

COURSE AND EXAMINATION

Florida Optometry Oral Drug Review

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Introduction and Legal Information

On April 23, 2013, Governor Rick Scott signed the Florida Optometry Oral Drug Bill into law (Chapter 2013-26, Laws of Florida). Importantly, this statutory language provides every “certified optometrist” with the opportunity to add the authority to administer and prescribe oral ocular pharmaceutical agents. Florida is one of the 47 states that allow optometrists to prescribe oral medications under certain conditions. The passage of this legislation signals a professional recognition that an integrated eye care model will benefit patients in Florida.

To become a “certified optometrist”, a Florida-licensed optometrist must meet the conditions set forth in Chapter 64B13-10, F.A.C. Essentially, this includes successful completion of at least 110 hours of Board-approved transcript quality coursework and clinical training in general and ocular pharmacology conducted by an accredited institution which has facilities for both didactic and clinical instruction in pharmacology; completion of at least one year of supervised experience in differential diagnosis of eye diseases or disorders; and successful completion of Part II of the NBEO examination. This basic certification allows an optometrist to administer and prescribe topical ocular pharmaceutical agents. Chapter 463, F.S. (Florida Optometry Practice Act) requires that any optometrist initially licensed in Florida after July 1, 1993 must be a “certified optometrist”. A licensed practitioner who is not certified may use topically applied anesthetics solely for the purpose of glaucoma examinations, but is otherwise prohibited from administering or prescribing topical ocular pharmaceutical agents. Certified optometrists may administer and prescribe only those topical ocular pharmaceutical agents identified by rule of the Board. The Formulary of Topical Ocular Pharmaceutical Agents (Topical Formulary) approved by the Florida Board of Optometry is contained in Rule 64B13-18.002, F.A.C.

With the passage of the Florida Optometry Oral Drug Bill, certified optometrists in Florida also have the option to pursue the authority to prescribe oral ocular pharmaceutical agents in addition to topical ocular pharmaceutical agents. The new law specifies that certified optometrist must complete a 20-hour Florida Optometry Board-approved course and examination on general and ocular pharmaceutical agents before being authorized to administer or prescribe oral agents. The entire 20 hours may be taken on-line. Successful completion of this course and examination may be used by a certified optometrist to satisfy 20 hours of his or her required continuing education only during the 2-year licensure term in which the course and examination are taken. If a certified optometrist does not elect to complete such a course and examination, the certified optometrist is still authorized to administer and prescribe Topical ocular pharmaceutical agents but not Oral ocular pharmaceutical agents.

Topical Ocular Pharmaceutical Agents Formulary Versus Oral Ocular Pharmaceutical Agents Formulary

While the Florida Board of Optometry is responsible for creating and managing the formulary of topical ocular pharmaceutical agents that certified optometrists in Florida may prescribe, the Florida Legislature has created a statutory formulary of oral ocular pharmaceutical agents that certified optometrists in Florida may prescribe.

The following chart depicts the current **Formulary of Oral Ocular Pharmaceutical Agents**.

The Oral Ocular Formulary may only be modified statutorily by the Florida Legislature. The only exception is if any oral ocular pharmaceutical agent listed in the formulary is subsequently

The following ANALGESICS or their generic or therapeutic equivalents:	
<i>Certified optometrists may administer/prescribe the following:</i>	
1. Tramadol hydrochloride	2. Acetaminophen 300 mg with No. 3 codeine phosphate 30 mg
The following ANTIBIOTICS or their generic or therapeutic equivalents:	
<i>Certified optometrists may administer/prescribe the following:</i>	
1. Amoxicillin with or without clavulanic acid	5. Doxycycline/Tetracycline
2. Azithromycin	6. Cephalexin (Keflex®)
3. Erythromycin	7. Minocycline
4. Dicloxacillin	
The following ANTIVIRALS or their generic or therapeutic equivalents:	
<i>Certified optometrists may administer/prescribe the following:</i>	
1. Acyclovir	3. Valacyclovir
2. Famciclovir	
The following ORAL ANTI-GLAUCOMA AGENTS or their generic or therapeutic equivalents, which may not be administered or prescribed for more than 72 hours:	
<i>Certified optometrists may administer/prescribe the following:</i>	
1. Acetazolamide	2. Methazolamide

determined by the United States Food and Drug Administration (FDA) to be unsafe for administration or prescription, that particular agent will automatically be considered deleted from the oral formulary.

