant)	Foltx	Folex
Fanapt	Xanax	fomepizole	omeprazole

Institute for Safe Medication Practice's (ISMP) List of *Confused Drug Names* [CONTINUED]

Drug Name	Confused Drug Name	Drug Name	Confused Drug Name
Foradil	Fortical	Hyalgan	Healon
Foradil	Toradol	hydr ALAZINE	hydr OXY zine
Fortical	Foradil	Hydrea	Lyrica
gentamicin	gentian violet	HYDRO codone	oxy CODONE
gentian violet	gentamicin	Hydrogesic	hydr OXY zine
glacial acetic acid	acetic acid for irrigation	HYDRO morphine	morphine
glipi ZIDE	gly BURIDE	hydr OXY zine	Hydrogesic
Glucotrol	Glycotrol	hydr OXY zine	hydr ALAZINE
gly BURIDE	glipi ZIDE	IDA rubicin	DAUNO rubicin
Glycotrol	Glucotrol	IDA rubicin	DOXO rubicin
Granulex	Regranex	Inderal	Adderall
guai FEN esin	guan FACINE	indinavir	Denavir
guan FACINE	guai FEN esin	in FLIX imab	ri TUX imab
HBIG (hepatitis B immune globulin)	BabyBIG	influenza virus vaccine	flumazenil
Healon	Hyalgan	influenza virus vaccine	perflutren lipid microspheres
heparin	Hespan	influenza virus vaccine	tuberculin purified protein derivative (PPD)
Hespan	heparin	Inspira	Spiriva
HMG-CoA reductase inhibitors ("statins")	nystatin	Intuniv	Invega
Huma LOG	Humu LIN	INV anz	AVIN za
Huma LOG	Novo LOG	Invega	Intuniv
Huma LOG Mix 75/25	Humu LIN 70/30	iodine	Lodine
Humapen Memoir (for use with Huma LOG)	Humira Pen	Isordil	Plendil
Humira Pen	Humapen Memoir (for use with Huma LOG)	ISO tretinoin	tretinoin
Humu LIN	Novo LIN	Jantoven	Janumet
Humu LIN	Huma LOG	Jantoven	Januvia
Humu LIN 70/30	Huma LOG Mix 75/25	Janumet	Jantoven
Humu LIN R U-100	Humu LIN R U-500	Janumet	Januvia
Humu LIN R U-500	Humu LIN R U-100	Janumet	Sinemet

Institute for Safe Medication Practice's (ISMP) List of *Confused Drug Names* [CONTINUED]

Drug Name	Confused Drug Name	Drug Name	Confused Drug Name
Januvia	Enjuvia	Lanoxin	levothyroxine
Januvia	Jantoven	Lanoxin	naloxone
Januvia	Janumet	lanthanum carbonate	lithium carbonate
K-Phos Neutral	Neutra-Phos-K	Lantus	Latuda
Kaopectate (bismuth subsalicylate)	Kaopectate (docusate calcium)	Lantus	Lente
Kaopectate (docusate calcium)	Kaopectate (bismuth subsalicylate)	Lariam	Levaquin
Kadian	Kapidex	Lasix	Luvox
Kaletra	Keppra	Latuda	Lantus
Kapidex	Capadex [non-US product]	Lente	Lantus
Kapidex	Capex	Letairis	Letaris [non-US product]
Kapidex	Casodex	Letaris [non-US product]	Letairis
Kapidex	Kadian	leucovorin calcium	Leukeran
Keflex	Keppra	leucovorin calcium	levoleucovorin
Keppra	Kaletra	Leukeran	Alkeran
Keppra	Keflex	Leukeran	Myleran
Ketalar	ketorolac	Leukeran	leucovorin calcium
ketorolac	Ketalar	Levaquin	Lariam
ketorolac	methadone	Levbid	Enbrel
Kineret	Amikin	levETIRAcetam	lamoTRIGine
KlonoPIN	cloNIDine	Levemir	Lovenox
Kuric	Carac	levETIRAcetam	levOCARNitine
Kwell	Qwell	levETIRAcetam	levofloxacin
LaMICTal	LamISIL	levOCARNitine	levETIRAcetam
LamISIL	LaMICTal	levofloxacin	levETIRAcetam
lamiVUDine	lamoTRIGine	levoleucovorin	leucovorin calcium
lamoTRIGine	lamiVUDine	levothyroxine	lamoTRIGine
lamoTRIGine	levETIRAcetam	levothyroxine	Lanoxin
lamoTRIGine	levothyroxine	levothyroxine	liothyronine

Institute for Safe Medication Practice's (ISMP) List of *Confused Drug Names* [CONTINUED]

Drug Name	Confused Drug Name	Drug Name	Confused Drug Name
Lexapro	Loxitane	Matulane	Materna
Lexiva	Pexeva	Materna	Matulane
liothyronine	levothyroxine	Maxzide	Microzide
Lipitor	Loniten	Menactra	Menomune
Lipitor	ZyrTEC	Menomune	Menactra
lithium	Ultram	Mephyton	methadone
lithium carbonate	lanthanum carbonate	Metadate	methadone
Lodine	codeine	Metadate CD	Metadate ER
Lodine	iodine	Metadate ER	Metadate CD
Loniten	Lipitor	Metadate ER	methadone
Lopressor	Lyrica	metFORMIN	metroNIDAZOLE
LORazepam	ALPRAZolam	methadone	dexmethylphenidate
LORazepam	clonazepam	methadone	ketorolac
LORazepam	Lovaza	methadone	Mephyton
Lotronex	Protonix	methadone	Metadate
Lovaza	LORazepam	methadone	Metadate ER
Lovenox	Levemir	methadone	methylphenidate
Loxitane	Lexapro	methadone	metolazone
Loxitane	FLUoxetine	Methergine	Brethine
Loxitane	Soriatane	methimazole	metolazone
Lunesta	Neulasta	methylene blue	VisionBlue
Lupron Depot-3 Month	Lupron Depot-Ped	methylphenidate	methadone
Lupron Depot-Ped	Lupron Depot-3 Month	metolazone	methadone
Luvox	Lasix	metolazone	methimazole
Lyrica	Hydrea	metoprolol succinate	metoprolol tartrate
Lyrica	Lopressor	metoprolol tartrate	metoprolol succinate
Maalox	Maalox Total Stomach Relief	metroNIDAZOLE	metFORMIN
Maalox Total Stomach Relief	Maalox	Mevacor	Benicar

Institute for Safe Medication Practice's (ISMP) List of *Confused Drug Names* [CONTINUED]

Drug Name	Confused Drug Name	Drug Name	Confused Drug Name
Micronase	Microzide	Natru-Vent	Atrovent
Microzide	Maxzide	Navane	Norvasc
Microzide	Micronase	Neo-Synephrine (oxymetazoline)	Neo-Synephrine (phenylephrine)
midodrine	Midrin	Neo-Synephrine (phenylephrine)	Neo-Synephrine (oxymetazoline)
Midrin	midodrine	Neulasta	Lunesta
mifepristone	misoprostol	Neulasta	Neumega
Miralax	Mirapex	Neulasta	Nuedexta
Mirapex	Miralax	Neumega	Neupogen
misoprostol	mifepristone	Neumega	Neulasta
mitoMYcin	mitoXANtrone	Neupogen	Neumega
mitoXANtrone	mitoMYcin	Neurontin	Motrin
morphine	HYDROmorphine	Neurontin	Noroxin
morphine - non-concentrated oral liquid	morphine - oral liquid concentrate	Neutra-Phos-K	K-Phos Neutral
morphine - oral liquid concentrate	morphine - non-concentrated oral liquid	NexAVAR	NexIUM
Motrin	Neurontin	NexIUM	NexAVAR
MS Contin	OxyCONTIN	niCARDipine	NIFEdipine
Mucinex	Mucinex Allergy	NIFEdipine	niCARDipine
Mucinex	Mucomyst	NIFEdipine	niMODipine
Mucinex Allergy	Mucinex	niMODipine	NIFEdipine
Mucinex D	Mucinex DM	Norcuron	Narcan
Mucinex DM	Mucinex D	Normodyne	Norpramin
Mucomyst	Mucinex	Noroxin	Neurontin
Myleran	Alkeran	Norpramin	Normodyne
Myleran	Leukeran	Norvasc	Navane
nalbuphine	naloxone	NovoLIN	HumuLIN
naloxone	Lanoxin	NovoLIN	NovoLOG
naloxone	nalbuphine	NovoLIN 70/30	NovoLOG Mix 70/30
Narcan	Norcuron	NovoLOG	HumaLOG

Institute for Safe Medication Practice's (ISMP) List of *Confused Drug Names* [CONTINUED]

Drug Name	Confused Drug Name	Drug Name	Confused Drug Name
Novo LOG	Novo LIN	Pamelor	Tambocor
Novo LOG Flexpen	Novo LOG Mix 70/30 Flexpen	Panlor DC	Pamelor
Novo LOG Mix 70/30 Flexpen	Novo LOG Flexpen	paregoric (camphorated tincture of opium)	opium tincture
Novo LOG Mix 70/30	Novo LIN 70/30	PAR oxetine	FLU oxetine
Nuedexta	Neulasta	PAR oxetine	piroxicam
nystatin	HMG-CoA reductase inhibitors ("statins")	Patanol	Platinol
Occlusal-HP	Ocuflox	Pavulon	Peptavlon
Ocuflox	Occlusal-HP	Paxil	Doxil
OLAN zapine	QUET iapine	Paxil	Taxol
Omacor	Amicar	Paxil	Plavix
omeprazole	fomepizole	PAZO Panib	PONAT inib
opium tincture	paregoric (camphorated tincture of opium)	PEME trexed	PRALA trexate
Oracea	Orencia	penicillin	penicillAMINE
Orencia	Oracea	penicillAMINE	penicillin
Orgaran	argatroban	Peptavlon	Pavulon
Ortho Tri-Cyclen	Ortho Tri-Cyclen LO	Percocet	Darvocet
Ortho Tri-Cyclen LO	Ortho Tri-Cyclen	Percocet	Procet
Os-Cal	Asacol	perflutren lipid microspheres	influenza virus vaccine
oxaprozin	OX carbazepine	Pexeva	Lexiva
OX carbazepine	oxaprozin	PENT obarbital	PHEN obarbital
OX carbazepine	car BAM azepine	PHEN obarbital	PENT obarbital
oxyCODONE	HYDRO codone	Pilocar	Dilacor XR
oxyCODONE	Oxy CONTIN	piroxicam	PAR oxetine
Oxy CONTIN	MS Contin	Platinol	Patanol
Oxy CONTIN	oxyCODONE	Plavix	Paxil
PACL itaxel	PACL itaxel protein-bound particles	Plavix	Pradax [Non-US Product]
PACL itaxel protein-bound particles	PACL itaxel	Plavix	Pradaxa
Pamelor	Panlor DC	Plendil	Isordil

Institute for Safe Medication Practice's (ISMP) List of *Confused Drug Names* [CONTINUED]

Drug Name	Confused Drug Name	Drug Name	Confused Drug Name
pneumococcal 7-valent vaccine	pneumococcal polyvalent vaccine	protamine	Protonix
pneumococcal polyvalent vaccine	pneumococcal 7-valent vaccine	proton pump inhibitors	ARI Piprazole
Polycitra	Bicitra	Protonix	Lotronex
PONAT inib	PAZO Panib	Protonix	protamine
potassium acetate	sodium acetate	Provera	Proscar
PRALA trexate	PEME trexed	Provera	PRO zac
Pradax [Non-US Product]	Plavix	PRO zac	Prograf
Pradaxa	Plavix	PRO zac	Pri LOSEC
Prandin	Avandia	PRO zac	Provera
Precare	Precose	Purinethol	propylthiouracil
Precose	Precare	Pyridium	pyridoxine
predni LONE	predni SONE	pyridoxine	Pyridium
predni SONE	predni LONE	QUET iapine	OLAN Zapine
Prenexa	Ranexa	qui NID ine	qui NINE
Pri LOSEC	Pristiq	qui NINE	qui NID ine
Pri LOSEC	PRO zac	Qwell	Kwell
Priscoline	Apresoline	RABE prazole	ARI Piprazole
Pristiq	Pri LOSEC	Ranexa	Prenexa
probenecid	Procanbid	Rapaflo	Rapamune
Procan SR	Procanbid	Rapamune	Rapaflo
Procanbid	probenecid	Razadyne	Rozerem
Procanbid	Procan SR	Recombivax HB	Comvax
Procardia XL	Protain XL	Regranex	Granulex
Procet	Percocet	Reminyl	Robinul
Prograf	PRO zac	Reminyl	Amaryl
propylthiouracil	Purinethol	Renagel	Renvela
Proscar	Provera	Renvela	Renagel
Protain XL	Procardia XL	Reprexain	Zy PREXA

Institute for Safe Medication Practice's (ISMP) List of *Confused Drug Names* [CONTINUED]

Drug Name	Confused Drug Name	Drug Name	Confused Drug Name
Restoril	Risper DAL	saquinavir mesylate	saquinavir (free base)
Retrovir	ritonavir	Sarafem	Serophene
Rifadin	Rifater	selegiline	Salagen
Rifamate	rifampin	Serophene	Sarafem
rifampin	Rifamate	SERO quel	Desyrel
rifampin	rifaximin	SERO quel	SERO quel XR
Rifater	Rifadin	SERO quel	Serzone
rifaximin	rifampin	SERO quel	SINE quan
Risper DAL	Restoril	SERO quel XR	SERO quel
risperi DONE	r OPINI Role	sertraline	cetirizine
Ritalin	ritodrine	sertraline	Soriatane
Ritalin LA	Ritalin SR	Serzone	SERO quel
Ritalin SR	Ritalin LA	siodosin	sirolimus
ritodrine	Ritalin	Sinemet	Janumet
ritonavir	Retrovir	SINE quan	saquinavir
ri TUX imab	in FLIX imab	SINE quan	SERO quel
Robinul	Reminyl	SINE quan	Singulair
r OPINI Role	risperi DONE	SINE quan	Zonegran
Roxanol	Roxicodone Intensol	Singulair	SINE quan
Roxanol	Roxicet	sirolimus	siodosin
Roxicet	Roxanol	sita GLIPT in	SUM Atriptan
Roxicodone Intensol	Roxanol	sodium acetate	potassium acetate
Rozerem	Razadyne	Solu- CORTEF	Solu- MEDROL
Salagen	selegiline	Solu- MEDROL	Depo-Medrol
Sand IMMUNE	Sando STATIN	Solu- MEDROL	Solu- CORTEF
Sando STATIN	Sand IMMUNE	Sonata	Soriatane
saquinavir	SINE quan	Soriatane	Loxitane
saquinavir (free base)	saquinavir mesylate	Soriatane	sertraline

Institute for Safe Medication Practice's (ISMP) List of *Confused Drug Names* [CONTINUED]

Drug Name	Confused Drug Name	Drug Name	Confused Drug Name
Soriatane	Sonata	Tequin	TEG retol
sotalol	Sudafed	Tequin	Ticlid
Spiriva	Apidra	Testoderm	Testoderm with Adhesive
Spiriva	Inspra	Testoderm	Testoderm TTS
stavudine	cetirizine	Testoderm with Adhesive	Testoderm
Sudafed	sotalol	Testoderm with Adhesive	Testoderm TTS
Sudafed	Sudafed PE	Testoderm TTS	Testoderm
Sudafed 12 Hour	Sudafed 12 Hour Pressure + Pain	Testoderm TTS	Testoderm with Adhesive
Sudafed 12 Hour Pressure + Pain	Sudafed 12 Hour	tetanus diphtheria toxoid (Td)	tuberculin purified protein derivative (PPD)
Sudafed PE	Sudafed	Thalomid	Thiamine
SUF entanil	fentaNYL	Thiamine	Thalomid
sulfADIAZINE	sulfaSALAZINE	tiaGABine	tiZANidine
sulfADIAZINE	sulfiSOXAZOLE	Tiazac	Ziac
sulfaSALAZINE	sulfADIAZINE	Ticlid	Tequin
sulfiSOXAZOLE	sulfADIAZINE	tiZANidine	tiaGABine
SUMA riptan	sitaGLIPTin	TNKase	Activase
SUMA riptan	ZOLM itriptan	TNKase	t-PA
Symbyax	Cymbalta	Tobradex	Tobrex
T-Gel	Bio-T-Gel	Tobrex	Tobradex
Tambocor	Pamelor	TOLAZ amide	TOLBUT amide
Taxol	Taxotere	TOLBUT amide	TOLAZ amide
Taxol	Paxil	Topamax	Toprol-XL
Taxotere	Taxol	Toprol-XL	Topamax
TEG retol	TEG retol XR	Toradol	Foradil
TEG retol	Tequin	t-PA	TNKase
TEG retol	TRE ntal	Tracleer	Tricor
TEG retol XR	TEG retol	traMADol	traZOD one
Tenex	Xanax	trastuzumab	ado-trastuzumab emtansine

Institute for Safe Medication Practice's (ISMP) List of *Confused Drug Names* [CONTINUED]

Drug Name	Confused Drug Name	Drug Name	Confused Drug Name
tra ZOD one	tra MAD ol	Viramune	Viracept
TRE ntal	TEG retol	Viramune (nevairapine)	Viramune (herbal product)
tretinoi n	ISO tretinoin	Viramune (herbal product)	Viramune (nevairapine)
Tricor	Tracleer	VisionBlue	methylene blue
tromethamine	Trophamine	Vosol	Vexol
Trophamine	tromethamine	VZIG (varicella-zoster immune globulin)	Varivax
tuberculin purified protein derivative (PPD)	influenza virus vaccine	Wellbutrin SR	Wellbutrin XL
tuberculin purified protein derivative (PPD)	tetanus diphtheria toxoid (Td)	Wellbutrin XL	Wellbutrin SR
Tylenol	Tylenol PM	Xanax	Fanapt
Tylenol PM	Tylenol	Xanax	Tenex
Ultracet	Duricef	Xanax	Zantac
Ultram	lithium	Xeloda	Xenical
valACY clovir	valGAN ciclovir	Xenical	Xeloda
Valcyte	Valtrex	Yasmin	Yaz
valGAN ciclovir	valACY clovir	Yaz	Yasmin
Valtrex	Valcyte	Zantac	Xanax
Varivax	VZIG (varicella-zoster immune globulin)	Zantac	Zyr TEC
Vesanoid	Vesicare	Zavesca (escitalopram) [non-US product]	Zavesca (miglustat)
Vesicare	Vesanoid	Zavesca (miglustat)	Zavesca (escitalopram) [non-US product]
Vexol	Vosol	Zebeta	Diabeta
Viagra	Allegra	Zebeta	Zetia
Videx	Bidex	Zegerid	Zestril
vinBLAS tine	vinCRIS tine	Zelapar (Zydis formulation)	Zy PREXA Zydis
vinCRIS tine	vinBLAS tine	Zerit	Zyr TEC
Viokase	Viokase 8	Zestril	Zegerid
Viokase 8	Viokase	Zestril	Zetia
Vioxx	Zyvox	Zestril	Zy PREXA
Viracept	Viramune	Zetia	Bextra

Institute for Safe Medication Practice's (ISMP) List of *Confused Drug Names* [CONTINUED]

Drug Name	Confused Drug Name	Drug Name	Confused Drug Name
Zetia	Zebeta	ZyPREXA	Reprexain
Zetia	Zestril	ZyPREXA	Zestril
Ziac	Tiazac	ZyPREXA	ZyrTEC
Zocor	Cozaar	ZyPREXA Zydis	Zelapar (Zydis formulation)
Zocor	ZyrTEC	ZyrTEC	Lipitor
ZOLM itriptan	SUM Atriptan	ZyrTEC	Zantac
zolpidem	Zyloprim	ZyrTEC	Zerit
Zonegran	SINE quan	ZyrTEC	Zocor
Zostrix	Zovirax	ZyrTEC	ZyPREXA
Zovirax	Doribax	ZyrTEC	ZyrTEC-D
Zovirax	Zyvox	ZyrTEC (cetirizine)	ZyrTEC Itchy Eye Drops (ketotifen fumarate)
Zovirax	Zostrix	ZyrTEC-D	ZyrTEC
Zyban	Diovan	ZyrTEC Itchy Eye Drops (ketotifen fumarate)	ZyrTEC (cetirizine)
Zyloprim	zolpidem	Zyvox	Vioxx
ZyPREXA	CeleXA	Zyvox	Zovirax

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ORGANIZATIONS

The following is an alphabetical compilation of relevant organizations listed in the *Resources* sections of the main body entries. Although the list is comprehensive, it is by no means exhaustive. It is a starting point for gathering further information. Many of the organizations listed provide information for multiple topics and have links to additional related websites. E-mail addresses and web addresses listed were provided by the associations; Gale is not responsible for the accuracy of the addresses or the contents of the websites.