Prescribing Controlled Substances

A certified optometrist may not administer or prescribe any Schedule III, Schedule IV, or Schedule V controlled substance listed in Florida Statute 893.03, **EXCEPT FOR** an oral analgesic placed on the Formulary of Oral Ocular Pharmaceutical Agents for the relief of pain due to ocular conditions of the eye and its appendages. Currently, the only controlled substance listed on the Formulary is Acetaminophen 300 mg with No. 3 codeine phosphate 30 mg.

It is important to note that under no circumstance may a certified optometrist prescribe a controlled substance for the treatment of **chronic nonmalignant pain** which is defined by Florida law as “pain unrelated to cancer which persists beyond the usual course of disease or the injury that is the cause of the pain or more than 90 days after surgery.”

Based on this prohibition, the registration provision of §456.44(2), Florida Statutes, will not apply to certified optometrists. This provision requires certain health care providers who prescribe any controlled substance (other than Schedule V) for the treatment of chronic nonmalignant pain to designate him or herself as a controlled substance prescribing practitioner on the physician’s practitioner profile. While Acetaminophen 300 mg with No. 3 codeine phosphate 30 mg is a Schedule III controlled substance, certified optometrists cannot prescribe this or any other medication for the relief of chronic nonmalignant pain, and therefore the registration provisions are not applicable. Likewise, the standards of practice set forth in §456.44(3), setting forth guidelines for the treatment of chronic nonmalignant pain, are not applicable to certified optometrists.

DEA Registration

Certified optometrists who plan to prescribe a controlled substance as listed on the Oral Formulary must apply for a DEA number if they do not already have one. This process may be completed [online at the DEA Website](#). Click on New Applications to apply for a number for the first time or Renewal Applications to renew a DEA number.

Applicants will need to have the following information at hand in order to complete the process online:

- Tax ID number and/or Social Security number
- State License Information
- State Controlled Substance Registration Information, if applicable

- **Credit Card**

The State of Florida does not have a second controlled substance license requirement.

[Click HERE](#) to view the A-Z Index, an information too on the DEA website to make it easier to quickly locate information within the [Diversion Control Program website](#).

Dispensing Practitioners

§465.0276(1)(a), Florida Statutes, provides that a health care practitioner “authorized by law to prescribe drugs may dispense such drugs to her or his patients in the regular course of her or his practice in compliance with this section.” A certified optometrist that wishes to become a dispensing practitioner must:

(a) Register with her or his professional licensing board as a dispensing practitioner and pay a fee not to exceed \$100 at the time of such registration and upon each renewal of her or his license.

(b) Comply with and be subject to all laws and rules applicable to pharmacists and pharmacies, including, but not limited to, chapters 499 and 893, F.S., and all federal laws and regulations.

(c) Before dispensing any drug, give the patient a written prescription and orally or in writing advise the patient that the prescription may be filled in the practitioner’s office or at any pharmacy.