A

Agency for Healthcare Research and Quality

540 Gaither Road
Rockville, MD 20850
Phone: (301) 427-1364
Website: <http://www.ahrq.gov/>

AIDSinfo

PO Box 4780
Rockville, MD 20849-6303
Phone: (301) 315-2816
Toll free: (800) HIV-0440 (448-0440)
Fax: (301) 315-2818
TTY: (888) 480-3739
E-mail: ContactUs@aidinfo.nih.gov
Website: <http://aidinfo.nih.gov/>

Alliance for the Prudent Use of Antibiotics (APUA)

136 Harrison Avenue, M&V Suite 111
Boston, MA 02111
Phone: (617) 636-0966
E-mail: apua@tufts.edu
Website: <http://www.tufts.edu/med/apua>

Alzheimer's Association

225 N. Michigan Avenue, Floor 17
Chicago, IL 60601-7633
Phone: (312) 335-8700
Toll free: (800) 272-3900
Fax: (866) 699-1246
TTY: (866) 403-3073
E-mail: info@alz.org
Website: <http://www.alz.org/>

Alzheimer's Foundation of America

322 Eighth Avenue, 7th Floor
New York, NY 10001
Phone: (646) 638-1542
Toll free: (866) 232-8484
Fax: (646) 638-1546
Website: <http://www.alzfdn.org/>

Alzheimer's Society

Devon House, 58 St. Katharine's Way
London E1W 1LB

England

Phone: +44 0300 222 11 22
E-mail: Enquiries@alzheimers.org.uk
Website: <http://www.alzheimers.org.uk/>

American Academy of Allergy, Asthma & Immunology (AAAAI)

555 E. Wells Street, Suite 1100
Milwaukee, WI 53202-3823
Phone: (414) 272-6071
Website: <http://www.aaaai.org/>

American Academy of Child and Adolescent Psychiatry

3615 Wisconsin Avenue NW
Washington, DC 20016-3007
Phone: (202) 966-7300
Fax: (202) 966-2891
Website: <http://aacap.org/>

American Academy of Clinical Toxicology

6728 Old McLean Village Drive
McLean, VA 22101
Phone: (703) 556-9222
Fax: (703) 556-8729
E-mail: admin@clintox.org
Website: <http://www.clintox.org/>

American Academy of Dermatology

930 E. Woodfield Road
Schaumburg, IL 60173
Phone: (847) 240-1280
Toll free: (866) 503-SKIN (7546)
Fax: (847) 240-1859
Website: <https://www.aad.org/>

American Academy of Family Physicians

11400 Tomahawk Creek Parkway
Leawood, KS 66211-2680
Phone: (913) 906-6000
Toll free: (800) 274-2237
Fax: (913) 906-6075
E-mail: contactcenter@aafp.org
Website: <http://www.aafp.org/>

American Academy of HIV Medicine

1705 DeSales Street NW, Suite 700
Washington, DC 20036
Phone: (202) 659-0699
Fax: (202) 659-0976
Website: <http://www.aahivm.org/>

American Academy of Neurology (AAN)

201 Chicago Avenue
Minneapolis, MN 55415
Phone: (612) 928-6000
Toll free: (800) 879-1960
Fax: (612) 454-2746
E-mail: memberservices@aan.com
Website: <http://www.aan.com/>

American Academy of Ophthalmology

655 Beach Street
San Francisco, CA 94109
Phone: (415) 561-8500
Fax: (415) 561-8533
E-mail: patientinfo@aao.org
Website: <http://www.aao.org/>

American Academy of Oral and Maxillofacial Pathology

214 North Hale Street
Wheaton, IL 60187
Phone: (630) 510-4552
Toll free: (888) 552-2667
Fax: (630) 510-4501
E-mail: info@aaomp.org
Website: <http://www.aaomp.org/>

American Academy of Orthopaedic Surgeons

9400 W. Higgins Road
Rosemont, IL 60018
Phone: (847) 823-7186
Fax: (847) 823-8125
Website: <http://aaos.org/>

American Academy of Pain Management

975 Morning Star Drive, Suite A
Sonoma, CA 95370

Phone: (209) 533-9744
E-mail: info@aapainmanage.org
Website: <http://www.aapainmanage.org/>

American Academy of Pain Medicine
8735 W. Higgins Road, Suite 300
Chicago, IL 60631-2738
Phone: (847) 375-4731
Fax: (847) 375-6477
E-mail: info@painmed.org
Website: <http://www.painmed.org/>

American Academy of Pediatrics
141 Northwest Point Boulevard
Elk Grove Village, IL 60007-1098
Phone: (847) 434-4000
Toll free: (800) 433-9016
Fax: (847) 434-8000
Website: <http://www.aap.org/>

American Academy of Physical Medicine and Rehabilitation
9700 West Bryn Mawr Avenue, Suite 200
Rosemont, IL 60018-5701
Phone: (847) 737-6000
E-mail: info@aapmr.org
Website: <http://www.aapmr.org/>

American Academy of Sleep Medicine
2510 North Frontage Road
Darien, IL 60561
Phone: (630) 737-9700
Fax: (630) 737-9790
E-mail: inquiries@aasmnet.org
Website: <http://www.aasmnet.org/>

American Association for the Study of Liver Diseases
1001 North Fairfax Street, Suite 400
Alexandria, VA 22314
Phone: (703) 299-9766
Fax: (703) 299-9622
E-mail: aasld@aasld.org
Website: <http://www.aasld.org/>

American Association of Clinical Endocrinologists
245 Riverside Avenue, Suite 200
Jacksonville, FL 32202
E-mail: contact@empoweryourhealth.org
Website: <http://www.empoweryourhealth.org/>

American Association of Clinical Urologists
1100 E. Woodfield Road, Suite 350
Schaumburg, IL 60173
Phone: 847-517-1050
Fax: 847-517-7229
E-mail: info@aacuweb.org
Website: <http://www.aacuweb.org/>

American Association for the Treatment of Opioid Dependence
225 Varick Street, Suite 402
New York, NY 10014
Phone: (212) 566-5555
Fax: (212) 366-4647
E-mail: info@aatod.org
Website: <http://www.aatod.org/>

American Cancer Society
250 Williams Street NW
Atlanta, GA 30303
Toll free: (800) 227-2345
Website: <http://www.cancer.org/>

American Chronic Pain Association
PO Box 850
Rocklin, CA 95677
Toll free: (800) 533-3231
Fax: (916) 632-3208
E-mail: ACPA@theacpa.org
Website: <http://www.theacpa.org/>

American College of Cardiology
Heart House, 2400 N Street NW
Washington, DC 20037
Phone: (202) 375-6000, ext. 5603
Toll free: (800) 253-4636, ext. 5603
Fax: (202) 375-7000
E-mail: resource@acc.org
Website: <http://www.acc.org/>

American College of Gastroenterology
6400 Goldsboro Road, Suite 200
Bethesda, MD 20817
Phone: (301) 263-9000
Website: <http://gi.org/>

American College of Neuropsychopharmacology
5034-A Thorroughbred Lane
Brentwood, TN 37027
Phone: (615) 324-2360
Fax: (615) 523-1715
E-mail: acnp@acnp.org
Website: <http://www.acnp.org/>

American College of Rheumatology
2200 Lake Boulevard NE
Atlanta, GA 30319
Phone: (404) 633-3777
Fax: (404) 633-1870
E-mail: acr@rheumatology.org
Website: <https://www.rheumatology.org/>

American College of Sports Medicine
401 West Michigan Street
Indianapolis, IN 46202-3233
Phone: (317) 637-9200
Fax: (317) 634-7817
Website: <http://www.acsm.org/>

American Congress of Obstetricians and Gynecologists
409 12th Street SW

Washington, DC 20024-2188
Phone: (202) 638-5577
Toll free: (800) 673-8444
E-mail: resources@acog.org
Website: <http://www.acog.org/>

American Dental Association
211 E. Chicago Avenue
Chicago, IL 60611-2678
Phone: (312) 440-2500
Website: <http://www.ada.org/>

American Dental Hygienists' Association
444 N. Michigan Avenue, Suite 3400
Chicago, IL 60611-3980
Phone: (312) 440-8900
Website: <http://www.adha.org/>

American Diabetes Association
1701 North Beauregard Street
Alexandria, VA 22311
Toll free: (800) DIABETES (342-2383)
Website: <http://www.diabetes.org/>

American Epilepsy Society
342 N Main Street
West Hartford, CT 06117-2507
Phone: (860) 586-7505
Website: <http://www.aesnet.org/>

American Gastroenterological Association
4930 Del Ray Avenue
Bethesda, MD 20814
Phone: (301) 654-2055
Fax: (301) 654-5920
E-mail: member@gastro.org
Website: <http://www.gastro.org/>

American Geriatrics Society
40 Fulton Street, 18th Floor
New York, NY 10038
Phone: (212) 308-1414
Fax: (212) 832-8646
E-mail: info.amger@americangeriatrics.org
Website: <http://www.americangeriatrics.org/>

American Headache Society
19 Mantua Road
Mount Royal, NJ 08061
Phone: (856) 423-0043
Fax: (856) 423-0082
E-mail: ahshq@talley.com
Website: <http://www.americanheadachesociety.org/>

American Heart Association
7272 Greenville Avenue
Dallas, TX 75231
Toll free: (800) AHA-USA-1 (242-8721)
Website: <http://www.heart.org/>

American Lung Association

55 W. Wacker Drive
Chicago, IL 60601
Toll free: (800) LUNGUSA (586-4872)
Fax: (202) 452-1805
Website: <http://www.lung.org/>

American Neurological Association

1120 Route 73, Suite 200
Mount Laurel, NJ 08054
Phone: (856) 380-6892
E-mail: info@myana.org
Website: <http://myana.org/>

American Osteopathic Association

142 E. Ontario Street
Chicago, IL 60611-2864
Phone: (312) 202-8000
Toll free: (800) 621-1773
Fax: (312) 202-8200
Website: <http://www.osteopathic.org/>

American Pain Society

8735 W. Higgins Road, Suite 300
Chicago, IL 60631
Phone: (847) 375-4715
Fax: (847) 375-6479
E-mail: info@americanpainsociety.org
Website: <http://www.americanpainsociety.org/>

American Psychiatric Association

1000 Wilson Boulevard, Suite 1825
Arlington, VA 22209-3901
Phone: (703) 907-7300
Toll free: (888) 35-PSYCH (357-7924)
E-mail: apa@psych.org
Website: <http://www.psych.org/>

American Psychological Association

750 First Street NE
Washington, DC 20002-4242
Phone: (202) 336-5500
Toll free: (800) 374-2721
TTY: (202) 336-6123
Website: <http://www.apa.org/>

American Sexually Transmitted Diseases Association

1005 Slater Road, Suite 330
Durham, NC 27709
Website: <http://www.astda.org/>

American Society for Clinical Pharmacology and Therapeutics

528 N. Washington Street
Alexandria, VA 22314
Phone: 703-836-6981
E-mail: info@ascpt.org
Website: <http://www.ascpt.org/>

American Society for Pharmacology and Experimental Therapeutics

9650 Rockville Pike
Bethesda, MD 20814-3995
Phone: (301) 634-7060
Website: <http://www.aspet.org/>

American Society for Preventative Cardiology (ASPC)

6816 Southpoint Parkway, Suite 1000
Jacksonville, FL 32216
Phone: (904) 309-6235
Fax: (904) 998-0855
Website: <https://www.asponline.org/>

American Society of Addiction Medicine

4601 N. Park Avenue, Upper Arcade #101
Chevy Chase, MD 20815
Phone: (301) 656-3920
Fax: (301) 656-3815
E-mail: email@asam.org
Website: <http://www.asam.org/>

American Society of Bariatric Physicians

2821 S. Parker Road, Suite 625
Aurora, CO 80014
Phone: (303) 770-2526
Fax: (303) 779-4834
Website: <http://www.asbp.org/>

American Society of Health-System Pharmacists

7272 Wisconsin Avenue
Bethesda, MD 20814
Toll free: (866) 279-0681
Website: <http://www.ashp.org/>

American Society of Hematology

2021 L Street NW, Suite 900
Washington, DC 20036
Phone: (202) 776-0544
Fax: (202) 776-0545
Website: <http://www.hematology.org/>

American Society of Hypertension

45 Main Street, Suite 712
Brooklyn, NY 11201
Phone: (212) 696-9099
Fax: (347) 916-0267
Website: <http://www.ash-us.org/>

American Thoracic Society

25 Broadway
New York, NY 10004
Phone: (212) 315-8600
Fax: (212) 315-6498
E-mail: ATSinfo@thoracic.org
Website: <http://www.thoracic.org/>

American Thyroid Association

6066 Leesburg Pike, Suite 550
Falls Church, VA 22041
Phone: (703) 998-8890
Fax: (703) 998-8893
E-mail: thyroid@thyroid.org
Website: <http://www.thyroid.org/>

amFAR (Foundation for AIDS Research)

120 Wall Street, 13th Floor
New York, NY 10005-3908

Phone: (212) 806-1600
Fax: (212) 806-1601
Website: <http://www.amfar.org/>

Anxiety Disorders Association of America

8701 Georgia Avenue, Suite 412
Silver Spring, MD 20910
Phone: (240) 485-1001
Website: <http://www.adaa.org/>

Arthritis Foundation

1330 W. Peachtree Street, Suite 100
Atlanta, GA 30309
Phone: (404) 872-7100
Website: <http://www.arthritis.org/>

Attention Deficit Disorder Association

PO Box 7557
Wilmington, DE 19803-9997
Toll free: (800) 939-1019
E-mail: info@adda.org
Website: <http://www.add.org/>

**Canadian Pain Society**

250 Consumers Road, Suite 301
Toronto
ON, M2J 4V6
Canada
Phone: (416) 642-6379
Fax: (416) 495-8723
E-mail: office@canadianpainsociety.ca
Website: <http://www.canadianpainsociety.ca/>

Centers for Disease Control and Prevention (CDC)

1600 Clifton Road
Atlanta, GA 30329
Phone: (404) 639-3534
Toll free: (800) CDC-INFO (800-232-4636)
TTY: (888) 232-6348
E-mail: inquiry@cdc.gov
Website: <http://www.cdc.gov/>

Children and Adults with Attention-Deficit/Hyperactivity Disorder

4601 Presidents Drive, Suite 300
Lanham, MD 20706
Phone: (301) 306-7070
Toll free: (800) 233-4050
Fax: (301) 306-7090
Website: <http://www.chadd.org/>

COPD Foundation

20 F Street NW, Suite 200A
Washington, DC 20001
Toll free: (866) 316-COPD (2673)
E-mail: info@copdfoundation.org
Website: <http://www.copdfoundation.org/>

Crohn's & Colitis Foundation of America

733 Third Avenue, Suite 510
New York, NY 10017
Toll free: (800) 932-2423
E-mail: info@ccfa.org
Website: <http://www.ccfa.org/>

D**Depression and Bipolar Support Alliance**

55 E. Jackson Boulevard, Suite 490
Chicago, IL 60604
Toll free: (800) 826-3632
Fax: (312) 642-7243
Website: <http://www.dbsalliance.org/>

E**Endocrine Society**

2055 L Street NW, Suite 600
Washington, DC 20036
Phone: (202) 971-3636
Toll free: (888) 363-6274
Fax: (202) 736-9705
E-mail: societyservices@endocrine.org
Website: <http://www.endocrine.org/>

Epilepsy Foundation

8301 Professional Place East, Suite 200
Landover, MD 20785-2353
Toll free: (800) 332-1000
E-mail: ContactUs@efa.org
Website: <http://www.epilepsy.com/>

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

31 Center Drive, Building 31,
Room 2A32
Bethesda, MD 20892-2425
Toll free: (800) 370-2943
TTY: (888) 320-6942
Fax: (866) 760-5947
E-mail: NICHDInformationResourceCenter@mail.nih.gov
Website: <http://www.nichd.nih.gov/>

F**Family Caregiver Alliance**

785 Market Street, Suite 750
San Francisco, CA 94103
Toll free: (800) 445-8106
Website: <http://www.caregiver.org/>

Fisher Center for Alzheimer's Research Foundation

110 East 42nd Street, 16th Floor

New York, NY 10017
Toll free: (800) ALZ-INFO (259-4636)
Fax: (212) 915-1319
E-mail: info@alzinfo.org
Website: <http://www.alzinfo.org/>

G**Glaucoma Research Foundation**

251 Post Street, Suite 600
San Francisco, CA 94108
Phone: (415) 986-3162
Toll free: (800) 826-669
E-mail: question@glaucoma.org
Website: <http://www.glaucoma.org/>

H**Heart Foundation**

80 William Street, Level 3
East Sydney NSW, 2011
Australia
Phone: +61 02 9219 2444
Toll free: 300 36 27 87
E-mail:
Website: <http://www.heartfoundation.org.au/>

HypoPARathyroidism (HPTH) Association

PO Box 2258
Idaho Falls, ID 83403
Phone: (208) 524-3857
Toll free: (866) 213-0394
E-mail: jsanders@hypopara.org
Website: <https://www.hypopara.org/>

I**Immunization Action Coalition (IAC)**

2550 University Avenue West, Suite 415 North
Saint Paul, MN 55114
Phone: (651) 647-9009
Fax: (651) 647-9131
E-mail: admin@immunize.org
Website: <http://www.immunize.org/>

Infectious Diseases Society of America

1300 Wilson Boulevard, Suite 300
Arlington, VA 22209
Phone: (703) 299-0200
Fax: (703) 299-0204
Website: <http://www.idsociety.org/>

International Committee Monitoring Assisted Reproductive Technologies

540 University Avenue, Suite 200

Palo Alto, CA 94301
Phone: (408) 647-9809
Fax: (408) 867-4751
E-mail: secretariat@icmartivf.org
Website: <http://www.icmartivf.org/>

International Diabetes Federation

166 Chaussee de La Hulpe
B-1170 Brussels
Belgium
Phone: +32 2 538 55 11
Fax: +32 2 538 51 14
E-mail: info@idf.org
Website: <http://www.idf.org/>

International Federation of Gynecology and Obstetrics

FIGO House, Suite 3—Waterloo Court,
10 Theed Street
London, SE1 8ST
United Kingdom
Phone: +44 20 7928 1166
Fax: +44 20 7928 7099
E-mail: figo@figo.org
Website: <http://www.figo.org/>

International Foundation for Functional Gastrointestinal Disorders

700 W. Virginia Street, #201
Milwaukee, WI 53204
Phone: (414) 964-1799
Toll free: (888) 964-2001
Fax: (414) 964-7176
E-mail: iffgd@iffgd.org
Website: <http://www.iffgd.org/>

L**Leukemia & Lymphoma Society**

1311 Mamaroneck Avenue, Suite 310
White Plains, NY 10605
Phone: (914) 949-5213
Fax: (914) 949-6691
E-mail: infocenter@lls.org
Website: <http://www.lls.org/>

Lighthouse Guild

15 W. 65th Street
New York, NY 10023
Toll free: (800) 284-4422
E-mail: info@lighthouseguild.org
Website: <http://www.lighthouseguild.org/>

Lupus Foundation of America

2000 L Street NW, Suite 410
Washington, DC 20036
Phone: (202) 349-1155
Fax: (202) 349-1156
E-mail: info@lupus.org
Website: <http://www.lupus.org/>

M

M.A.G.N.U.M., Inc., The National Migraine Association

100 North Union Street, Suite B
Alexandria, VA 22314
Phone: (703) 349-1929
E-mail: comments@migraines.org
Website: <http://www.migraines.org/>

Mental Health America

2000 N. Beauregard Street, 6th Floor
Alexandria, VA 22311
Phone: (703) 684-7722
Toll free: (800) 969-6642
Fax: (703) 684-5968
Website: <http://www1.nmha.org/>

The Michael J. Fox Foundation for Parkinson's Research

Grand Central Station, PO Box 4777
New York City, NY 10163-4777
Toll free: (800) 708-7644
Website: <https://www.michaeljfox.org/>

Multiple Sclerosis Association of America (MSAA)

706 Haddonfield Road
Cherry Hill, NJ 08002
Phone: (856) 488-4500
Toll free: (800) 532-7667
Fax: (856) 661-9797
E-mail: MSquestions@mymsaa.org
Website: <http://www.mymsaa.org/>

N

National Alliance of Advocates for Buprenorphine Treatment (NAABT)

PO Box 333
Farmington, CT 06034
Fax: (860) 269-4391
Website: <http://www.naabt.org/>

National Alliance on Mental Illness (NAMI)

3803 N. Fairfax Drive, Suite 100
Arlington, VA 22203
Phone: (703) 524-7600
Toll free: (800) 950-NAMI (6264)
Fax: (703) 524-9094
Website: <http://www.nami.org/>

National Cancer Institute

9609 Medical Center Drive, BG 9609
MSC 9760
Bethesda, MD 20892-9760
Toll free: (800) 4-CANCER (422-6237)
Website: <http://www.cancer.gov/>

National Center on Sleep Disorders Research

6701 Rockledge Drive
Bethesda, MD 20892
Phone: (301) 435-0199
Fax: (301) 480-3451
E-mail: twery@nih.gov
Website: <http://www.nhlbi.nih.gov/about/ncsdr/index.htm>

National Diabetes Education Program

One Diabetes Way
Bethesda, MD 20814-9692
Phone: (301) 496-3583
Website: <http://www.ndep.nih.gov/>

National Diabetes Information Clearinghouse

1 Information Way
Bethesda, MD 20892-3560
Toll free: (800) 860-8747
TTY: (866) 569-1162
Fax: (703) 738-4929
E-mail: ndic@info.niddk.nih.gov
Website: <http://diabetes.niddk.nih.gov/>

National Digestive Diseases Information Clearinghouse

2 Information Way
Bethesda, MD 20892
Toll free: (800) 891-5389
Website: <http://www.digestive.niddk.nih.gov/>

National Endocrine and Metabolic Diseases Information Service

6 Information Way
Bethesda, MD 20892-3569
Toll free: (888) 828-0904
TTY: (866) 569-1162
Fax: (703) 738-4929
E-mail: endoandmeta@info.niddk.nih.gov
Website: <http://www.endocrine.niddk.nih.gov/>

National Eye Institute

31 Center Drive MSC 2510
Bethesda, MD 20892-2510
Phone: (301) 496-5248
E-mail: 2020@nei.nih.gov
Website: <http://www.nei.nih.gov/>

National Foundation for Infectious Diseases

7201 Wisconsin Avenue, Suite 750
Bethesda, MD 20814
Phone: (301) 656-0003
Fax: (301) 907-0878
Website: <http://www.nfid.org/>

National Foundation for Transplants

5350 Poplar Avenue, Suite 430
Memphis, TN 38119
Phone: (901) 684-1697
Toll free: (800) 489-3863
Fax: (901) 684-1128

E-mail: info@transplants.org
Website: <http://www.transplants.org/>

National Heart, Lung, and Blood Institute (NHLBI)

PO Box 30105
Bethesda, MD 20824-0105
Phone: (301) 592-8573
E-mail: nhlbinfo@nhlbi.org
Website: <http://www.nhlbi.nih.gov/>

National Institute of Allergy and Infectious Disease

5601 Fishers Lane, MSC 9806
Bethesda, MD 20892-9806
Phone: (301) 496-5717
Fax: (301) 402-3573
Toll free: (866) 284-4107
TTY: (800) 877-8339
E-mail: ocpostoffice@niaid.nih.gov
Website: <http://www.niaid.nih.gov/>

National Institute of Arthritis and Musculoskeletal and Skin Diseases

1 AMS Circle
Bethesda, MD 20892-3675
Toll free: (877) 22-NIAMS (226-4267)
Phone: (301) 495-4484
Fax: (301) 718-6366
Website: <http://www.niams.nih.gov/>

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

9000 Rockville Pike
Bethesda, MD 20892-2560
Phone: (301) 496-3583
Website: <http://www.niddk.nih.gov/>

National Institute of Mental Health (NIMH)

6001 Executive Boulevard, Room 6200, MSC 9663
Bethesda, MD 20892-9663
Toll free: (866) 615-6464
TTY: (866) 415-8051
Website: <http://www.nimh.nih.gov/>

National Institute of Neurological Disorders and Stroke (NINDS)

PO Box 5801
Bethesda, MD 20824
Phone: (301) 496-5751
Toll free: (800) 352-9424
Website: <http://www.ninds.nih.gov/>

National Institute on Drug Abuse

6001 Executive Boulevard, Room 5213, MSC 9561
Bethesda, MD 20892-9561
Phone: (301) 443-1124
Website: <http://www.drugabuse.gov/>

National Institutes of Health

9000 Rockville Pike
Bethesda, MD 20892
Website: <http://www.nih.gov/>

National Kidney and Urologic Diseases Information Clearinghouse

3 Information Way
Bethesda, MD 20892-3580
Toll free: (800) 891-5390
Fax: (703) 7384929
E-mail: nkudic@info.niddk.nih.gov
Website: <http://kidney.niddk.nih.gov/>

National Multiple Sclerosis Society

Toll free: (800) 344-4867
Website: <http://www.nationalmssociety.org/>

National Network for Immunization Information (NNII)

301 University Boulevard
Galveston, TX 77555-0350
Phone: (702) 200-0201
Fax: (409) 772-5208
E-mail: dipineda@utmb.edu
Website: <http://www.immunizationinfo.org/>

National Osteoporosis Foundation

1150 17th Street NW, Suite 850
Washington, DC 20036
Toll free: (800) 231-4222
Fax: (202) 223-2237
E-mail: info@nof.org
Website: <http://nof.org/>

National Pain Foundation

14828 W 6 Avenue, Suite 16-B,
Room 1
Golden, CO 80401-5000
Phone: (720) 541-6808
Fax: (720) 541-6809
Website: <http://www.thenationalpainfoundation.org/>

National Shingles Foundation

603 West 115th Street, #371
New York, NY 10025
Phone: (212) 222-3390
Fax: (212) 222-8627
E-mail: Shingles@ShinglesFoundation.org
Website: <http://shinglesfoundation.org/>

National Sleep Foundation

1010 N. Glebe Road, Suite 310
Arlington, VA 22201
Phone: (703) 243-1697
E-mail: nsf@sleepfoundation.org
Website: <http://sleepfoundation.org/>

National Tourette Syndrome Association

42-40 Bell Boulevard
Bayside, NY 11361
Phone: (718) 224-2999
Fax: (718) 279-9596
Website: <http://www.tsa-usa.org/>

National Vaccine Program Office (NVPO)

200 Independence Avenue, SW, Room 715-H
Washington, DC 20201
Phone: (202) 690-5566
E-mail: nvpo@hhs.gov
Website: <http://www.hhs.gov/nvpo>

NIH Osteoporosis and Related Bone Diseases National Resource Center

2 AMS Circle
Bethesda, MD 20892-3676
Phone: (202) 223-0344
Toll free: (800) 624-2663
Fax: (202) 293-2356
E-mail: NIHBoneInfo@mail.nih.gov
Website: <http://www.bones.nih.gov/>

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

1501 Bethlehem Pike
Flourtown, PA 19031
Phone: (215) 233-0808
E-mail: naspgghan@naspgghan.org
Website: <http://www.gikids.org/>

O

The Obesity Society

8757 Georgia Avenue, Suite 1320
Silver Spring, MD 20910
Phone: (301) 563-6526
Fax: (301) 563-6595
Website: <http://www.obesity.org/>

Office on Women's Health, U.S. Department of Health and Human Services

200 Independence Avenue SW, Room 712E
Washington, DC 20201
Phone: (202) 690-7650
Toll free: (800) 994-9662
Fax: (202) 205-2631
Website: <http://www.womenshealth.gov/>

P

Parkinson's Disease Foundation

1359 Broadway, Suite 1509
New York, NY 10018
Phone: (212) 923-4700
Fax: (212) 923-4778
Website: <http://www.pdf.org/en/index>

Planned Parenthood Federation of America

434 West 33rd Street
New York, NY 10001
Phone: (212) 541-7800

Toll free: (800) 230-PLAN (7526)
Fax: (212) 245-1845
Website: <http://www.plannedparenthood.org/>

Pulmonary Hypertension Association

801 Roeder Road, Suite 1000
Silver Spring, MD 20910
Phone: (301) 565-3004
Fax: (301) 565-3994
Toll free: (800) 748-7274
E-mail: PHA@PHAssociation.org
Website: <http://www.phassociation.org/>

R

Restless Legs Syndrome Foundation

3006 Bee Caves Road, Suite D206
Austin, TX 78746
Phone: (512) 366-9109
Fax: (512) 366-9189
E-mail: info@rls.org
Website: <http://www.rls.org/>

S

San Francisco AIDS Foundation

1035 Market Street, Suite 400
San Francisco, CA 94103
Phone: (415) 487-3000
Toll free: (866) 245-3424
E-mail: info@aidslifecycle.org
Website: <http://sfaf.org/>

Society for Assisted Reproductive Technologies

1209 Montgomery Highway
Birmingham, AL 35216-2809
Phone: (205) 978-5000
Fax: (205) 978-5018
E-mail: kjefferson@asrm.org
Website: <http://www.sart.org/>

Society for Pediatric Dermatology

8365 Keystone Crossing, Suite 107
Indianapolis, IN 46240
Phone: (317) 202-0224
Fax: (317) 205-9481
E-mail: info@pedsderm.net
Website: <http://www.pedsderm.net/index.php>

Substance Abuse and Mental Health Services Administration

1 Choke Cherry Road
Rockville, MD 20857
Toll free: (877) SAMHSA-7 (726-4727)
TTY: (800) 487-4889
Website: <http://www.samhsa.gov/>

U

Urology Care Foundation

1000 Corporate Boulevard

Linthicum, MD 21090

Phone: (410) 689-3700

Toll free: (800) 828-7866

Fax: (410) 689-3998

E-mail: info@urologycarefoundation.org

Website: <http://www.urologyhealth.org/>

U.S. Food and Drug Administration

10903 New Hampshire Avenue

Silver Spring, MD 20993-0002

Toll free: (888) INFO-FDA (463-6332)

Website: <http://www.fda.gov/>

V

Vestibular Disorders Association

5018 NE 15th Avenue

Portland, OR 97211

Toll free: (800) 837-8428 (VESTIBU)

Fax: (503) 229-8064

W

World Health Organization

Avenue Appia 20

1211 Geneva Switzerland, 27

Phone: +41 791 21 11

Fax: +41 791 31 11

E-mail: info@who.int

Website: <http://www.who.int/en>

GLOSSARY

The glossary is an alphabetical compilation of terms and definitions listed in the *Key Terms* sections of the main body entries. Although the list is comprehensive, it is by no means exhaustive.

A

ABDOMINAL DISTENTION. The swelling or expansion of the abdomen.

ABORTIFACIENT. A drug or substance that will induce an abortion or miscarriage.

ABSCESS. A localized pocket of pus due to infection.

ABSENCE SEIZURE. Absence (petit mal) seizures usually begin with a brief loss of consciousness and last up to 20 seconds. People having a petit mal seizure become very quiet and may blink, stare blankly, roll their eyes, or move their lips. When it ends, the individual resumes whatever he or she was doing before the seizure began, and may not realize that anything unusual happened.

ACE INHIBITORS. A group of drugs used to treat high blood pressure. These drugs work by decreasing production of a certain chemical in the kidneys that causes constriction of blood vessels.

ACETAMINOPHEN. A drug for relieving pain and fever. Tylenol is the most common example.

ACETYLCHOLINE. A naturally occurring chemical in the body that transmits nerve impulses from cell to cell. Acetylcholine causes blood vessels to dilate, lowers blood pressure, and slows the heartbeat. Central nervous system well-being is dependent on a balance among the neurotransmitters acetylcholine, dopamine, serotonin, and norepinephrine.

ACETYLCHOLINESTERASE. The chemical responsible for the breakdown of acetylcholine.

ACNE. A common skin condition causing pimples on the face and upper torso.

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS). A disease caused by infection with the human immunodeficiency virus (HIV). In people with this disease, the

immune system breaks down, increasing vulnerability to other infections and some types of cancer.

ACROMEGALY. Overproduction of growth hormone by the pituitary gland; inhibited by octreotide.

ACTINIC KERATOSIS (AK). Dry, scaly lesions or patches on the skin from long-term sun exposure that are considered the earliest stage in the development of squamous cell carcinoma; also known as solar keratosis.

ACUTE. Having a sudden onset and lasting a short time.

ACUTE MYELOGENOUS LEUKEMIA (AML). A type of cancer of the blood, characterized by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells.

ACUTE MYOCARDIAL INFECTION. Heart attack.

ACYCLOVIR. An antiviral agent that is formed from valacyclovir in the body.

ADALIMUMAB. Humira. A tumor necrosis factor inhibitor similar to etanercept.

ADCIRCA. The brand name of tadalafil for treating pulmonary arterial hypertension.

ADDISONIAN CRISIS. A condition of severe adrenal insufficiency marked by convulsions, fever, fainting, low blood pressure, severe nausea, vomiting, and dehydration, confusion and slurred speech, and severe pain in the legs or lower back. It can result from the sudden withdrawal of prednisone in a patient who has become dependent on the drug, as well as from known adrenal insufficiency or sudden trauma to the adrenal glands.

ADDISON'S DISEASE. Also known as primary adrenal insufficiency, a disease of adrenocortical under-activity.

ADENOSINE DIPHOSPHATE (ADP). A nucleotide with a variety of essential functions in the body, including activation and aggregation of platelets for blood-clot formation.

ADJUVANT. A substance added to a vaccine to increase the immune response.

ADJUVANT THERAPY. Therapy given in addition to the primary treatment. In cancer treatment, adjuvant therapy usually refers to chemotherapy or radiation therapy given after surgery to prevent recurrence of the cancer.

ADRENAL GLAND. An endocrine gland located above each kidney. The inner part of each gland secretes epinephrine (adrenaline), and the outer part secretes steroid hormones.

ADRENERGIC. Activated by epinephrine (adrenaline) or similar substances.

ADRENERGIC RECEPTORS. Certain hormone binding sites throughout the body.

AGGREGATION. A clumping together of platelets induced by various agents as part of the mechanism leading to clot formation.

AGONIST. A substance that acts like another substance and therefore stimulates an action. Agonist is the opposite of antagonist.

AGRANULOCYTOSIS. A type of blood disorder in which infection-fighting white blood cells called granulocytes are markedly reduced.

AIDS. Acquired immune deficiency syndrome; a serious disease that affects the immune system and is caused by human immunodeficiency virus.

ALAGILLE SYNDROME. An inherited condition in which the liver lacks small bile ducts.

ALDOSTERONE. A steroid hormone produced by the adrenal cortex that regulates salt and water balance in the body.

ALKALOID. A naturally occurring compound that contains both nitrogen and carbon and acts as a base, which means it takes a hydrogen ion from an acid. Well-known alkaloids include morphine, ephedrine, and nicotine.

ALLERGEN. Any food, particle, or other substance that the immune system reacts to, causing an allergic reaction.

ALLERGIC RHINITIS. Also called hay fever or allergies; the immune system's overreaction to allergens, usually particles in the air such as pollen. Symptoms include a runny nose, sneezing, and itchy, watery eyes and throat.

ALLERGY. A damaging immune response by the body to a substance (such as peanuts, pollen, insect bites, bee

stings, or cat dander) to which it has become hypersensitive.

ALLOGENIC. Being genetically different but from individuals of the same species—for example, a blood transfusion in which a patient is given blood donated by another person.

ALLYLAMINE. A very basic liquid used in the synthesis of drugs such as terbinafine.

ALOPECIA. The medical term for baldness.

ALPHA-2-ADRENERGIC AGONIST. A drug, such as tizanidine, that mimics the effects of the binding of endogenous substances, such as epinephrine and norepinephrine, to the alpha-2 subtype of adrenergic receptors.

ALPHA-4 BETA-2 NICOTINIC ACETYLCHOLINE RECEPTORS (NACHR). Nicotine receptors in the brain that bind varenicline.

ALPHA-BLOCKERS. Drugs for treating high blood pressure and other conditions.

ALPHA-RECEPTORS. Receptors on the cell surfaces of organs and tissues that bind specific adrenergic agents to constrict blood vessels and contract smooth muscles; blocked by terazosin.

ALPORT SYNDROME. A genetic disorder characterized by scarring of kidney tissue and eventual end-stage renal disease.

ALVEOLI. Small spherical sacs at the ends of the bronchioles in the lungs in which blood gases are exchanged.

ALZHEIMER'S DISEASE. A progressive, neurodegenerative disease characterized by loss of function and death of nerve cells in several areas of the brain, leading to loss of mental functions, including memory and learning. Alzheimer's disease is the most common cause of dementia.

AMENORRHEA. Abnormal cessation of menstruation.

AMYOTROPHIC LATERAL SCLEROSIS (ALS). A neurodegenerative disorder characterized by the progressive loss of muscle strength, resulting in difficulty swallowing, speaking, and breathing. It is also known as Lou Gehrig's disease.

ANAEROBIC BACTERIA. Bacteria that can grow in areas with low oxygen, such as the abdomen, intestines, mouth, and vagina, and cause specific types of infections, such as gangrene and tetanus.

ANALGESIC. A drug used to relieve pain.

ANAPHYLAXIS. An intense and sudden allergic reaction. The effects may include sudden drops in blood

pressure, narrowing of airways, and a weak pulse. Failure to get prompt treatment may lead to loss of consciousness and death.

ANDROGENS. A group of hormones that produce masculine characteristics; male sex hormones.

ANEMIA. A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values.

ANESTHETIC. A substance or effect that causes a person to lose feeling and to feel no pain in part or all of the body.

ANGINA. Chest pain due to reduced blood flow to the heart. There are two types: stable angina (angina pectoris) and unstable angina. The chest pain of angina pectoris is typically associated with physical activity or stress, while the pain of unstable angina can occur at any time.

ANGIOEDEMA. Severe, painful, allergic swelling of the skin and sometimes other organs, including the mouth and throat.

ANGIOGENESIS. Physiological process involving the growth of new blood vessels from pre-existing blood vessels; a process used by some cancers to create their own blood supply.

ANGIOPLASTY. Repair or opening of a blood vessel.

ANGIOTENSIN II. A peptide hormone that narrows blood vessels (vasoconstriction), especially in the kidneys, and raises blood pressure.

ANGIOTENSIN II RECEPTOR ANTAGONISTS. Drugs that regulate the hormone system (the renin-angiotensin-aldosterone system) that controls blood pressure and the fluid balance in the body; also called angiotensin II receptor blockers (ARBs).

ANGIOTENSIN TYPE 1 (AT1) AND TYPE 2 (AT2) RECEPTORS. Receptors located throughout the body that bind angiotensin II to mediate its vasoconstricting effects.

ANGIOTENSIN-CONVERTING ENZYME (ACE). An enzyme that converts a hormone known as angiotensin I into another form known as angiotensin II, which constricts blood vessels and contributes to high blood pressure.

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITOR. A blood-pressure-lowering drug that inhibits the enzyme that converts angiotensin I to active angiotensin II.

ANGIOTENSIN-RECEPTOR BLOCKER (ARB). A blood-pressure-lowering drug that may be an alternative to an angiotensin-converting enzyme inhibitor such as lisinopril.

ANKYLOSING SPONDYLITIS. A type of arthritis in the spine that leads to stiffening and fusion of the vertebral (spinal) bones.

ANOREXIA NERVOSA. A serious physical and emotional illness in which an abnormal fear of being overweight leads to very poor eating habits and dangerous weight loss.

ANTAGONIST. A drug that blocks the action of a substance by binding to its receptors.

ANTEROGRADE AMNESIA. The inability to form new memories.

ANTHELMINTIC. A drug that is used to treat an infection with parasitic worms.

ANTHRAX. An infectious disease caused by a type of bacterium. The disease can be passed from animals to people and usually is fatal. Symptoms include sores on the skin.

ANTIBIOTIC. A drug used to treat infections caused by bacteria and other microorganisms.

ANTIBIOTIC RESISTANCE. The ability of infectious agents to change their biochemistry in such a way as to make an antibiotic no longer effective.

ANTIBODY. A protective protein made by the immune system in response to an antigen, also called an immunoglobulin.

ANTICHOLINERASE AGENT. Drugs that promote or augment action in the parasympathetic nervous system. They are used mostly in the treatment of Alzheimer's disease, and sometimes to treat gastrointestinal problems such as obstructions.

ANTICHOLINERGIC. A drug that blocks the effects of acetylcholine. There are several kinds of anticholinergic drugs, but in general these drugs have a relaxing effect, particularly on the muscles of the stomach, intestine, and bladder. They can be used to prevent nausea, vomiting, and motion sickness. Anticholinergics can be used for painful menstruation, runny nose, and to prevent urination during sleep.

ANTICOAGULANT. A medication that prevents the formation of new blood clots and keeps existing blood clots from growing larger.

ANTICONVULSANT. Any drug given to control seizures. Anticonvulsants are also called antiepileptic drugs or AEDs.

ANTIDEPRESSANT. Any of a group of medications given to relieve mood disorders, including anxiety disorders as well as major depression. Antidepressants

include monoamine oxidase inhibitors (MAOIs), tricyclic (TCAs) and tetracyclic (TeCAs) antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs).

ANTIEMETIC. Any medication given to prevent or treat nausea and vomiting.

ANTIESTROGEN. A drug that prevents the hormone estrogen from influencing the behavior of specific types of cells.

ANTIFUNGAL. A medicine used to treat infections caused by a fungus.

ANTIGEN. Any foreign substance, usually a protein, that stimulates the body's immune system to produce antibodies.

ANTIHISTAMINES. Medicines that block the action of histamines, which are chemicals in the body that trigger allergic reactions and the release of stomach acid. Antihistamines are used to treat allergies and gastroesophageal reflux disease (GERD).

ANTIHYPERTENSIVE. Any medication given to lower blood glucose levels.

ANTIHYPERTENSIVE. Any medication given to control high blood pressure.

ANTI-INFLAMMATORY. A drug that reduces inflammation.

ANTIMETABOLITE. Anticancer drugs that prevent cells from growing and dividing by blocking the chemical reactions required in the cells to produce DNA.

ANTIMUSCARINIC. Drugs that block certain nerve receptors to relax smooth muscles in the body.

ANTIMYCOBACTERIAL. A bacteriostatic drug that specifically targets mycobacteria to eliminate them from the body.

ANTINEOPLASTIC. Agents that inhibit or prevent the development of cancers by stopping the maturation and proliferation of malignant cells.

ANTIPLATELET AGENTS. Compounds that prevent blood clots from forming in blood vessels.

ANTIPROTOZOALS. Drugs that fight infections caused by small, one-celled animals called protozoa.

ANTI-PSYCHOTIC. A drug used to treat serious mental disorders that cause hallucinations or delusions, such as schizophrenia or psychosis.

ANTIRETROVIRAL AGENTS. Drugs that prevent, limit, or treat infections with retroviruses such as HIV.

ANTISEPTIC. A substance that kills or inhibits the growth of microorganisms.

ANTISPASMODIC. Drugs that prevent or stop spasms, or the involuntary tightening and movement of muscles.

ANTITHROMBOTIC. A type of drug that prevents the development of blood clots.

ANXIETY. A psychological state characterized by strong feelings of worry, nervousness, apprehension, or agitation; may also be accompanied by physical symptoms, including sweating, tension, and increased pulse.

ANXIOLYTIC. Any of a group of medications prescribed to relieve anxiety. Also called tranquilizers, anxiolytics include benzodiazepines, some of the selective serotonin reuptake inhibitors (SSRIs), barbiturates, and buspirone.

AORTIC STENOSIS. A narrowed aortic valve in the heart.

APLASTIC ANEMIA. A type of blood disorder in which bone marrow activity is suppressed and not enough immature red cells, white cells, and platelets are produced to maintain sufficient numbers of these cells in the blood circulation. This may be the result of a toxic reaction to therapy with specific drugs.

APOCRINE SWEAT GLANDS. Sweat glands found under the armpits, the breasts, the inner thighs, and a few other body areas that secrete an oily fluid that produces a characteristic body odor when degraded by bacteria.

APOLIPOPROTEINS. Proteins that bind with fats (lipids) to form lipoproteins. Detection of these apolipoproteins indicates risk of developing cardiovascular disease.

APOPTOSIS. Programmed cell death.

AQUEOUS HUMOR. A transparent liquid, contained within the eye, that is composed of water, sugars, vitamins, proteins, and other nutrients.

AROMATASE INHIBITORS. Medications used for preventing or treating breast cancer in postmenopausal women by inhibiting the body's production of estrogen.

ARRHYTHMIA. An abnormal or irregular heart rhythm.

ARTERIAL THROMBOSIS. Blood clots that have developed in arteries anywhere in the body.

ARTHRITIS. A condition characterized by damage to a joint. There are a number of different types of arthritis, but the primary two are rheumatoid and osteoarthritis.

ASCITES. Accumulation of fluid in the peritoneal cavity, often associated with cirrhosis of the liver or congestive heart failure.

ASTHMA. A lung condition, usually of allergic origin, in which the airways become narrow due to smooth muscle contraction, causing wheezing, coughing, and shortness of breath.

ATHEROSCLEROSIS. Stiffening of large- and medium-sized arteries as a result of the formation of fatty plaques along the vessel walls. The process of plaque formation may eventually interfere with blood flow to vital organs.

ATOPIC DERMATITIS. An inflammatory, noncontagious, itchy skin disorder, often chronic in nature. It is also known as eczema.

ATRIA. The two upper chambers (right and left atria) of the heart that receive blood from the body.

ATRIAL FIBRILLATION. An irregular and usually rapid heart rate that results in poor blood flow to body organs.

ATRIAL FLUTTER. A rapid pulsation of the upper chamber of the heart that interferes with normal function.

ATRIUM (PLURAL, ATRIA). The two upper chambers (right and left atria) of the heart that receive blood from the body.

ATROPHIC URETHRITIS. Inflammation of the outer urinary tract due to thinning and shrinking of tissue, which result from reduced estrogen levels.

ATROPHIC VAGINITIS. Thinning, drying, and inflammation of the vaginal walls due to reduced estrogen levels.

ATROPHY. The wasting away or decrease in size of an organ or tissue in the body.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD). A condition characterized by lack of concentration, impulsive or inappropriate behavior (relative to age level), and hyperactivity.

ATYPICAL ANTIPSYCHOTIC. A class of newer-generation antipsychotic medications that are used to treat schizophrenia and other psychotic disorders.

AURA. Visual and other sensory disturbances that can precede the onset of a migraine headache.

AUTOIMMUNE DISEASE. A disorder in which the body's antibodies mistake the body's own tissues for

foreign invaders. The immune system then attacks and causes damage to these tissues.

AUTOLOGUS. Cells from the same individual—for example, when a patient banks their blood in advance of surgery so that their own blood can be returned to them in case of need.

AXON. The long, slender projection of a nerve cell that conducts electrical impulses away from the body of the nerve cell.

B

B CELL. Type of lymphocyte (white blood cell) that creates antibodies to fight infection; also referred to as a B-cell lymphocyte.

BACTERIA. Tiny, single-celled forms of life that can cause diseases and infections.

BACTERICIDAL. An agent that kills bacteria (as opposed to one that simply inhibits bacterial growth).

BACTERICIDE. An antibacterial drug that acts to kill bacteria in the body and thereby to stop infection from becoming worse or spreading.

BACTERIOSTAT. An antibacterial drug that acts to stop specific bacterial cells from reproducing, thereby stopping infection and preventing the spread of the bacteria from one person to another.

BARBITURATES. A class of medications that causes sedation and drowsiness. They may be prescribed legally but are also used as drugs of abuse.

BARBOTAGE. Barbotage is the alternating injection and withdrawal of a fluid used to administer an injectable therapeutic or anesthetic agent into an area of the spine called the intrathecal space.

BASAL INSULIN. A term that refers to long-acting insulins that are released slowly and provide 24 hours or more of background insulin in diabetic patients.

BCD. The combined chemotherapy treatment of bleomycin, cyclophosphamide, and dactinomycin.

BENEDICT'S TEST. A diagnostic test typically used for diabetes.

BENIGN. Noncancerous. A benign tumor is a growth that does not invade surrounding tissue or spread to other parts of the body.

BENIGN INTRACRANIAL HYPERTENSION. A condition in which the pressure around the brain increases in the absence of a tumor or other diseases. It is characterized

by headache, nausea and vomiting, ringing in the ears, and visual disturbances. It is also known as pseudotumor cerebri.

BENIGN PROSTATE HYPERPLASIA (BPH). A noncancerous swelling of the prostate.

BENZODIAZEPINES. A group of central nervous system depressants used to relieve anxiety or to induce sleep.

BETA ADRENERGIC RECEPTORS. A class of G protein-coupled receptors that are targeted by the stress hormones adrenaline and noradrenaline. They are also called beta adrenoceptors.

BETA AGONISTS. Also known as long-acting beta agonists (LABA) or beta-adrenergic agonists, this group of drugs is used to relax muscles around the airways, specifically the bronchi and bronchioles.

BETA-BLOCKER. A class of drugs that are widely used to treat high blood pressure and congestive heart failure. Beta blockers work by blocking the effects of epinephrine (adrenaline) and slowing the heart's rate, thereby decreasing the heart's demand for oxygen.

BIGUANIDES. A class of medications used primarily in the treatment of type 2 diabetes; some drugs in this class are used in the prophylactic treatment of malaria.

BILE. Fluid secreted by the liver to the gallbladder and duodenum where it helps in the digestion and absorption of fats and removal of toxins and waste products.

BILE ACID. A detergent that is made in the liver and excreted into the intestine to aid in the absorption of fats.

BILE ACID SEQUESTRANTS. A group of drugs used to bind certain components of bile within the digestive tract. They are often used to lower blood cholesterol levels.

BILIARY ATRESIA. Absence or underdevelopment of bile ducts.

BILIRUBIN. A reddish-yellow pigment in bile and blood.

BIOAVAILABILITY. The fraction of an unchanged administered drug that reaches the systemic circulation. The bioavailability of drugs administered intravenously is usually close to 100% but that of drugs taken by mouth is usually significantly lower.

BIOLOGICS. Naturally occurring compounds in the human body, usually proteins, that are used to treat disease.

BIPHASIC INSULIN. An insulin formulation consisting of a mixture of short-acting and intermediate-acting insulin.

BIPOLAR DEPRESSION. Depression with the presence of at least one manic episode.

BIPOLAR DISORDER. A mood disorder marked by alternating episodes of extremely low mood (depression) and exuberant highs (mania); formerly known as manic-depressive disorder.

BISPHOSPHONATES. A class of drugs that bind to the minerals in bone tissue and lessen the amount of bone loss associated with conditions such as Paget's disease and osteoporosis.

BLACKHEAD. An open comedo. A comedo, the primary sign of acne, consists of a widened hair follicle filled with skin debris, bacteria, and oil called sebum. A blackhead has a wide opening to the skin and is capped with a blackened mass of skin debris.

BLASTOMYCOSIS. Either of two infectious diseases (North American and South American) caused by yeast-like fungi of the genus *Blastomyces* or *Paracoccidioides*.

BLOOD CLOT. A clump of blood that forms in or around a vessel to stop blood loss. The formation of blood clots when the body has been cut is essential because without blood clots to stop the bleeding, a person would bleed to death from a relatively small wound. However, clots can become dangerous if they get lodged in the vessel and block blood flow within the body.

BLOOD GLUCOSE. The main sugar that the body makes from the food in the diet; also referred to as blood sugar.

BLOOD PRESSURE. The pressure of circulating blood on the walls of blood vessels. If blood pressure is too high, it can lead to heart attacks, strokes, and damage to vital organs such as the kidneys. Low blood pressure can lead to dizziness and fainting.

BOXED WARNING. A warning label required by the U.S. Food and Drug Administration for all drugs sold in the United States that carry a risk of severe or life-threatening side effects. Its name comes from the fact that it must be formatted with a border or box around the text.

BRADYCARDIA. Abnormally slow heart rate.

BRONCHI. Two major divisions of the airways that lead into the right and left lungs.

BRONCHIOLES. Very small, thin-walled air passages in the lungs that branch off from the bronchi.

BRONCHODILATOR. A medicine that relaxes the muscles around the airways, or bronchi, making it easier to breathe.

BRONCHOSPASM. Sudden tightening of the muscles around the airways that leads to difficulty breathing.

BRONCHOSPASTIC DISEASE. Any disease that causes spasms in the bronchi, which are airways within the lungs.

BUCCAL. The lining of the inside of the cheek.

BUPROPION. Zyban; Wellbutrin; an antidepressant and smoking-cessation medication.

BURSITIS. Inflammation of a fluid-filled sac within a joint.

C

CACHEXIA. General wasting and malnutrition usually associated with chronic disease.

CALCINEURIN. A protein phosphatase that activates T cells in the immune system and can be blocked by drugs like pimecrolimus.

CALCIUM CHANNEL BLOCKER. One of a number of medications designed to disrupt the movement of calcium in certain muscle cells, which can cause blood vessels to dilate and the heart to pump less forcefully.

CALCULUS. Calcium salt deposits on the teeth; may cause gum irritation.

CANCER. A disease caused by uncontrolled growth of the body's cells.

CANDIDA. Various species of yeast-like fungi, especially *C. albicans*, that are normal inhabitants of the human body but that can overgrow and cause infections.

CANDIDEMIA. Invasive or disseminated candidiasis. Candida infection that spreads from the bloodstream to other parts of the body.

CANDIDIASIS. Yeast infection caused by *Candida* spp.

CAPILLARIES. Tiny branching blood vessels that connect small arteries and veins.

CARBONIC ANHYDRASE INHIBITORS. A group of drugs that inhibit the production of fluid inside the eye, lowering the pressure on the optic nerve.

CARCINOID. A benign or cancerous tumor usually arising from the mucosa of the gastrointestinal tract.

CARCINOID HEART DISEASE (CHD). Heart abnormalities arising from carcinoid syndrome.

CARCINOID SYNDROME. Symptoms caused by hormones and other substances produced by carcinoid tumors that may be treated with octreotide.

CARCINOID TUMOR. A slow-growing tumor that produces hormones. Often originates in the lungs or gastrointestinal system.

CARDIOVASCULAR DISEASE. A structural or functional abnormality of the heart, or of the blood vessels supplying the heart, that impairs its normal function.

CAROTID ARTERY. Major artery leading to the brain, blockages of which can cause temporary or permanent strokes.

CAROTID ARTERY DISEASE. A condition in which the arteries in the neck that supply blood to the brain become clogged, causing the danger of a stroke.

CATAPLEXY. A symptom of narcolepsy marked by a sudden episode of muscle weakness triggered by strong emotions. The muscle weakness may cause the person's knees to buckle, or the head to drop. In severe cases, the patient may become paralyzed for a few seconds or minutes.

CATECHOLAMINE. A group of neurotransmitters synthesized from the amino acid tyrosine and released by the hypothalamic-pituitary-adrenal system in the brain in response to acute stress. The catecholamines include dopamine, serotonin, norepinephrine, and epinephrine.

CATHETERIZATION. Placing a tube in the bladder so that it can be emptied of urine.

CD4 COUNT. A measure of the strength of the immune system.

CD20. A protein found on the surface of normal and malignant B cells.

CENTRAL NERVOUS SYSTEM. The part of the nervous system that includes the brain and spinal cord.

CENTRAL NERVOUS SYSTEM (CNS) DEPRESSANT. Any drug that tends to reduce the activity of the central nervous system. The major drug categories included in this classification are: alcohol, anesthetics, anti-anxiety medications, antihistamines, antipsychotics, hypnotics, narcotics, sedatives, and tranquilizers.

CEPHALOSPORIN. The cephalosporins are a class of antibiotics originally derived from the fungus *Acremonium*. They are chemically related to penicillin.

CEREBRAL PALSY. Muscular incoordination and speech disturbances resulting from brain damage before, during, or shortly after birth.

CEREBROVASCULAR ACCIDENT. A stroke, or the loss of brain function due to interrupted blood flow to the brain. Such loss of blood flow is often caused by a blood clot or piece of a blood clot called a thromboembolism.

CESAREAN SECTION. Also called a C-section; delivery of a baby through an incision in the mother's abdomen instead of through the vagina.

CHANTIX. The brand name for varenicline.

CHEMICAL CASTRATION. Administration of pharmacological agents to decrease testosterone levels to prepubescent levels and suppress deviant sexual thinking and behavior.

CHEMOTHERAPY. Administration of special cell-killing drugs into the body by injection or orally where they will circulate and kill cancer cells.

CHOLERA. An infection of the small intestine caused by a type of bacterium. The disease is spread by drinking water or eating seafood or other foods that have been contaminated with the feces of infected people. It occurs in parts of Asia, Africa, Latin America, India, and the Middle East. Symptoms include watery diarrhea and exhaustion and are often fatal to young children and the elderly.

CHOLESTASIS. Reduced or failed bile flow.

CHOLESTATIC. Referring to total or partial blockage of the flow of bile from the liver.

CHOLESTEROL. A waxy substance made by the liver that circulates in the bloodstream; it is also acquired through diet. Cholesterol is essential to the human body, but too much can increase the risk of cardiovascular disease and other conditions.

CHROMOMYCOSIS. A fungal skin disease usually caused by pigmented fungi in the genera *Phialophora*, *Cladosporium*, or *Fonsecaea*.

CHRONIC. Progressing slowly but persisting or recurring over time.

CHRONIC IDIOPATHIC URTICARIA. The near daily occurrence of hives, or wheals, and itching, caused by a problem in a person's autoimmune system that releases histamine and other substances into the body.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL). A cancer characterized by an abnormal increase in mature lymphocytes, which are a type of white blood cell.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD). A group of respiratory, or lung, diseases that cause blocked airflow and difficulty breathing. The most common are chronic bronchitis and emphysema. COPD usually becomes progressively worse over time, and the lung damage cannot be reversed.

CHRONIC RENAL FAILURE. Progressive loss of kidney function over several years, which can result in permanent kidney failure requiring dialysis.

CIALIS. The brand name of tadalafil for erectile dysfunction and benign prostate hyperplasia.

CIRCADIAN RHYTHM. A 24-hour cycle of physiological and behavioral activity, including the sleep/wake cycle under the control of melatonin.

CIRRHOSIS. A chronic degenerative disease of the liver, in which normal cells are replaced by fibrous tissue and normal liver function is disrupted. If left untreated, cirrhosis leads to liver failure.

CLAUDICATION. Pain and weakness usually in the legs caused by inadequate blood supply.

CLINICAL TRIAL. A controlled scientific experiment designed to investigate the effectiveness of a drug or treatment in curing or lessening the symptoms of a disease or disorder.

CLOPIDOGREL. Plavix; an antiplatelet medication similar to prasugrel.

CLOSTRIDIUM DIFFICILE. A type of bacteria that occurs normally in the human intestine. *C. difficile* becomes a problem if treatment with antibiotics kills the other intestinal bacteria, allowing the *C. difficile* to grow. *C. difficile* produces a toxin that damages the lining of the intestine. Symptoms of *C. difficile* infection include frequent watery diarrhea, severe abdominal pain, and fever. Treatment requires special antibiotics.

CLOSTRIDIUM-DIFFICILE ASSOCIATED DIARRHEA (CDAD). Diarrhea caused by *Clostridium difficile*, a type of bacteria that can develop with antibiotic use.

CLOTING FACTORS. Also known as coagulation factors; proteins in the plasma that serve to activate various parts of the blood clotting process by being transformed from inactive to active form.

CLUSTER HEADACHE. Severe pain in one eye or temple.

COAGULATION. The blood's natural tendency to clump and stick, forming clots.

COAGULATION CASCADE. The sequence of biochemical activities, involving clotting factors, that stop bleeding by forming a clot.

COAGULATION FACTORS. Proteins in blood plasma that serve to activate various parts of the blood-clotting process by being transformed from inactive to active forms.

COCCIDIOIDOMYCOSIS. Valley fever; a disease caused by the fungus *Coccidioides immitis* or cocci.

COGNITIVE. Associated with thinking, learning, perception, awareness, and judgment.

COLD SORE. A fluid-filled blister usually found on or near the lips caused by the herpes simplex virus type 1 (HSV 1); also called a fever blister.

COLITIS. Inflammation of the colon, a part of the intestine that extends down toward the rectum.

COLON. The last part of the human intestine, located between the small intestine and the rectum. It is often called the large intestine, although the large intestine technically includes the cecum, rectum, and anus, as well as the colon.

COLORECTAL CANCER. Cancer involving both the colon and the rectum of the gastrointestinal tract.

COMMUNITY ACQUIRED. Contracted outside of a hospital or health facility.

CONGENITAL ADRENAL HYPERPLASIA (CAH). A term used to describe a group of autosomal recessive genetic disorders characterized by a deficiency of cortisol, a steroid hormone produced in the cortex of the adrenal glands.

CONGESTIVE HEART FAILURE (CHF). A condition in which the heart cannot pump enough blood to supply the body's tissues with sufficient oxygen and nutrients; back up of blood in vessels and the lungs causes buildup of fluid (congestion) in the tissues.

CONJUNCTIVITIS. Swelling and irritation of the conjunctiva, the clear lining of the eyelids and the whites of the eyes. Allergic conjunctivitis is caused by exposure to allergens.

CONTACT DERMATITIS. A localized rash or patch of inflamed skin caused by contact with an irritant or allergen, often nickel or chromium, or the oily toxins produced by poison oak, poison ivy, and poison sumac.

CONTRACEPTION. Prevention of becoming pregnant.

CONTRACEPTIVE. A method of birth control.

COPOLYMERS. Chains of molecules formed from two or more types of molecule. If a single type of molecule binds with others of the same type to form a chain, it is called a polymer. If two or more molecules form a chain with each other, it is a copolymer.

CORONARY ARTERY. The vessels that carry blood to the heart.

CORONARY ARTERY DISEASE (CAD). A condition in which the arteries that supply blood to the heart narrow and close. The narrowing is caused by plaque that builds up on the walls of the arteries because of too much cholesterol in the blood. CAD is also called atherosclerosis.

CORTICOSTEROID. A medication that acts like a type of hormone (cortisol) produced by the adrenal gland of the body. Corticosteroids produced by the body stimulate specific types of functional activity. As a drug, a corticosteroid (sometimes just called a steroid) helps treat inflammation, infection, or trauma to the body.

CORTISOL. A naturally occurring hormone with numerous functions in the body, including the suppression of the immune system so that inflammatory responses are dampened.

COWPOX. A mild disease in cows that is caused by a poxvirus.

C-REACTIVE PROTEIN (CRP). A ring-shaped protein found in blood plasma whose levels rise in response to inflammation. High basal levels of CRP are thought to indicate increased risk of type 2 diabetes, cardiovascular disease, and high blood pressure.

CREATININE CLEARANCE. A test of kidney function that compares the amount of creatinine in the blood to the amount of creatinine in the urine.

CROHN'S DISEASE. An inflammatory bowel disease that can cause damage to deep-tissue layers of the intestines, causing pain, severe diarrhea, weight loss, and malnutrition.

CRYPTOCOCCUS. A genus of yeast-like fungi that can cause serious illness, especially in immunocompromised patients.

CUSHING SYNDROME. A group of conditions caused by increased production of cortisol hormones or by the administration of glucocorticoid hormones (cortisone-like hormones); symptoms include fat accumulation, high blood pressure, bone loss, and emotional disturbances.

CYCLIC ADENOSINE MONOPHOSPHATE (CAMP). A compound that prevents platelets from clumping.

CYCLIC GUANOSINE MONOPHOSPHATE (CGMP). A second messenger in the body that, among many other functions, enables the achievement and maintenance of penile erections; vardenafil slows its breakdown.

CYCLIC VOMITING SYNDROME (CVS). Recurrent episodes of nausea, vomiting, and lethargy that are sometimes treated with sumatriptan.

CYST. An abnormal sac or enclosed cavity in the body, filled with liquid or partially solid material.

CYSTIC FIBROSIS. An inherited disease that causes mucus accumulation in the airways and blocked bile ducts in the liver.

CYSTITIS. Inflammation of the bladder. When caused by an infection, this can also be called a urinary tract infection.

CYTISINE. A plant alkaloid that binds nicotinic acetylcholine receptors and has been widely used as a smoking-cessation aid in Eastern Europe.

CYTOCHROME P450 (CYP450). Enzymes present in the liver that metabolize drugs.

CYTOCHROME P450 3A4 (CYP3A4) INHIBITORS. Substances, such as a drug or grapefruit juice, that inhibit a liver enzyme that is required to metabolize and detoxify drugs.

CYTOKINES. Proteins, such as interferons, that regulate immune responses and mediate intercellular communication. At high levels, they may be toxic to nerve cells in the developing brain.

CYTOMEGALOVIRUS (CMV). A common human herpes virus that is normally not harmful but may cause severe complications if transmitted to a fetus.

CYTOSTATIC. Inhibiting or suppressing cellular growth and multiplication.

CYTOTOXIC. Having a toxic effect on cells.

CYTOTOXIC DRUG. A medicine that kills (cancer) cells.

D

DEEP VEIN THROMBOSIS (DVT). A blood clot (thrombus) in a deep vein that returns blood to the heart. DVT usually occurs in veins in the calf or thigh, and may be more prevalent after surgery, trauma, or prolonged periods of bed rest.

DEHYDRATION. Abnormal depletion of body fluids, as from vomiting, diarrhea, or a diuretic.

DELIRIUM. A disturbance of consciousness marked by confusion, agitation, inattention, delusions, and/or hallucinations.

DELUSIONS. Irrational beliefs that defy normal reasoning and remain firm even when overwhelming proof is presented to dispute them. Delusions are distinct from culturally or religiously based beliefs that may be seen as untrue by other groups.

DEMADEX. The U.S. brand name for torsemide.

DEMENCIA. A disease characterized by the progressive deterioration of intellectual functions, such as memory, reasoning, and language. Other symptoms include changes in personality, deterioration in personal grooming, and disorientation.

DEPENDENCE. A state in which a person requires a steady concentration of a particular substance in order to avoid withdrawal symptoms.

DEPERSONALIZATION. A dissociative symptom in which a patient feels that his or her body is unreal, is changing, or is dissolving.

DEPRESSANT. Any psychoactive substance that lowers the function or activity level of a specific part of the body or brain. Depressants are sometimes referred to as “downers.”

DEPRESSION. A mental state characterized by excessive sadness and loss of interest in life; other symptoms may include altered sleep or eating patterns, loss of concentration, agitation, lack of energy, and, in severe cases, attempts at self-harm or suicide.

DERMATITIS. Also called eczema, dermatitis is a skin rash with itching, redness, and swelling that can be chronic or caused by an allergic reaction.

DERMATOPHYTE. A fungal parasite on skin, hair, or nails.

DERMATOPHYTOSES. Diseases of the skin, hair, or nails caused by parasitic fungi.

DERMIS. The sensitive, vascular inner mesodermic layer of skin.

DIABETES MELLITUS. A disease in which insufficient insulin is made by the body to metabolize sugars. In type 1 diabetes, the pancreas does not produce sufficient amounts of insulin. In type 2 diabetes, the body does not properly utilize glucose (blood sugar).

DIABETIC KETOACIDOSIS (DKA). A potentially life-threatening complication of diabetes in which a shortage of insulin causes the body to burn fatty acids and produce

acidic ketone bodies, resulting in such symptoms as nausea, vomiting, and intense thirst.

DIABETIC NEUROPATHY. A complication of diabetes in which damage to the capillaries in the circulatory system leads to nerve damage. The patient may feel tingling or burning sensations along the nerve endings, or may lose sensation in such areas as the lower legs and feet.

DIABETIC RETINOPATHY. A condition in which the tiny blood vessels to the retina, the tissues that sense light at the back of the eye, are damaged, leading to blurred vision, sudden blindness, or black spots, lines, or flashing lights in the field of vision.

DIALYSIS. A blood filtration therapy that replaces the function of the kidneys, filtering fluids and waste products out of the bloodstream. There are two types of dialysis treatment: hemodialysis, which uses an artificial kidney, or dialyzer, as a blood filter; and peritoneal dialysis, which uses the patient's abdominal cavity (peritoneum) as a blood filter.

DIARRHEA. Technically described as three or more loose or watery bowel movements each day, usually lasting for a period of two or three days.

DIASTOLIC BLOOD PRESSURE. Pressure when the heart relaxes.

DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS. A group of oral antidiabetic drugs that work by inhibiting an enzyme that slows down the lowering of blood glucose levels. DPP-4 inhibitors are also known as gliptins.

DIPHTHERIA. A serious infectious disease that produces a toxin (poison) and an inflammation in the membrane lining of the throat, nose, trachea, and other tissues.

DIPLOPIA. Double vision (seeing two images).

DISEASE-MODIFYING ANTIRHEUMATIC DRUG (DMARD). A drug that suppresses the immune system to decrease inflammation from rheumatoid arthritis.

DISEASE-MODIFYING DRUG (DMD). A drug, such as interferon beta 1a, that modulates the immune system to decrease inflammation.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC). The abnormal and extensive activation of the coagulation cascade that finally results in small blood clots forming in blood vessels throughout the body. If not stopped, this can compromise the flow of blood throughout the body and lead to multiple organ damage.

DIURESE. Reduction of fluid, usually pertains to reduction of fluid and swelling due to an increase in urine output.

DIURETICS. Drugs designed to encourage excretion of urine in people who accumulate excess fluid, such as individuals with high blood pressure or heart conditions; also called water pills.

DNA. A molecule found in all living cells that contains tiny bits of genetic information.

DOPAMINE. A neurotransmitter, or chemical, in the brain that influences many of the brain's functions, including movement, areas of thinking, pleasure, and control of hormones.

DRUG SCHEDULE. A system of classifying drugs, including narcotics, sedatives, hallucinogenics and other drugs, that are restricted under federal and state laws in the United States. Schedule I substances have no approved medical use, while Schedules II, III, and IV have approved uses. The higher the schedule, the lower the degree of restriction.

DUODENUM. The first portion of the small intestine, which is the tube-like organ between the stomach and the large intestine that helps with food digestion.

DYSKINESIA. Difficulty in performing voluntary muscular movements.

DYSLIPIDEMIA. The medical term for an abnormal level of lipids (cholesterol and other fats) in the blood. Most dyslipidemias are hyperlipidemias; that is, the level of lipids is abnormally high rather than abnormally low.

DYSPHAGIA. Difficulty swallowing.

DYSRHYTHMIA. Disordered rhythm in the electrical activity of the heart.

DYSTONIA. Abnormal muscle tone.

DYSURIA. Painful or difficult urination.

E

ECTOPIC PREGNANCY. A complication of pregnancy in which the embryo implants outside the uterus, most often in the fallopian tubes.

ECZEMA. Also called atopic dermatitis, eczema is characterized by an itchy, red rash that can cause intense itching and discomfort.

EDEMA. Swelling of the body's tissues caused by excess fluids.

ELECTROCARDIOGRAPHY (ECG OR EKG). Recording of the electrical potential during the heartbeat.

ELECTROLYTE. Salts and minerals that ionize in body fluids. The major human electrolytes are sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), chloride (Cl^-), phosphate (HPO_4^{2-}), bicarbonate (HCO_3^-), and sulfate (SO_4^{2-}). Electrolytes control the fluid balance of the body and are important in muscle contraction, energy generation, and almost all major biochemical reactions in the body.

EMBOLISM. The blocking of the flow of blood in an artery by an embolus. When an embolism blocks the blood supply to a tissue or organ, the tissue the artery feeds dies (infarction). Without immediate and appropriate treatment, an embolism can be fatal.

EMBOLUS (PLURAL, EMBOLI). A blood clot, gas bubble, piece of tumor tissue, or other foreign matter that moves through the bloodstream from its site of origin to obstruct a blood vessel.

EMETOGENIC. Referring to a substance or procedure intended or likely to cause vomiting.

ENCEPHALITIS. Inflammation of the brain, usually caused by a virus. The inflammation may interfere with normal brain function and may cause seizures, sleepiness, confusion, personality changes, weakness in one or more parts of the body, and even coma.

ENCEPHALOPATHY. Syndrome of global brain disease or injury.

ENDOCARDITIS. Inflammation of the endocardium, the layer of tissue that lines the inside of the heart.

ENDOCRINE. A gland that releases a hormone directly into the blood stream.

ENDOGENOUS DEPRESSION. Depression arising from causes within a person, such as chemical or hormonal imbalances.

ENDOMETRIAL CANCER. Cancer of the uterus.

ENDOMETRIOSIS. A condition in which tissue, like that normally found in the lining of the uterus, is present outside the uterus. The condition often causes pain and bleeding.

ENDOPHTHALMITIS. Inflammation inside the eye usually caused by an infection; associated with injections, surgery, or trauma to the eye.

ENDOTHELIAL CELLS. The cells lining the inside of blood vessels.

ENTERIC-COATED. A drug that has a coating that only breaks apart in the intestine, not the stomach. Enteric

coatings may be used for drugs that would cause stomach irritation, as a way of delaying the release of the drug into the blood stream, or for drugs that would be harmed by stomach acid.

ENURESIS. Involuntary urination.

ENZYME. Any protein that acts as a catalyst, increasing the rate of a chemical reaction.

EPICONDYLITIS. Inflammation of either of the two epicondyles, the rounded ends of the humerus bone. Lateral epicondylitis is commonly known as tennis elbow, and medial epicondylitis as golfer's elbow or pitcher's elbow.

EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR). A protein on the cell surface that can initiate growth and proliferation.

EPIDERMIS. The outer layer of skin.

EPIDURAL. A method of pain relief in which local anesthetic or analgesic (pain reliever) is injected into the epidural space in the middle and lower back.

EPILEPSY. A neurological disorder characterized by the onset of seizures. Seizures are caused by a disturbance in the electrical activity in the brain and can cause loss of consciousness, muscle spasms, rhythmic movements, abnormal sensory experiences, or altered mental states.

EPINEPHRINE. Also called adrenaline, epinephrine is a stress-triggered hormone that causes such responses as increased heart rate and muscle strength, elevated blood pressure, and heightened sugar metabolism.

EPISODIC THERAPY. Antiviral treatment at the first sign of a genital herpes outbreak.

EPSTEIN-BARR VIRUS. A herpes virus that causes infectious mononucleosis.

ERECTILE DYSFUNCTION (ED). The consistent inability to achieve or maintain a penile erection.

ERYTHROPOESIS. Production of red blood cells.

ERYTHROPOIETIN. A hormone produced by the kidneys that stimulates the production of red blood cells by bone marrow.

ESOPHAGITIS. Inflammation of the esophagus, the tube that connects the throat with the stomach.

ESOPHAGUS. The tube that carries food from the mouth to the stomach.

ESTRADIOL. The primary human female sex hormone; it is the most physiologically active form of estrogen.

ESTROGEN. A female hormone produced by the ovaries that stimulates the growth of the lining of the uterus.

ESTROGEN RECEPTORS. A group of proteins found inside cells that are activated by the sex hormone estrogen.

ESTROGENS. Various naturally occurring steroid hormones, such as estradiol, and synthetic or semisynthetic steroids, such as ethinyl estradiol, that promote the growth and maintenance of the female reproductive system.

EXTRAPYRAMIDAL. Related to the motor system in the brain, the symptoms of which affect movement and coordination, including abnormal muscle movements and drooling.

EXTRAPYRAMIDAL SYMPTOMS (EPS). A group of side effects associated with antipsychotic medications and characterized by involuntary muscle movements, including contraction and tremor.

F

FALLOPIAN TUBES. Part of the internal female anatomy that carries eggs from the ovaries to the uterus.

FAMCICLOVIR. An antiviral medication similar to valacyclovir.

FAMILIAL DYSBETALIPOPROTEINEMIA. A genetic disorder characterized by high triglyceride levels, high LDL cholesterol levels, low HDL cholesterol levels, and the early onset of atherosclerosis.

FAMILIAL HYPERCHOLESTEROLEMIA (FH). A genetic disorder characterized by high levels of LDL cholesterol in the blood and cardiovascular disease early in life. The heterozygous form is more common and can be treated with statins; the homozygous form is very rare (about one case in every million live births) and may respond only to liver transplantation.

FAMILIAL MEDITERRANEAN FEVER. A hereditary disorder characterized by recurring fevers and inflammation.

FATTY ACIDS. Complex molecules produced during the breakdown of fats and oils.

FEBRILE NEUTROPENIA (FN). Deficiency of neutrophils accompanied by fever.

FECES. The solid waste that is left after food is digested. Feces form in the intestines and pass out of the body through the anus. Also called stool.

FEMALE HYPOGONADISM. Dysfunction or failure of the ovaries resulting in lack of production of female hormones.

FETUS. A developing baby inside the womb.

FIBRATES. A group of carboxylic acid drugs used to lower blood cholesterol levels and thus reduce the patient's risk of atherosclerosis. Fenofibrate is one of the older medications in this class.

FIBRIN. The protein formed as the end product of the blood clotting process when fibrinogen (another blood protein) interacts with thrombin (an enzyme).

FIBRINOLYSIS. The clot-dissolving portion of the coagulation process.

FIBRINOLYTICS. Agents that decompose fibrin, a protein produced in the clotting process.

FIBROID TUMOR. A noncancerous tumor formed of fibrous tissue.

FIBROIDS. Benign (noncancerous) growths that arise from the smooth muscle layer and connective tissue of the uterus. They sometimes cause secondary dysmenorrhea.

FIBROMYALGIA. A chronic disorder characterized by widespread tenderness, pain, and stiffness of muscles and associated connective tissues, often accompanied by fatigue, headache, and sleep disturbances.

FILGRASTIM. The short-acting form of pegfilgrastim.

FINASTERIDE. A drug used to treat benign prostatic hyperplasia.

FISTULA. Abnormal connection or passageway between two organs or vessels that normally do not connect.

5-HYDROXYTRYPTAMINE₁ (5-HT₁). A serotonin receptor in blood vessels in the brain.

FLUCONAZOLE. An antifungal agent similar to ketoconazole but more effective for systemic infections and less toxic.

FOLLICLE. As part of the female reproductive system, a fluid-filled sac containing an immature egg.

FOLLICLE-STIMULATING HORMONE. A hormone produced by the pituitary gland that, in women, stimulates the growth of the ovum-containing follicles in the ovaries.

FOLLICULAR. Relating to one of the round cells in the ovary that contain an ovum.

G

GALLBLADDER. The muscular sac that stores bile from the liver.

GALLSTONES. Hard deposits, usually of cholesterol, that form in the gallbladder or bile ducts.

GAMMA-AMINOBUTYRIC ACID (GABA). A neurotransmitter that helps to lower or reduce the level of excitement in the nerves, leading to muscle relaxation, calmness, sleep, and the prevention of seizures.

GASTROENTERITIS. An inflammation of the lining of the stomach and intestines, usually caused by a viral or bacterial infection.

GASTROESOPHAGEAL REFLUX DISEASE (GERD). A condition in which gastric juice from the stomach backs up into the bottom of the esophagus, causing irritation, inflammation, or erosion of the cells lining the esophagus.

GASTROINTESTINAL (GI). Refers to areas of the digestive system, especially the stomach and intestines.

GASTROINTESTINAL STROMAL TUMOR (GIST). Tumor of the gastrointestinal tract derived from connective tissue.

GASTROINTESTINAL SYSTEM. The gastrointestinal system includes the stomach, esophagus, intestine, rectum, and anus. It also is called the digestive system.

GASTROPARESIS. Partial paralysis of the stomach, characterized by nausea, vomiting, and abdominal distension.

GENERALIZED ANXIETY DISORDER (GAD). An anxiety disorder characterized by daily irrational worry that is often excessive and uncontrolled.

GENITAL HERPES. A sexually transmitted infection in both men and women that can cause pain, itching, and irritation in the genital area caused by the herpes simplex virus type 2 (HSV 2).

GENITAL WARTS. Venereal warts, anogenital warts, or condylomata acuminata; painless, pink or grayish growths on the skin and mucous membranes of the genitals and anal area caused by sexually transmitted human papillomavirus.

GENOTYPE. The genetic composition of an organism; there are different genotypes of the hepatitis C virus that may require different treatments.

GESTATIONAL DIABETES. A condition in which women without previously diagnosed diabetes develop high blood sugar levels during pregnancy.

GIANT CELL ARTERITIS. An inflammatory disorder that affects the large- and medium-sized arteries in the head. It may result in sudden blindness as well as ringing in the ears, severe headache, and pain in the jaw and tongue when chewing.

GINGIVITIS. Inflammation of the gums.

GLAUCOMA. A condition in which increased fluid pressure inside the eye damages the optic nerve (the nerve that goes from the eye to the brain). If left untreated, glaucoma can lead to blindness.

GLIOBLASTOMA. Most aggressive and common type of primary brain tumor.

GLOMERULAR FILTRATION RATE (GFR). A blood test that assesses kidney function. The GFR measures the amount of blood that passes through the glomeruli, which are tiny blood vessels in the kidneys that remove waste products from the blood.

GLP-1 RECEPTOR AGONISTS. A group of medications for the treatment of type 2 diabetes that work by stimulating insulin secretion by the pancreas. They are also called incretin mimetics.

GLUCAGON. A peptide hormone produced by the pancreas. It acts to increase low blood glucose levels.

GLUCOCORTICOIDS. Medications made to closely resemble human hormones that affect mostly the body's metabolism.

GLUCOSE. A simple sugar produced when carbohydrates are broken down in the small intestine. It is the primary source of energy for the body.

GONADOTROPINS. Protein hormones secreted by the pituitary gland that affect and stimulate the ovaries or testes.

GOUT. A type of arthritis in which uric acid, a waste product that normally passes out of the body in urine, collects in the joints and the kidneys, resulting in swollen, painful joints and possibly kidney stones.

GRAFT-VERSUS-HOST DISEASE (GVHD). A potentially life-threatening complication of bone marrow or stem cell transplants in which the donated cells attack the patient's own cells.

GRANULOCYTE-COLONY STIMULATING FACTOR (G-CSF). A protein that stimulates the maturation of neutrophils; pegfilgrastim is a G-CSF produced in the laboratory.

GRANULOCYTES. White blood cells, such as neutrophils, that contain granules of immune-system chemicals.

GRANULOSA CELLS. Cells that form the wall of the ovarian follicle and produce various steroid hormones.

GROWTH HORMONE (GH). A polypeptide hormone that regulates growth and is secreted by the anterior lobe of the pituitary gland.

GS-331007. The circulating metabolite of sofosbuvir that is taken up by liver cells and converted to the active drug.

GUILLAIN-BARRÉ SYNDROME (GBS). A disease of the nerves with symptoms that include sudden numbness and weakness in the arms and legs, sometimes leading to paralysis. The disease is serious and requires medical treatment, but most people recover completely.

H

HALLUCINATIONS. Seeing, hearing, feeling, smelling, or tasting things that do not exist.

HDL CHOLESTEROL. High-density lipoprotein, or “good” cholesterol. A lipoprotein in the blood that is primarily protein with small amounts of triglyceride and cholesterol that helps protect against heart disease.

HEART ATTACK. Also called myocardial infarction; myocardial means heart muscle, and infarction means death of tissue from lack of oxygen.

HEART BLOCK. A disorder of the electrical system of the heart, causing lightheadedness, fainting, and palpitations.

HEART FAILURE. A condition in which a damaged or overworked heart cannot pump enough blood to meet the oxygen and nutrient needs of the body.

HEMAGGLUTININ (HA, H). A protein in the outer coat of viruses that enables them to bind to cells and initiate infection.

HEMATOMA. A collection of blood forming outside of blood vessels with tissue. A hematoma can form after a specific injury or may form when bleeding occurs under the skin for other reasons.

HEMATOPOIETIC GROWTH FACTOR. A protein, such as granulocyte-colony stimulating factor, that promotes the proliferation and maturation of blood cells.

HEMOGLOBIN. A protein-iron compound in red blood cells that functions primarily in carrying oxygen from the lungs to the tissues of the body.

HEMOGLOBIN A1C (HBA1C). Glycated hemoglobin; a stable binding of glucose to hemoglobin A in the blood,

which can be used to determine the average blood glucose level for the previous two to three months.

HEMOPHILIA. An inherited bleeding disorder caused by a deficiency of factor VIII, one of a series of blood proteins essential for blood clotting.

HEMOSTASIS. The process of how the body stops bleeding from an injured blood vessel.

HEPARIN. An injectable drug that is used to prevent blood clotting. Heparin does not break down clots that have already formed. The term “heparin” normally refers to unfractionated heparin, which has largely been replaced in use by low molecular weight heparin, which is formed by fragmentation of the heparin molecule.

HEPATIC. Related to the liver.

HEPATIC IMPAIRMENT. Reduced liver function.

HEPATITIS. An inflammation of the liver that can be due to infection or damage from chemical agents, including medications.

HEPATITIS B VIRUS (HBV). A virus that attacks the liver.

HEPATITIS C VIRUS (HCV). A single-stranded RNA virus that causes liver disease.

HEPATOMEGALY. Enlargement of the liver beyond normal size. This is a symptom of a large number of conditions including cancer and several types of infections.

HERPES LABIALIS. Oral herpes; herpes simplex virus affecting the lips and nose.

HERPES SIMPLEX VIRUS TYPE 1 (HSV-1). The virus that is usually responsible for cold sores.

HERPES SIMPLEX VIRUS TYPE 2 (HSV-2). The virus that causes genital and sometimes oral herpes.

HERPES ZOSTER OPHTHALMICUS. Shingles that affects the eyes.

HETEROZYGOUS. Possessing two different forms of a particular gene, one inherited from each parent.

HIDRADENITIS SUPPURATIVE (HA). A chronic, painful, draining, and foul-smelling autoimmune disease of the sweat glands in the armpits, groin, and under the breasts.

HIGH-DENSITY LIPOPROTEIN (HDL). “Good” cholesterol; protein in the blood that includes small amounts of triglyceride and cholesterol and helps protect against heart disease.

HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART).

An individualized combination or drug cocktail of three or more antiretroviral drugs for treating HIV/AIDS.

HIRSUTISM. Male-pattern hair growth (excess hair on face, chest and back) in women.

HISTAMINE. A chemical found naturally in the body that produces inflammation and increases blood flow; the symptoms of an allergy attack or an allergic reaction are generally caused by the release of histamine.

HISTOPLASMOSIS. A respiratory disease with flu-like symptoms caused by the fungus *Histoplasma capsulatum*, endemic to the Mississippi and Ohio River valleys.

HMG-COA REDUCTASE. An enzyme that affects the production of cholesterol in the liver. Drugs known as statins lower blood cholesterol levels by inhibiting the activity of this enzyme.

HODGKIN LYMPHOMA. A human malignant disorder of the lymph tissue that appears to originate in a particular lymph node and later spreads to the spleen, liver, and bone marrow.

HOLTER MONITOR. Portable heart monitor device worn by a patient over an extended period of time (usually a 24-48 hour period) in order to monitor and track cardiac rhythm. The device is held in a pouch worn at the neck or waist.

HORMONES. Substances that are produced in one area of the body and travel through the bloodstream to other parts of the body, where they exert their effects.

HUMAN IMMUNODEFICIENCY VIRUS (HIV). The virus that causes acquired immune deficiency syndrome (AIDS).

HUMAN PAPILLOMAVIRUS (HPV). A large family of viruses, some of which cause genital and anal warts.

HUMANIZATION. Fusing the constant and variable framework region of one or more human immunoglobulins with the binding region of an animal immunoglobulin, done to reduce human reaction against the fusion antibody.

HUMANIZED MONOCLONAL ANTIBODY. Human-like antibodies usually genetically engineered in mice and used in a therapeutic manner.

HYDATID. A cyst (fluid-filled sac) containing the dog tapeworm *Echinococcus granulosus*.

HYDROCHLOROTHIAZIDE. A diuretic drug that acts by inhibiting the kidneys' ability to retain water. It is often given together in fixed combinations with an ACE inhibitor.

HYPERCHOLESTEROLEMIA. High blood cholesterol.

HYPEREMESIS GRAVIDARUM. A complication of pregnancy marked by intractable nausea, vomiting, and dehydration.

HYPERGLYCEMIA. High blood glucose (blood sugar).

HYPERKALEMIA. High blood potassium.

HYPERLIPIDEMIA. High levels of lipids in the blood, including elevated total cholesterol, LDL cholesterol, non-HDL cholesterol, and apolipoproteins.

HYPERNATREMIA. An abnormally high concentration of sodium in the blood. The usual reference range for sodium is 135 to 145 mmol/L (or mEq/L).

HYPERPIGMENTATION. A common, usually harmless condition in which patches of the skin become darker in color. This can be associated with aging and/or deposits of excess melanin, the brown pigment that gives skin its color; "liver spots" as a result of sun exposure, typically appearing on the face or hands, are a common form of hyperpigmentation.

HYPERPLASIA. The enlargement of an organ or tissue due to an increase in its cellular growth rate.

HYPERTENSION. High blood pressure.

HYPERTHYROIDISM. A condition in which the thyroid gland in the throat is overactive and produces too much thyroid hormone.

HYPERURICEMIA. An abnormally high level of uric acid in the blood due to an imbalance in the amount of purines ingested as food or due to the activity of certain drugs that may decrease the excretion of uric acid. Excess uric acid is associated with gout and gouty arthritis.

HYPNOTIC. A medication that causes sleep.

HYPOCALCEMIA. An abnormally low level of calcium in the blood.

HYPOESTROGENISM. Low levels of estrogen. This may be caused by failure of the ovaries to produce enough hormones, or by surgical removal of the ovaries.

HYPOGLYCEMIA. Low blood glucose (blood sugar).

HYPOKALEMIA. Low blood potassium.

HYPOLIPIDEMICS. A group of drugs used to lower the levels of cholesterol and other lipids (fatty substances) in the blood. The fibrates are one type of antilipidemic agents.

HYPONATREMIA. An abnormally low concentration of sodium in the blood.

HYPOPARATHYROIDISM. A condition in which parathyroid glands, which are glands located in the neck, do not secrete enough parathyroid hormone.

HYPOPITUITARISM. Failure of the pituitary gland to produce normal amounts of the pituitary hormones.

HYPOTENSION. Low blood pressure.

HYPOTHALAMUS. A structure within the brain responsible for a large number of normal functions throughout the body, including regulating sleep, body temperature, hunger, and sexual development. The hypothalamus also regulates the functions of the pituitary gland by directing the pituitary to stop or start production of its hormones.

HYPOTHYROIDISM. A condition in which the thyroid gland does not produce enough thyroid hormone.

HYPOVENTILATION. Reduced ventilation in the air sacs in the lungs, resulting in above-normal carbon dioxide pressure.

HYPOVOLEMIC SHOCK. Low blood pressure caused by blood loss as in injury.



IBUPROFEN. A nonsteroidal anti-inflammatory drug that may be used to relieve mild to moderate pain and reduce fever. Common brand names are Advil and Motrin.

ICHTHYOSES (SINGULAR, ICHTHYOSIS). A group of about 28 skin disorders, mostly genetic in origin, in which a person's skin forms heavy or thick flakes or patches of dry skin resembling the scales of a fish. The name of the group of disorders is derived from the Greek word for fish.

IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP). A bleeding disorder in which the patient has a low platelet count in the absence of other causes of this condition. ITP is characterized by a purple skin rash and an increased tendency to bleed.

ILEOSTOMY. An opening in the abdominal wall for the removal of fecal matter from the intestine.

ILEUS. A blockage of the intestines due to a lack of the normal abdominal muscle contractions known as peristalsis.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS). The reactivation of infections or development of new diseases that may occur as the immune system improves with the start of antiretroviral therapy.

IMMUNE SYSTEM. The cells, organs, and tissues throughout the body that help protect the body from infection and maintain health.

IMMUNIZATION. Administering a vaccine that stimulates the body to create antibodies to a specific disease (immunity) without causing symptoms of the disease.

IMMUNOCOMPETENT. Having a healthy immune system.

IMMUNOMODULATORS. A class of drugs, including interferon beta 1a, that act by altering the immune response.

IMMUNOSUPPRESSANT. Any agent that decreases the response of the immune response of an individual.

IMMUNOSUPPRESSIVE DRUGS. Medications used to suppress the immune system.

IMMUNOTHERAPY. Therapy that stimulates, enhances, or suppresses the body's immune response; includes products such as monoclonal antibodies, vaccines, and growth factors.

INCONTINENCE. Inability to control urination or defecation.

INCRETINS. Metabolic hormones that reduce blood glucose levels by increasing insulin secretion.

INFECTIOUS DISEASE. Any disease caused by the invasion of a pathogen that subsequently grows and multiplies in the body.

INFLAMMATION. Pain, redness, swelling, and heat that usually develop in response to injury or illness.

INFLAMMATORY BOWEL DISEASE (IBD). A disease that causes inflammation of the colon and rectum.

INFLUENZA. A disease caused by viruses that infect the respiratory tract.

INFLUENZA A. A common, moderate-to-severe respiratory disease that affects humans and animals such as swine and birds and has caused global pandemics.

INFLUENZA B. A relatively genetically stable virus that only infects humans, especially children, and usually causes milder illness than influenza A and epidemics rather than pandemics.

INFUSION THERAPY. Administration of a medication as a liquid through an intravenous (IV) device.

INSOMNIA. A sleep disorder characterized by the inability to fall asleep or remain asleep.

INSULIN. A hormone secreted by the pancreas that controls blood glucose (sugar) levels by moving excess glucose into muscle, liver, and other cells for storage.

INSULIN ANALOGUE. An insulin that has been altered by genetic engineering to affect its absorption, distribution, metabolism, and excretion rates, but can still be used by the human body to maintain glycemic control.

INSULIN RESISTANCE. A condition in which the cells of the body fail to respond normally to insulin and are unable to use it effectively.

INSULIN-LIKE GROWTH FACTOR-1 (IGF-1). A growth factor that normally declines after puberty but that may be increased in certain cancers and other conditions.

INTERFERON. A potent immune-defense protein (cytokine) produced by viral-infected cells. Manufactured interferon is used as an anticancer and antiviral drug.

INTRAMUSCULAR. Into the muscle.

INTRANASAL. In the nose.

INTRAOCULAR. Within the eye.

INTRATHECAL INJECTION. An injection delivered into the intrathecal space, which is the fluid-filled space between thin layers of tissue that cover the spinal cord.

INTRAVENOUS LINE. A tube that is inserted directly into a vein to carry medicine directly to the blood stream, bypassing the stomach and other digestive organs that might alter the medicine.

ION. Charged molecule such as sodium or chloride used in neuronal signaling in the brain.

ION CHANNEL. Physical opening on the surface of neurons that allows the passage of charged ions propagating neuronal signaling in the brain.

IONTOPHORETIC. Introduction of an ionized drug through the skin by application of an electric current.

IRITIS. Inflammation of the iris of the eye.

IRRITABLE BOWEL SYNDROME. A condition affecting the large intestine that causes bloating, cramping, and changes to bowel habits.

J

JAUNDICE. A condition in which bilirubin, a waste product caused by the normal breakdown of red blood cells, builds up in the body faster than the liver can break it down. People with jaundice develop yellowish skin and

the whites of their eyes become yellow. The condition can occur in newborns and people with liver damage.

JUVENILE IDIOPATHIC ARTHRITIS (JIA). A type of autoimmune arthritis that affects children aged 16 and younger and that can delay growth and development.

K

KCL. Potassium chloride.

KERATIN. Fibrous proteins that form the basis of tissues such as hair and nails.

KERATITIS. Inflammation of the cornea, the clear front portion of the eye.

KERION. An inflammatory ringworm infection of the hair follicles of the scalp or beard that is usually accompanied by a secondary bacterial infection.

KETOACIDOSIS. Condition that may occur with untreated diabetes from the body's attempt to burn fat for fuel when carbohydrates cannot be utilized. Ketones, the byproduct of fat metabolism, enter the bloodstream and make the blood more acidic than the body's tissues.

KIDNEY STONE. A concretion in the kidney made of various materials, such as uric acid crystals, calcium, or lipids. These concretions, or stones, cause severe pain when they are transported from the kidney into the bladder and out of the body.

KILOGRAM (KG). Metric measure that equals 2.2 pounds.

KINASE. An enzyme.

L

LACTATION. Secretion of milk from the breasts; the act of breastfeeding.

LACTIC ACIDOSIS. Buildup of lactic acid in the blood faster than it can be removed. While this condition may be caused by intense exercise, it is also seen in HIV disease, cancer, kidney failure, respiratory failure, and infections. Common symptoms are nausea and weakness.

LARVAL. The earliest lifestyle form of a worm.

LDL CHOLESTEROL. Low-density lipoprotein (LDL) cholesterol is the primary cholesterol molecule. High levels of LDL increase the risk of coronary heart disease. LDL is nicknamed "bad cholesterol."

LEDIPASVIR. A drug used in combination with sofosbuvir to treat hepatitis C.

LEFT VENTRICULAR HYPERTROPHY (LVH). A heart condition in which the walls of the left side of the heart are enlarged.

LENNOX-GASTAUT SYNDROME. A disorder that causes seizures and developmental delays.

LEUCOVORIN. The antidote for high-dose treatments of methotrexate.

LEUKEMIA. A type of cancer in which the bone marrow produces an excessive number of abnormal (leukemic) white blood cells. White blood cells protect the body against infection, but the abnormal cells suppress the production of normal white blood cells.

LEUKOPENIA. Abnormally low circulating white blood cells.

LEUKOTRIENE RECEPTOR AGONIST. Also called a leukotriene modifier, a type of medication that treats allergy and asthma symptoms by blocking or altering leukotriene action. Leukotrienes are chemicals released in the body when the body senses exposure to an allergen that cause the airways to contract, or tighten, along with other symptoms.

LEVITRA. The brand name of vardenafil tablets.

LEWY BODY DISEASE. A type of dementia that resembles Alzheimer's disease but progresses more rapidly. Common symptoms include fluctuations in confusion and recurring visual hallucinations. In this disease, abnormal brain cells are distributed throughout the brain.

LIPIDS. A group of fats and fat-like substances that are not soluble in water, are stored in the body, and serve as a source of fuel for the body.

LIPODYSTROPHY. Abnormal distribution or degeneration of the body's adipose (fatty) tissue. It may be congenital or acquired as a side effect of antiretroviral drugs given to treat HIV infection.

LIPOPROTEIN. A protein present in blood plasma.

LONG QT SYNDROME. An inherited heart condition in which delayed repolarization of the heart muscle following a heartbeat increases the risk of ventricular arrhythmias, which may lead in turn to dizziness, fainting, and sudden death due to ventricular fibrillation.

LONG-ACTING BETA-AGONIST. A medication that helps relax muscles around airways to open the air passages and improve breathing. Long-acting beta

agonists usually last about 12 hours and are used to prevent symptoms, not to relieve them immediately.

LOOP DIURETIC. A “water pill” that increases urine excretion and removes water and salt from the body by interfering with sodium and chloride reabsorption in the loop of Henle.

LOOP OF HENLE. The portion of a nephron that leads from the proximal convoluted tubule to the distal convoluted tubule. It is named for Friedrich Henle (1809–1885), the German anatomist who first identified it.

LOW-DENSITY LIPOPROTEIN (LDL). A type of lipoprotein that consists of about 50% cholesterol and is associated with an increased risk of coronary artery disease; it is also referred to as the “bad” cholesterol.

LOWER URINARY TRACT SYMPTOMS (LUTS). Symptoms such as difficult, painful, or frequent urination that may be caused by benign prostatic hyperplasia.

LUPUS. A group of diseases in which the patient's immune system attacks healthy tissue.

LUTEINIZING HORMONE. A hormone secreted by the pituitary gland that, in women, stimulates ovulation.

LYME DISEASE. A tick-transmitted disease with symptoms that include a rash (often described as a bull's-eye shape) and flu-like symptoms. Left untreated, Lyme disease can cause joint, heart, and central-nervous-system issues.

LYMPHATIC SYSTEM. The part of the immune system that includes lymph nodes and tissue. The lymphatic system collects and returns fluid in tissues to the blood vessels and produces defensive agents for fighting infection and invasion by foreign bodies.

LYMPHOCYTE. A type of white blood cell that defends the body against infection and disease. Lymphocytes are found in the bloodstream, the lymphatic system, and lymphoid organs. The two main types of lymphocytes are the B cells (produced in the bone marrow) and the T cells (produced in the thymus).

LYMPHOCYTIC LEUKEMIA. An acute form of childhood leukemia characterized by the development of abnormal cells in the bone marrow and lymph cells found in blood-forming tissues.

M

MACROLIDES. A class of antibiotic drugs, named for the macrolide ring within a macrolide drug's structure.

MACULAR DEGENERATION. A condition usually associated with age in which the area of the retina called

the macula is impaired due to hardening of the arteries (arteriosclerosis). This condition interferes with vision.

MAGNETIC RESONANCE IMAGING (MRI). A diagnostic technique that provides cross-sectional images of structures within the body via a magnetic imaging device.

MAJOR DEPRESSIVE DISORDER. A clinical psychiatric diagnosis of chronic depressed mood that interferes with normal life activities.

MALARIA. A mosquito-transmitted disease that causes fever, headache, and vomiting, and can be fatal if left untreated.

MANIA. An elevated or euphoric mood or irritable state that is characteristic of bipolar and certain other psychiatric disorders. Mania is characterized by mental and physical hyperactivity, disorganization of behavior, and inappropriate elevation of mood.

MARFAN SYNDROME. An inherited connective-tissue disorder that leads to severe heart problems, including unchecked growth of the aorta, which can cause aortic rupture and death.

MEASLES. An acute and highly contagious viral disease that occurs primarily in children marked by distinct red spots followed by a rash.

MEDIAN SURVIVAL TIME. The time from either diagnosis or treatment at which half of the patients with a given disease are expected to still be alive.

MELATONIN. A hormone involved in regulation of the sleep-wake cycle and other circadian rhythms.

MENINGITIS. Inflammation of the meninges—membranes covering the brain and spinal cord.

MENINGOCOCCAL. Disease (usually meningitis) caused by the bacteria *Neisseria meningitidis*.

MENOPAUSE. The end of a woman's menstrual periods when a woman no longer can conceive a child.

MEPROBAMATE. A metabolite of carisoprodol.

METABOLIC ACIDOSIS. A disturbance in the body's acid-base balance that results in excessive acidity of the blood.

METABOLITE. In terms of drugs, a metabolite is a modified form of a drug that is produced when the body processes that drug.

METABOLIZE. The change of a chemical from one form to another, most often in the liver. Drugs that are taken in an inactive form but are metabolized to an active form, such as enalapril, are known as prodrugs.

METASTATIC. Referring to a cancer that has spread to an organ or tissue from a primary cancer located elsewhere in the body.

METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA). An infection with a Staph organism that has developed resistance to the common antibiotics that were previously used to treat such infections.

METHOTREXATE (MTX). A drug used to treat severe psoriasis and rheumatoid arthritis.

METHYLPHENIDATE. A mild central nervous system stimulant that is used to treat hyperactivity.

MICROBE. A microorganism, especially a bacterium, that causes disease.

MIGRAINE HEADACHE. An intense throbbing pain that occurs on one or both sides of the head. The headache is usually accompanied by other symptoms, such as nausea, vomiting, and aversion to light.

MILLIEQUIVALENT (MEQ). One-thousandth of an equivalent of an element; used for the concentration of electrolytes in a solution; 1 mEq of potassium chloride is 1 millimole or 75 mg.

MILLIGRAM (MG). One-thousandth of a gram. A gram is the metric measure that equals about 0.035 ounces.

MM HG. Millimeters of mercury; based on the old-fashioned method of measuring blood pressure by seeing how much pressure would raise a column of mercury, the liquid metal also found in thermometers, in a tube. Although the mercury has mostly been replaced by electronic measurements, the unit of millimeters of mercury remains in use.

MONOAMINE OXIDASE A (MAO-A) INHIBITORS. A class of antidepressants.

MONOAMINE OXIDASE INHIBITOR (MAOI). An older class of antidepressants. These drugs act by preventing the metabolism of stimulatory neurohormones but are no longer widely used because they have potentially serious food and drug interactions.

MONOCLONAL ANTIBODIES. Genetically engineered antibodies specific for one antigen.

MONOTHERAPY. The use of a single medication or therapy to treat a disease or condition.

MRSA. Methicillin-resistant *Staphylococcus aureus*, a staphylococcal organism that has developed the ability to resist killing by many conventional antibiotics.

MUCOUS MEMBRANE. Moist, thin tissues that line parts of the body, including the nose and mouth.

MUCUS. Thick fluid produced by the moist membranes that line many body cavities and structures.

MULTIPLE SCLEROSIS (MS). A degenerative nervous system disorder in which the protective covering of the nerves in the brain are damaged, leading to tremor and paralysis.

MUMPS. An acute and highly contagious viral illness that usually occurs in childhood.

MUSCULOSKELETAL. Related to muscle and bone.

MYASTHENIA GRAVIS. Myasthenia gravis is an autoimmune or congenital neuromuscular disorder that involves muscles throughout the body and the nerves that control them. The main characteristics of the disease are muscular weakness and fatigue of any muscles people control themselves (voluntary control), including eye and facial muscles and muscles used in swallowing.

MYCOBACTERIA. A group of bacteria that includes *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis, and other forms that cause related illnesses.

MYCOSIS FUNGOIDES. The most common form of T-cell lymphoma of the skin; symptoms include rash, tumors, skin lesions, and itchy skin.

MYELIN BASIC PROTEIN (MBP). A protein that is important in maintaining the structure of myelin, a material that forms an insulating sheath around the axon of a nerve cell.

MYELIN SHEATH. A protective cover that surrounds nerve cells and helps to increase the speed by which information travels along the nerve.

MYELOYDPLASTIC SYNDROME (MDS). Bone marrow disorders that are late effects of cancer treatment and that may progress to acute myelogenous leukemia.

MYELOSUPPRESSION. Suppression of blood cell production in the bone marrow.

MYOCARDIAL INFARCTION. Commonly known as a heart attack, a myocardial infarction is an episode in which some of the heart's blood supply is severely cut off or restricted, causing the heart muscle to suffer and die from lack of oxygen.

MYOCARDIUM. The middle layer of the heart wall, composed of muscle.

N

NARCOLEPSY. A disorder characterized by frequent and uncontrollable attacks of deep sleep.

NARCOTICS. A class of chemicals that contain opium or opium derivatives. These drugs decrease pain, often cause drowsiness, may induce a sense of euphoria or well-being, and have profound side effects that include respiratory depression in overdoses and addictive potential.

NARROW-ANGLE GLAUCOMA. An eye disorder caused by a buildup of fluid pressure inside the eyeball due to an abnormally small angle between the iris (the colored portion of the eye) and the cornea (the transparent front part of the eye).

NEBULIZER. A machine, usually run by a small compressor, that delivers a fine liquid mist with medicine through a mouth tube or face mask. The nebulizer is used as a breathing treatment for people who have respiratory, or lung, diseases.

NEGATIVE SYMPTOMS. Symptoms of schizophrenia characterized by the absence or elimination of certain behaviors, such as initiative, speech, or affect.

NEPHRON. The basic structural unit of the kidney, responsible for regulating the concentration of water and soluble chemicals in the blood by filtering the blood, reabsorbing the compounds needed by the body, and excreting the rest in the urine.

NEPHROPATHY. Kidney damage or disease that can affect kidney function. Diabetic nephropathy refers to kidney damage caused by diabetes, which can lead to kidney failure.

NEPHROTIC SYNDROME. A kidney disorder characterized by edema (swelling), ascites (fluid accumulation in the abdomen), high levels of protein in the urine, and low levels of albumin in the blood.

NERVE ENDING. The structure in which the distal end of the axon of a nerve fiber terminates.

NETHERTON SYNDROME. A rare genetic disorder of the skin characterized by red, itchy skin susceptible to infections, allergies to nuts and fish, and abnormal development of the shafts of the hair. It is named for the American dermatologist who first identified it in 1958.

NEURALGIA. Acute pain that radiates along the course of one or more nerves, usually without a change in the nerve structure.

NEURAMINIDASE (NA, N). An enzyme on the surfaces of flu viruses that is involved in the release of viral particles from infected cells and that is inhibited by oseltamivir.

NEURAXIAL SYSTEM. Nerves of the central nervous system.

NEUROCYSTICERCOSIS. An infection of the brain by the pork tapeworm called *Taenia solium*, resulting in the establishment of larva-containing cysts throughout the brain substance.

NEUROENDOCRINE. The endocrine system involves cells that make hormones in the body. Neuroendocrine refers to cells that are found in organs that make hormones but also have nerve cells. They may be found in organs throughout the body.

NEUROLEPTIC MALIGNANT SYNDROME. A rare but dangerous reaction to antipsychotic medications that involves temperature instability, muscular rigidity, and altered mental status.

NEURON. Nerve cells in the brain that produce nerve impulses.

NEURONAL SIGNALING. The electrical or chemical pathway by which neurons communicate.

NEUROPATHIC PAIN. State of pain related to the nervous system; also known as neurogenic pain.

NEUROPSYCHIATRIC. Refers to disorders that affect the mind and nervous system.

NEUROTRANSMITTER. A naturally occurring chemical in the body that carries chemical messages to nerve cells, often by transmitting nerve impulses. Central nervous system well-being is dependent on a balance among the neurotransmitters acetylcholine, dopamine, serotonin, and norepinephrine.

NEUROTRANSMITTER RECEPTOR. A physical recipient for chemicals called neurotransmitters. Receptors sit on the surface of cells that make up body tissues, and once bound to the neurotransmitter, they initiate the chemical signaling pathway associated with neurotransmitters.

NEUTROPENIA. Deficiency of white blood cells, primarily neutrophils.

NEUTROPHIL. The major immune-system phagocytic or cytotoxic white blood cell.

NEW DAILY PERSISTENT HEADACHE (NDPH). A treatment-resistant chronic headache that begins abruptly and may last for years.

NICOTINE REPLACEMENT THERAPY (NRT). Over-the-counter and prescription products that supply low doses of nicotine as smoking-cessation aids.

NITRATES. Drugs that dilate, or widen, blood vessels. Dilating vessels helps improve blood flow and blood pressure in the arteries.

NITRIC OXIDE (NO). A regulator of various bodily processes, including penile erection.

NOCTURIA. Excessive need to urinate at night.

NODULAR ACNE. Severe acne characterized by large papules (elevated areas of skin without visible fluid) that may be as much as 5–10 mm (0.2–0.4 inches) in size.

NONGONOCOCCAL URETHRITIS. Inflammation of the urethra that is not caused by gonorrhea.

NON-HODGKIN LYMPHOMA. A cancer of the lymph system that causes the accumulation of large numbers of cancerous immune system cells.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS. A class of antiretroviral drugs that work by inhibiting reverse transcriptase.

NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID). A type of medicine (also known as NSAID) that controls pain and inflammation. Many are sold without a prescription, such as ibuprofen and acetaminophen, while others are prescribed by doctors.

NOREPINEPHRINE. Also called noradrenaline, a chemical messenger in the brain that regulates attention and that powers the “fight-or-flight” stress response; precursor of epinephrine.

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NRTI). An antiretroviral drug that interferes with the action of viral reverse transcriptase inside infected cells, preventing the virus from replicating.

NUCLEOTIDE POLYMERASE INHIBITOR. A drug, such as sofosbuvir, that is similar (an analog) to a component of RNA or DNA and inhibits the polymerase enzyme that synthesizes the genetic material.

NYSTAGMUS. A condition of the eyes that is characterized by involuntary eye movement and results in reduced or limited vision.

O

OBSESSIVE-COMPULSIVE DISORDER (OCD). A disorder in which affected individuals have an obsession (such as a fear of contamination, or thoughts they do not like to have and cannot control) and feel compelled to perform certain acts to neutralize the obsession (such as repeated hand washing).

OBSTRUCTIVE CORONARY ARTERY DISEASE. Plaque-induced narrowing of arteries to the heart.

OBSTRUCTIVE SLEEP APNEA (OSA). A potentially life-threatening condition characterized by episodes of breathing cessation during sleep alternating with snoring or disordered breathing. The low levels of oxygen in the

blood of patients with OSA may eventually cause heart problems or stroke.

OCTAPEPTIDE. A peptide chain of eight amino acids, such as octreotide.

OFF-LABEL USE. The use of a prescription medication to treat conditions outside the indications approved by the U.S. Food and Drug Administration (FDA). It is legal for physicians to administer drugs for off-label uses, but it is not legal for pharmaceutical companies to advertise drugs for off-label uses.

ONCOLOGIST. A physician who specializes in the diagnosis and treatment of patients with cancer.

ONYCHOMYCOSIS. Tinea unguium; a fungal disease of the fingernails or toenails.

OPEN-ANGLE GLAUCOMA. A progressive form of glaucoma in which the drainage channel for the aqueous humor remains open; serious reduction in vision occurs in advanced stages.

OPIATE. A drug containing or derived from opium—such as codeine, morphine, and heroin—that alleviates pain and induces sleep.

OPIOID. A substance that resembles opium and binds to the same types of receptors in the body, producing similar effects in pain relief, pleasure, and addictiveness. These substances do not actually contain opium, but are synthetically produced to mimic its therapeutic benefits.

OPPORTUNISTIC INFECTION. An infection that is normally mild in a healthy individual, but that takes advantage of an ill person's weakened immune system to move into the body, grow, spread, and cause serious illness.

ORAL LICHEN PLANUS. A disorder of the mucous membranes lining the mouth characterized by erosive ulcers, plaque-like white patches, or a web-like pattern of white lines.

ORGANIC BRAIN SYNDROME. A class of disorders characterized by progressive deterioration of mental processes caused by temporary brain dysfunction or permanent brain damage. Symptoms include delusions, dementia, amnesia, and delirium that are not caused by drugs, alcohol, or as a side effect of medication.

ORPHAN DRUG. A medication that has been developed to treat a rare disease, defined in the United States as a disease or disorder affecting fewer than 200,000 people.

ORTHOSTATIC HYPOTENSION. A drop in blood pressure when moving from a lying to a standing position. May cause dizziness or fainting upon standing.

OSSIFICATION. The creation of new bone.

OSTEOARTHRITIS (OA). The most common form of arthritis, characterized by erosion of the cartilage layer that lies between the bones in weight-bearing joints. It occurs mainly in older people. OA is also known as degenerative joint disease (DJD).

OSTEOCLAST. Large cells associated with bone resorption, or removal, and normally helping to allow new bone to form.

OSTEOPOROSIS. A chronic and progressive disease that leads to bone weakening and brittleness.

OTITIS EXTERNA. Inflammation of the outer ear, between the ear drum and the external opening.

OTITIS MEDIA. Inflammation of the eardrum.

OVARIAN FOLLICLE. Several layers of cells that surround a maturing egg in the ovary.

OVARY. A reproductive organ in females that produces eggs and hormones.

OVERACTIVE BLADDER. A problem with many causes, such as age, pregnancy, and obesity, that results in frequent and urgent trips to the restroom to urinate and sometimes in leakage of urine.

OVULATION. The phase of the female monthly cycle when a developed egg is released from the ovary into the fallopian tube for possible fertilization.

P

PAGET'S DISEASE OF THE BONE. A rare, chronic bone condition that causes some bones in the affected person to soften.

PALLIATIVE CARE. Care given to relieve pain and other symptoms of a disease, but not to cure the disease.

PALPITATIONS. Having an unpleasant awareness of your own heartbeat. The heartbeat may be completely normal or may be abnormal.

PANCREAS. A small organ in the upper abdomen that produces insulin and enzymes that aid in food digestion.

PANCREATITIS. Inflammation of the pancreas, either acute (sudden and episodic) or chronic, usually caused by excessive alcohol intake or gallbladder disease.

PANIC DISORDER. An anxiety disorder in which an individual experiences sudden, debilitating attacks of intense fear.

PAPILLEDEMA. Swelling of the optic disk due to increased intracranial pressure.

PARACOCCIDIOIDOMYCOSIS. South American blastomycosis caused by the fungus *Paracoccidioides brasiliensis*.

PARANOIA. Condition in which an individual has an irrational suspicion about another person or situation.

PARASITE. A type of organism that survives within another living host and nourishes itself by using that host's energy stores without providing the host with any benefit.

PARASYMPATHETIC. The portion of the nervous system that is concerned with normal maintenance functions including digestion and normal heart rate.

PARATHYROID HORMONE. A hormone that controls the concentration of calcium, vitamin D, and phosphorus in the blood.

PARENTERAL. Administered inside the body but outside the digestive tract.

PARKINSONIAN. Related to symptoms associated with Parkinson's disease, a nervous system disorder characterized by abnormal muscle movement of the tongue, face, and neck; inability to walk or move quickly; walking in a shuffling manner; restlessness; and/or tremors.

PARKINSONISM. A progressive nervous system disorder that affects normal movement.

PARKINSON'S DISEASE. A disease of the nervous system most common in people over age 60, characterized by a shuffling gait, muscle stiffness, and tremors.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA. A regular, fast (160 to 220 beats per minute) heart rate that begins and ends suddenly and originates in heart tissue other than that in the ventricles. This condition is most common among young people and may occur as a result of vigorous exercise.

PARTIAL AGONIST. A substance that partially activates a receptor in the brain while blocking the neurotransmitter for that receptor from binding to it.

PARTIAL SEIZURE. A seizure that affects only one hemisphere of the brain.

PASTILLE. Lozenge; troche; a solid, usually sweetened, medication designed to dissolve in the mouth.

PATHOGEN. A disease-causing organism.

PEGINTERFERON ALFA. Pegylated interferon; an antiviral drug used in combination with sofosbuvir for treating hepatitis C.

PEGYLATED. Attachment of polyethylene glycol to a drug.

PELVIC INFLAMMATORY DISEASE (PID). Inflammation of the female reproductive tract, caused by any of several microorganisms. Symptoms include severe abdominal pain, high fever, and vaginal discharge. Severe cases can result in sterility.

PEMPHIGUS. A blistering autoimmune disease that affects the skin and mucous membranes.

PENCICLOVIR. The active antiviral agent that is formed from famciclovir in the body.

PENICILLIN. An antibiotic that is used to treat bacterial infections.

PERICARDITIS. Inflammation of the sac around the heart.

PERIMENOPAUSE. The early years preceding menopause when the natural transition to infertility is just beginning and estrogen levels are reducing gradually.

PERIPHERAL ARTERIAL DISEASE (PAD). A disease characterized by plaque buildup in the arteries.

PERIPHERAL EDEMA. Swelling of the tissues due to fluid accumulation; occurs most often in the legs.

PERIPHERAL NEUROPATHY. Damage to the peripheral nerves (in the extremities of the body) causing numbness, tingling, or pain.

PERIPHERAL VASCULAR DISEASE. Narrowing or occlusion of arteries usually due to atherosclerosis.

PERITONEUM. The smooth membrane that lines the abdominal cavity.

PERTUSSIS. Whooping cough.

PHENYLKETONURIA (PKU). An inherited disorder in which the body lacks an enzyme needed to digest the amino acid phenylalanine. Untreated PKU results in intellectual disabilities and seizures; treatment requires lifelong adherence to a diet low in phenylalanine.

PHEOCHROMOCYTOMA. A tumor of specialized cells of the adrenal gland.

PHOSPHODIESTERASE. An enzyme that breaks down the chemical known as chemical cyclic adenosine monophosphate (cAMP).

PHOSPHODIESTERASE-5 (PDE5). An enzyme that interferes with penile erections by breaking down cyclic guanosine monophosphate (cGMP).

PHOTOSENSITIVITY. An abnormally high sensitivity to sunlight involving immune system activity and manifesting as a skin (cutaneous) reaction that is sometimes described as a sun allergy. Photosensitivity increases the risk of serious sunburn. Certain disease conditions (e.g., systemic lupus erythematosus) and taking certain drugs may cause photosensitivity.

PINEAL GLAND. A small endocrine gland in the brain that produces melatonin.

PITUITARY GLAND. A gland located at the base of the brain and controlled by the hypothalamus. It controls most endocrine functions and is responsible for things such as kidney function, lactation, and growth and development.

PLACEBO. A pill or liquid given during the study of a drug or dietary supplement that contains no medication or active ingredient. Usually study participants do not know if they are receiving a pill containing the drug or an identical-appearing placebo.

PLAGUE. A highly infectious disease that can be fatal if not treated promptly. The bacteria that cause plague mainly infect rats, mice, squirrels, and other wild rodents. The disease is passed to people through fleas. Infected people can then spread the disease to other people.

PLAQUE. A compound made up of fat, cholesterol, calcium, and other substances found in the blood. It can stick to the walls of arteries, partially or totally blocking blood flow.

PLAQUE PSORIASIS. An autoimmune disorder that causes patches of inflamed skin.

PLATELETS. Tiny blood cells that are components of the blood coagulation process in the body. Platelets are formed in the bone marrow and then circulate in the bloodstream.

POLYCYSTIC OVARY SYNDROME (PCOS). An endocrine disorder in women characterized by ovarian cysts, infertility, amenorrhea (absence of menstrual periods), acne, and a male pattern of body hair. It is also known as Stein-Leventhal syndrome.

POLYENES. Organic compounds with many double bonds, especially within a long hydrocarbon chain.

POLYETHYLENE GLYCOL (PEG). A polymer attached to filgrastim to produce pegfilgrastim, which lasts much longer in the body.

POLYP. A lump of tissue protruding from the lining of an organ, such as the nose, bladder, or intestine. Polyps can sometimes block the passages in which they are found.

POSITIVE SYMPTOMS. Symptoms that are characterized by the production or presence of abnormal or excessive behaviors, including hallucinations and thought-process disorder.

POSTHERPETIC. Occurring after and especially as a result of herpes, which is the virus that causes shingles.

POSTHERPETIC NEURALGIA. Nerve pain caused by the varicella zoster virus (shingles).

POSTMENARCHAL. After menstrual function begins.

POSTMENOPAUSAL. The time after which a woman has reached menopause or has not had a menstrual period for 12 consecutive months.

POST-TRAUMATIC STRESS SYNDROME (PTSD). Psychiatric disorder in which the patient experiences persistent disturbing anxiety based symptoms after experiencing a traumatic event.

PREDNISOLONE. A corticosteroid that is the active metabolite of prednisone. Prednisone is converted to prednisolone in the liver.

PREFRONTAL CORTEX. Area of the brain involved in attention span, judgment, response to external stimuli, memory, motor function, and impulse control.

PREGNANCY CATEGORY. A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk but no human studies exist, or adverse effects have been seen in animals but not in well-controlled human studies. Category C: No adequate human or animal studies exist, or adverse fetal effects have occurred in animal studies but there is no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk, and risks outweigh any benefits.

PREMENSTRUAL SYNDROME (PMS). A combination of emotional, physical, psychological, and mood disturbances that occur after ovulation and normally end with the onset of the menstrual flow.

PRIAPISM. Condition in which the penis remains erect for four or more hours. Usually painful, requires immediate medical treatment to minimize potential for scarring and permanent erectile dysfunction.

PRIMARY BILIARY CIRRHOSIS (PBC). A chronic liver disease characterized by inflammation of the small bile ducts in the liver.

PRODRUG. The inactive form of a drug that is metabolized into an active compound inside the body.

PROGESTERONE. A female hormone that prepares the uterus for pregnancy.

PROGESTINS. Natural hormones, such as progesterone, and synthetic hormones, such as norelgestromin, that prepare the lining of the uterus for implantation with a fertilized egg and maintain pregnancy.

PROLACTIN. Hormone responsible for endocrine function, including lactation.

PROPHYLACTIC. Protective measures to prevent disease.

PROPHYLAXIS. Prevention.

PROSTAGLANDIN. A hormone-like chemical produced in the body. Prostaglandins have a wide variety of effects and may be responsible for the production of some types of pain and inflammation.

PROSTATE. The walnut-shaped gland that surrounds the urethra at the neck of the bladder in males and supplies fluid for semen.

PROSTATE-SPECIFIC ANTIGEN (PSA). A protein made by the cells of the prostate that is increased by both BPH and prostate cancer.

PROSTHETIC JOINT. An artificial joint, implanted to take the place of a damaged or destroyed joint.

PROTHROMBIN. A type of protein (called a glycoprotein) that is involved in the blood-clotting process.

PROTHROMBIN TIME. A test that determines how quickly a person's blood will clot.

PROTON. A hydrogen atom that has been stripped of its electron. Solutions that contain an excess of protons (H^+) are acids.

PROTON PUMP INHIBITOR (PPI). A type of medicine that reduces how much acid is made by glands that are located in the stomach's lining. When less acid is made, less makes its way back into the esophagus, and the symptoms of gastroesophageal reflux disease are eased.

PROTOZOA. A type of single-celled organism. Some protozoa can cause disease. Protozoa are members of the larger group called prokaryotes.

PRURITIS. Itchy skin.

PSEUDOTUMOR CEREBRI. A condition characterized by increased pressure around the brain in the absence of a tumor or other identifiable disorder. It is also called idiopathic intracranial hypertension.

PSORIASIS. A chronic inflammatory condition that includes the presence of raised, red patches on the skin that are layered over with a whitish, flaky buildup of dead skin cells.

PSORIATIC ARTHRITIS (PSA). Joint inflammation that develops in some psoriasis patients.

PSYCHOSIS. Loss of contact with reality that may involve false beliefs or hallucinations.

PULMONARY ARTERIAL HYPERTENSION (PAH). High blood pressure in the pulmonary arteries that carry blood from the heart to the lungs.

PULMONARY EMBOLISM. An obstruction of a blood vessel in the lungs, usually caused by a blood clot that blocks a coronary artery. Pulmonary embolism can be very serious and, in some cases, fatal.

PYELONEPHRITIS. A urinary tract infection that progresses up the urinary system to the kidneys and ureters.

Q

QT INTERVAL. A segment of the EKG that represents the electrical conduction that occurs during the beating and relaxing of the ventricles (pumping chambers of the heart).

QT PROLONGATION. A heart arrhythmia that can be caused by ketoconazole.

QUINOLONE. A group of synthetic antibacterial agents. Fluoroquinolones have a fluorine atom attached to the central ring system.

R

RABIES. A rare but serious disease caused by a virus carried in saliva. It is transmitted when an infected animal bites a person.

RADIATION THERAPY. The use of high-energy radiation from x-rays, cobalt, radium, and other sources to kill cancer cells and shrink tumors.

RAYNAUD'S DISEASE. A disease found mainly in young women that causes decreased circulation to the hands and feet. Its cause is unknown.

REBOUND. A physical reaction to stopping a medication characterized by the reappearance of the symptom(s) that the medication was given to suppress. For example, people who stop taking temazepam may experience rebound excitability and sleeping problems.

RECEPTOR. A molecule, usually a protein, inside or on the surface of a cell, that binds to specific substances, such as hormones, to affect physiological processes.

RECTAL. Referring to the rectum, the lowest part of the intestine, from the colon to the anus.

RELAPSE. A recurrence of symptoms after a period of improvement or recovery.

RENAL. Referring to the kidneys.

RENIN. An enzyme produced in the kidneys that controls the activation of the hormone angiotensin, which stimulates the adrenal glands to produce aldosterone.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS). A signaling pathway that regulates blood pressure.

RESISTANCE. The ability of infectious agents such as viruses to change their biochemistry in such a way that renders drug treatments no longer effective.

RESPIRATORY. Breathing.

RESPIRATORY DEPRESSION. Very low breathing rate, characterized as 12 or fewer breaths per minute; also known as hypoventilation.

RESPIRATORY TRACT. The parts of the body devoted to breathing. The respiratory tract runs from the nose to the lungs and includes the larynx, trachea, bronchi, and bronchioles, as well as the different parts of the lungs.

RETINA. The tissue that forms the inner surface of the back of the eyeballs; it receives the light that enters the eye and transmits it through the optic nerves to the brain to produce visual images.

RETROVIRUS. A single-stranded RNA virus, such as HIV, that transcribes its RNA into DNA and inserts the DNA into the genetic material of infected cells.

REVERSE TRANSCRIPTASE. An enzyme that is essential to the reproduction of HIV cells.

REYE SYNDROME. A life-threatening disease that affects the liver and the brain and sometimes occurs after a viral infection, such as flu or chickenpox. Children or teenagers who are given aspirin for flu or chickenpox are at increased risk of developing Reye syndrome.

RHABDOMYOLYSIS. A condition in which damaged skeletal muscle undergoes rapid breakdown. It is a rare but potentially serious effect of taking statin drugs.

RHEUMATOID ARTHRITIS (RA). A chronic disease of the immune system that causes the body to attack the joints by mistake. The joints swell, or become inflamed, and joints and organs become damaged.

RHINITIS. An inflammation of the mucous membranes that line the nasal passages.

RIBAVIRIN. An antiviral drug used in combination with sofosbuvir for treating hepatitis C.

RINGWORM. Any of several contagious fungal diseases of the skin, hair, or nails characterized by ring-shaped patches.

RITONAVIR. An antiviral drug that inhibits cytochrome P450 and can prevent certain drugs from being properly metabolized.

RNA. A molecule found in all living cells that plays a role in transmitting information from the DNA to the protein-forming system of the cell.

ROSACEA. A chronic skin disease characterized by persistent redness of the skin and periodic outbreaks of pustules, usually affecting the middle third of the face.

ROUNDWORM. A type of worm with a long body that lives in the intestines of mammals.

RUBELLA. A contagious viral disease that is milder than typical measles but is damaging to the fetus when it occurs early in pregnancy. Also called German measles.

S

SALICYLATES. A group of drugs that includes aspirin and related compounds. Salicylates are used to relieve pain, reduce inflammation, and lower fever.

SARCOIDOSIS. A disorder characterized by small groups of inflammatory cells (granulomas) that form as nodules in the lungs or other organs.

SATIETY. A feeling of fullness or satisfaction after consuming a meal, which may reduce the amount of food consumed.

SCHIZOAFFECTIVE DISORDER. Having symptoms of both schizophrenia and bipolar disorder.

SCHIZOPHRENIA. A severe mental illness in which a person has difficulty distinguishing what is real from what is not real. It is often characterized by hallucinations, delusions, language and communication disturbances, and withdrawal from people and social activities.

SCLERODERMA. A chronic, systemic autoimmune disorder in which the patient's skin thickens and hardens.

The diffuse form of scleroderma also affects the internal organs, most often the kidneys, esophagus, and lungs.

SCLEROSING CHOLANGITIS. Inflammation, swelling, scarring, and destruction of bile ducts inside and outside the liver.

SEBACEOUS GLANDS. Tiny structures in the skin that produce oil (sebum). If they become plugged, sebum collects inside and forms a nurturing place for bacteria to grow.

SEBORRHEIC DERMATITIS. An inflammatory skin disorder that produces itchy, red, scaly skin on the scalp, face, and torso. It is called cradle cap when it occurs in infants.

SECONDARY INFECTION. An infection by a microbe that occurs because the body is weakened by a primary infection caused by a different kind of microbe; also called an opportunistic infection.

SECRETAGOGUE. Any substance that causes another substance to be secreted. Glimepiride is an insulin secretagogue.

SEDATION. A state of emotional or physical relaxation. The term is usually used to refer to this condition when it is produced by a medication.

SEDATIVE. A drug that calms or tranquilizes nervousness or excitement.

SEIZURE. A sudden attack, spasm, or convulsion.

SELECTIVE ESTROGEN RECEPTOR MODULATOR (SERM). A drug that has estrogenic effects in some body tissues and antiestrogenic effects in other tissues.

SELECTIVE SEROTONIN RECEPTOR AGONISTS (SSRAS). Drugs that bind to specific serotonin receptors, mimicking the effects of serotonin binding.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS). A class of antidepressants that works by blocking the reabsorption of serotonin in brain cells, raising the level of the chemical in the brain.

SEMISYNTHETIC. A drug that is derived from a natural substance but is chemically modified to alter certain properties, such as to make the drug more effective or safer.

SEROTONERGIC. Containing, activating, or otherwise involving serotonin, a chemical that occurs throughout the body with numerous effects, including neurotransmission in the brain.

SEROTONIN. 5-Hydroxytryptamine; a substance that occurs throughout the body with numerous effects, including neurotransmission. Low serotonin levels are associated with mood disorders, particularly depression and obsessive-compulsive disorder.

SEROTONIN SYNDROME. A potentially life-threatening drug reaction involving an excess of the neurotransmitter serotonin, usually occurring when too many medications that increase serotonin are taken together, such as antimigraine triptans and certain antidepressants.

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS). A class of antidepressants that increase the levels of the neurotransmitters serotonin and norepinephrine by preventing their reuptake.

SEXUALLY TRANSMITTED DISEASE (STD). A disease that is passed from one person to another through sexual intercourse or other intimate sexual contact; also referred to as a sexually transmitted infection (STI). STDs include gonorrhea, chlamydia, and syphilis.

SHIFT WORK DISORDER. A sleep disorder caused by rotating work shift patterns or working nontraditional hours.

SHINGLES. Herpes zoster; a blistering rash and nerve pain that primarily affects older adults and is caused by reactivation of the varicella zoster virus that causes chickenpox.

SICK SINUS SYNDROME. A general term for a group of cardiac arrhythmias caused by a malfunction of the sinus node, which is the heart's pacemaker.

SJÖGREN'S SYNDROME. A chronic autoimmune disease with common symptoms of dry eyes and dry mouth.

SKELETAL MUSCLE. The muscle that a person controls to power the movement of the skeleton: lifting arms, walking, typing, nodding the head, etc.

SMALLPOX. A highly contagious viral disease characterized by fever, weakness, and skin eruption with pustules that form scabs that slough off, leaving scars.

SOCIAL PHOBIA. An anxiety disorder characterized by a strong and persistent fear of social or performance situations.

SOMATOSTATIN. A 14-amino-acid peptide hormone that inhibits the release of other hormones, such as growth hormone, insulin, and gastrin.

SOMATOSTATIN RECEPTOR SCINTIGRAPHY (SRS). A diagnostic technique using radioactive octreotide for locating certain carcinoid tumors.

SPASMS. Sudden involuntary muscle movement or contraction.

SPASTICITY. Hypertonic (overly toned) muscles with increased tendon reflexes.

SPOROTRICHOSIS. Skin infection with a fungus in the genus *Sporothrix* or *Sporotrichum*.

SPRAIN. An injury to the ligaments around a joint. Ligaments are strong, flexible fibers that hold bones together. When a ligament is stretched too far or tears, the joint will become painful and swell.

STATINS. A group of medications, given to lower blood cholesterol levels, that work by inhibiting an enzyme involved in cholesterol formation. Statins are also known as HMG-CoA reductase inhibitors.

STAXYN. The brand name for vardenafil rapidly dissolving oral tablets.

STEATOSIS. Fatty accumulations in the liver.

STEM CELLS. Immature cells that can give rise to differentiated cells, such as different types of blood cells in the bone marrow.

STENT. A metal or plastic tube or mesh placed in a blood vessel to hold it open.

STEVENS-JOHNSON SYNDROME. A rare, but severe disorder that affects the skin and mucous membranes (thin layers that line organs such as the nose). It usually occurs as a reaction to a drug or infection and starts with flulike symptoms, followed by purplish bumps that spread and blister. It is a medical emergency requiring hospitalization.

STIMULANT. A type of psychoactive substance that increases alertness or wakefulness. Stimulants may be prescribed to treat disorders such as autism or attention deficit hyperactivity disorder but are also illegally abused.

STRAIN. An injury to a muscle in which over stretching makes the muscle fibers tear.

STREPTOCOCCAL INFECTIONS. Also called strep infections; a group of diseases caused by *Streptococci* bacteria, including strep throat, scarlet fever, impetigo, toxic shock syndrome, cellulitis, meningitis, and blood infections.

STROKE. Irreversible damage to the brain caused by insufficient blood flow to the brain as the result of a blocked artery. Damage can include loss of speech or vision, paralysis, cognitive impairment, and death.

SUBCUTANEOUS. Into the skin.

SUBGINGIVAL. Beneath the gum line.

SUBLINGUAL. Under the tongue.

SULFONAMIDES. A common class of medications that includes hydrochlorothiazide and sulfa drugs.

SULFONYLUREAS. Antidiabetic drugs that help manage type 2 diabetes mellitus by increasing the release of insulin from beta cells in the pancreas.

SUMATRIPTANS. Various formulations of first-generation triptans.

SUPERFICIAL BASAL CELL CARCINOMA (SBCC). A subtype of basal cell carcinoma that originates in basal cells of the skin.

SUPERINFECTION. Infection by a second virus after a previous infection with a different virus has become well established.

SUPPOSITORY. A small cylinder or cone that melts when it comes in contact with normal body temperature, designed to be inserted into a body cavity such as the rectum to deliver medication.

SUPPRESS. Prevent recurrence.

SUPPRESSIVE THERAPY. Low-dose antiviral therapy to prevent outbreaks and transmission of genital herpes.

SUPRACHIASMATIC NUCLEUS (SCN). A pair of nerve clusters in the hypothalamus of the brain that receives light input from the retina via the optic nerve and regulates circadian rhythms.

SUSTAINED RELEASE (SR). A dosage form that releases a drug slowly over an extended period of time.

SYMPATHETIC NERVOUS SYSTEM. Part of the nervous system that increases heart rate and blood pressure, sweating, pupil dilation, and mental stress arousal.

SYNCOPE. Also called fainting, a loss of consciousness over a short period of time due to temporary insufficient blood flow to the brain.

SYSTEMIC. Having effects throughout the body.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE). A chronic, inflammatory, autoimmune disorder in which the individual's immune system attacks, injures, and destroys the body's own organs and tissues. It may affect many organ systems, including the skin, joints, lungs, heart, and kidneys.

SYSTOLIC BLOOD PRESSURE. Pressure when the heart contracts.

T

T CELLS. White blood cells that originate in the thymus gland. T cells regulate the immune system's response to infections.

TACHYCARDIA. An abnormally rapid heart rate.

TAMIFLU. The brand name of oseltamivir phosphate.

TAPEWORM. A type of flatworm that has many segments and lives within the intestines of its hosts, which can include humans and other animals that have backbones (vertebrates).

TARDIVE DYSKINESIA. A neurological condition characterized by involuntary, uncontrollable movements, especially of the mouth, tongue, trunk, and limbs; occurs especially as a side effect of prolonged use of certain medications.

TENDINITIS. An inflammation or irritation of a tendon, a thick cord that attaches bone to muscle.

TENSION HEADACHE. A type of headache that has sometimes been theorized to be caused by contraction of muscles in the head. The sensation of a tension headache is often described as the feeling of a painfully tight band squeezing the head.

TERATOGEN. Any drug or other agent capable of interfering with the development of a fetus, causing birth defects or loss of the pregnancy. Isotretinoin is a known teratogen.

TERATOGENIC. Causing developmental malformations in a fetus.

TESTOSTERONE. A steroid hormone, one of the androgens. Testosterone is produced primarily in the testes but also in the adrenal gland and ovaries.

TETANUS. Also known as lockjaw, tetanus is a sometimes-fatal infection with the bacterium *Clostridium tetani*. Primary symptoms are muscle spasms, which can be severe.

THIAZIDE DIURETIC. A type of diuretic (“water pill”) that removes water and salt from the body to treat high blood pressure.

THIAZOLIDINEDIONES (TZDS). A class of oral diabetes drugs.

THROMBIN. An enzyme in blood plasma that helps to convert fibrinogen to fibrin during the last stage of the clotting process.

THROMBOCYTOPENIA. A severely reduced platelet count, which may result in coagulation problems and bleeding.

THROMBOEMBOLI. Blood clots that develop in the circulation and lodge in capillary beds of tissues and organs.

THROMBOEMBOLIC DISEASE. A condition in which a blood vessel is obstructed by an embolus carried in the bloodstream from the site of formation.

THROMBOEMBOLIC EVENT. Formation in a blood vessel of a clot (thrombus) that breaks loose (embolus), is carried by the blood stream, and blocks another vessel, such as in a stroke.

THROMBOEMBOLISM. A blood clot that blocks a blood vessel in the cardiovascular system.

THROMBOSIS. Formation of a clot in the blood that either blocks or partially blocks a blood vessel. The thrombus may lead to infarction, or death of tissue, due to the blocked blood supply.

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP). A rare disorder in which clots form in small blood vessels throughout the body, which can occur with prasugrel.

THROMBOXANE. A platelet enzyme that helps platelets bind to one another and form a blood clot.

THROMBUS. A blood clot that may form in a blood vessel or in one of the cavities of the heart.

THRUSH. Infection with the fungus *Candida albicans* that causes white patches in the oral cavity.

TICS. Involuntary movements (such as twitching or facial grimacing) or vocalizations (such as throat clearing or barking) associated with Tourette syndrome.

TINEA BARBAE. Ringworm of the face and neck, also known as “barber’s itch.”

TINEA CAPITIS. A contagious fungal infection (ringworm) of the scalp.

TINEA CORPORIS. Fungal infection of the body affecting any skin region other than the scalp, groin, palms, and soles; commonly referred to as ringworm.

TINEA CRURIS. A fungal infection of the groin and perineum; also referred to as “jock itch.”

TINEA FACIEI. A superficial fungal infection of the skin of the face.

TINEA PEDIS. Fungal infection of the foot; commonly referred to as athlete’s foot.

TINEA UNGUIUM. Onychomycosis: the most common fungal nail infection.

TINEA VERSICOLOR. A chronic skin infection caused by the fungus *Pityrosporum orbiculare*.

TOLERANCE. A decrease in tolerance to a drug, requiring an individual to take more and more of the drug to achieve the same effect.

TOLL-LIKE RECEPTOR 7 (TLR7). A protein receptor with important roles in immune responses that binds imiquimod.

TONIC-CLONIC SEIZURE. This is the most common type of seizure among all age groups and is categorized into several phases beginning with vague symptoms hours or days before an attack. These seizures are sometimes called grand mal seizures.

TOPICAL. Referring to any drug applied to the skin, hair, nails, or other exterior surfaces of the body.

TORSADES DE POINTES. French term meaning “twisting of the spikes,” a type of ventricular tachycardia with definitive characteristic peaks seen on electrocardiogram. Considered an unstable heart arrhythmia often leading to ventricular fibrillation. Associated with prolonged QT interval.

TOURETTE SYNDROME. An abnormal condition that causes uncontrollable facial grimaces and tics as well as arm and shoulder movements. Tourette syndrome is perhaps best known for uncontrollable vocal tics that include grunts, shouts, and use of obscene language (coprolalia).

TRABECULAR MESHWORK. A sponge-like tissue located near the cornea and iris that functions to drain the aqueous humor from the eye into the blood.

TRACHEA. Commonly called the windpipe, it is the air pathway that connects the nose and mouth to the lungs.

TRANSIENT ISCHEMIC ATTACK (TIA). Occlusion (blockage) of a smaller blood vessel in the brain that can produce stroke-like symptoms for a few minutes to 24 hours, but does not usually cause permanent damage.

TRANSPLANT. The removal of tissue from one part of the body for implantation to another part of the body, or the removal of tissue or an organ from one individual and its implantation in another individual by surgery.

TREMOR. Involuntary shaking.

TRICHINOSIS. A parasitic disease caused by eating raw or undercooked pork infested with a roundworm called *Trichinella spiralis*.

TRICYCLIC ANTIDEPRESSANTS. An older group of antidepressant drugs.

TRIGEMINAL NEURALGIA. A disorder of the trigeminal nerve that causes severe facial pain.

TRIGLYCERIDES. Substances formed in the body from fat in the diet. Triglycerides are the main fatty materials in the blood. Together with protein, they make up high- and low-density lipoproteins (HDLs and LDLs).

TRIPTANS. A class of drugs that bind to serotonin receptors and mimic the action of serotonin; believed to treat migraine headaches by constricting cranial blood vessels, inhibiting inflammatory neuropeptides, and blocking the transmission of pain signals.

TUBERCULOSIS (TB). A severe, contagious bacterial infection of the lungs. Untreated, tuberculosis can also affect other organs of the body.

TUMOR. An abnormal mass of tissue that serves no purpose. Tumors may be either benign (non-cancerous) or malignant (cancerous).

TUMOR LYSIS SYNDROME. A potentially life-threatening condition caused by cancer chemotherapy associated with very high blood levels of uric acid, phosphate, and potassium; low calcium; and acute kidney failure.

TUMOR NECROSIS FACTOR (TNF)-ALPHA. A protein called a cytokine that mediates inflammation throughout the body and activates immune system cells.

TYMPANOSTOMY. A method of treating recurrent ear infections. In this procedure, a tiny tube is inserted through the eardrum to balance the outside pressure with the pressure in the middle ear.

TYPE 1 DIABETES. A chronic immune system disorder in which the pancreas does not produce sufficient amounts of insulin, a hormone that enables cells to use glucose for energy. Formerly called juvenile diabetes, it must be treated with insulin injections.

TYPE 2 DIABETES. A form of diabetes that typically develops later in life. The disease prevents the body from properly using glucose (sugar), but it can often be controlled with diet and exercise.

TYPHOID FEVER. An infectious disease caused by a type of bacterium. People with this disease have a lingering fever and feel depressed and exhausted. Diarrhea and rose-colored spots on the chest and abdomen are other symptoms. The disease is spread through poor sanitation.

TYROSINE. A nonessential amino acid. Amino acids are the building blocks of protein. They are the raw materials used by the body to make protein. Tyrosine is labeled “nonessential” because when it is lacking in the diet, it can be manufactured by the body.

U

ULCER. A sore or break in the skin or lining of an organ.

ULCERATIVE COLITIS (UC). A chronic, episodic, inflammatory autoimmune disease of the large intestine and rectum characterized by bloody diarrhea.

URETHRA. The tube that carries urine from the bladder to outside the body.

URIC ACID. White, poorly soluble crystals found in the urine. Sometimes uric acid forms small solid stones or crystals that are deposited in different organs in the body, such as the kidney. High levels of uric acid can be seen in patients with gout or cancer.

URINARY INCONTINENCE. The loss of bladder control, usually with symptoms that vary from minor leaking to wetting that cannot be controlled.

URINARY RETENTION. Excessive storage of urine in the body.

URSODEOXYCHOLIC ACID. Ursodiol.

URTICARIA. Hives; raised, itchy areas of skin that usually indicate an allergic reaction.

UTERUS. A hollow organ in a female in which a fetus develops until birth.

V

VAGINOSIS. A bacterial infection of the vagina that causes a bad-smelling white discharge.

VARICELLA. Chickenpox; a disease caused by the varicella zoster virus.

VARICELLA ZOSTER VIRUS (VZV). The virus that causes chickenpox and remains dormant in the nerves where its reactivation causes shingles.

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF). A chemical compound in the body that contributes to the growth of new blood vessels.

VASOACTIVE INTESTINAL PEPTIDE (VIP). A 28-amino-acid protein hormone with many physiological activities, including stimulating secretion by the small intestine and pancreas and dilating (relaxing) blood vessels.

VASOACTIVE INTESTINAL PEPTIDE-SECRETING ADENOMAS. Pancreatic tumors that secrete vasoactive intestinal peptide and may be treated with octreotide; also referred to as VIPomas.

VASOCONSTRICTION. Constriction of a blood vessel.

VASOMOTOR RHINITIS. Nasal irritation that is not caused by allergies; symptoms include a stuffy or runny nose.

VEIN THROMBOSIS. A condition characterized by a blood clot in a vein.

VENOUS THROMBOEMBOLISM (VTE). A blood clot in a vein that can break off and block a blood vessel elsewhere in the body.

VENTRICLE. A lower pumping chamber of the heart. There are two ventricles, right and left. The right ventricle pumps oxygen-poor blood to the lungs to be re-oxygenated. The left ventricle pumps oxygen-rich blood to the body.

VENTRICULAR FIBRILLATION. Irregular chaotic heart-beat resulting in no effective cardiac contractions and no cardiac output. A life-threatening medical emergency necessitating immediate defibrillation by medical personnel in a hospital setting or by use of an automated external defibrillator (AED) by non-clinicians outside of a hospital setting.

VENTRICULAR TACHYCARDIA. Irregular chaotic heart-beat where the ventricles are quivering rather than beating and circulating blood in a normal fashion. May lead to ventricular fibrillation. Considered a life-threatening medical emergency necessitating cardiac drugs and defibrillation by trained medical personnel.

VERTIGO. The sensation of moving around in space, or objects moving around a person. It is a disturbance of equilibrium.

VESICLES. Small, fluid-filled sacs that may develop on the skin or internally.

VIRUS. A tiny, disease-causing particle that can reproduce only in living cells.

VISUAL ACUITY. Pertaining to the sharpness or clearness of vision; usually assessed as part of an eye examination.

VITAMIN D DEFICIENCY. Also known as hypovitaminosis D, it is an abnormally low level of vitamin D in the body that can cause bone, cardiovascular, and other problems.

VITILIGO. A condition that causes depigmentation of areas of the skin, most commonly on the extremities. Its cause is unknown but may be related to an autoimmune disorder.

W

WHEAL. A welt, or small swollen and red area on the skin's surface that can itch and burn.

WHOOPING COUGH. An infectious disease, also called pertussis, that is caused by a bacterium and is marked by a convulsive, spasmodic cough, sometimes followed by a shrill intake of breath. This disease is more common in infants and children.

WILSON'S DISEASE. An inherited disorder of abnormal copper metabolism that causes dystonia.

WITHDRAWAL SYMPTOMS. A group of physical or mental symptoms that may occur when a drug is discontinued after prolonged regular use.

Y

YELLOW FEVER. An infectious disease caused by a virus. The disease, which is spread by mosquitoes, is most common in Central and South America and central Africa. Symptoms include high fever, jaundice (yellow eyes and skin), and dark-colored vomit, a sign of internal bleeding. Yellow fever can be fatal.

YUZPE REGIMEN. An older form of emergency contraception consisting of estrogen and levonorgestrel started within 72 hours after intercourse. It was developed in 1974 by A. Albert Yuzpe, a Canadian gynecologist, but is now considered obsolete.

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