According to §465.0276(5):

A practitioner who confines her or his activities to the dispensing of complimentary packages of medicinal drugs to the practitioner’s own patients in the regular course of her or his practice, without the payment of fee or remuneration of any kind, whether direct or indirect, and who herself or himself dispenses such drugs is not required to register pursuant to this section. The practitioner must dispense such drugs in the manufacturer’s labeled package with the practitioner’s name, patient’s name, and date dispensed, or, if such drugs are not dispensed in the manufacturer’s labeled package, they must be dispensed in a container which bears the following information:

- (a) Practitioner’s name;*
- (b) Patient’s name;*
- (c) Date dispensed;*
- (d) Name and strength of drug; and*
- (e) Directions for use.”*

Certified optometrists need to keep in mind that §465.0276 prohibits any dispensing practitioner from dispensing a controlled substance listed in Schedule II or Schedule III as provided in §893.03, excepted as provided below:

(a) The dispensing of complimentary packages of medicinal drugs which are labeled as a drug sample or complimentary drug as defined in §499.028 to the practitioner’s own patients in the regular course of her or his practice without the payment of a fee or remuneration of any kind, whether direct or indirect.

(b) The dispensing of controlled substances in the health care system of the Department of Corrections.

(c) The dispensing of a controlled substance listed in Schedule II or Schedule III in connection with the performance of a surgical procedure. There are qualifications to this provision, but in that chapter 463 prohibits a certified optometrist performing surgery of any kind, this exception is most likely not applicable.

(d) The dispensing of a controlled substance listed in Schedule II or Schedule III pursuant to an approved clinical trial. For purposes of this subparagraph, the term “approved clinical trial” means a clinical research study or clinical investigation that, in whole or in part, is state or federally funded or is conducted under an investigational new drug application that is reviewed by the US Food and Drug Administration.

(e) The dispensing of methadone in certain facilities (not applicable).

(f) The dispensing of a controlled substance listed in Schedule II or Schedule III to a patient of a facility licensed under part IV of chapter 400.

Florida’s Prescription Drug Monitoring Program (PDMP) - E-FORSCE

The Executive Summary of Florida’s Prescription

Drug Diversion and Abuse Roadmap 2012-2015 indicates that “prescription drug abuse remains Florida’s fastest-growing and deadliest public safety issue” and that “more than seven Floridians die on average each day from prescription drug-related overdoses.” So far in 2022, there have been nearly 2,000 fatal overdoses in Florida. For these reasons, it is important that all licensed health care practitioners familiarize themselves with Florida’s PDMP, E-FORSCE - the Electronic Florida Online Reporting of Controlled Substances Evaluation program. The PDMP was created by the 2009 Florida legislature in an effort to encourage safer prescribing of controlled substances and to reduce drug abuse and diversion within the state of Florida.

E-FORSCE manages a database that collects and stores prescribing and dispensing data for controlled substances in Schedules II, III, IV and V. The purpose of the PDMP is to provide the information that will be collected in the database to health care practitioners to guide their decisions in prescribing and dispensing these prescription drugs which are often highly-abused. §893.055, Florida Statutes, requires health care practitioners to report to the PDMP each time a controlled substance is dispensed to an individual. This information is to be reported through the electronic system as soon

as possible but no later than the close of the next business day after the day the controlled substance is dispensed unless an extension or exemption is approved by the department. §893.02(7), Florida Statutes, defines dispensing as “the transfer of possession of one or more doses of a medicinal drug by a pharmacist or other licensed practitioner to the ultimate consumer thereof or to one who represents that it is his or her intention not to consume or use the same but to transfer the same to the ultimate consumer or user for consumption by the ultimate consumer or user.”

Health care practitioners (including certified optometrists) who prescribe, but do not dispense, controlled substances are NOT required to report to E-FORSCE, but along with their designees are required to consult the system to review a patient’s controlled substance dispensing history before prescribing or dispensing a controlled substance for a patient age 16 or older. The requirement to consult the system does not apply when prescribing or dispensing a nonopioid controlled substance listed in Schedule V of §893.03 or 21 U.S.C. 812 or prescribing or dispensing a controlled substance to a patient who has been admitted to hospice pursuant to §400.6095. All practitioners are encouraged to use the database as a tool to improve patient care.

Medications Sections

Overview of Analgesics

Analgesics are those drugs that mainly provide pain relief. The primary classes of analgesics are the narcotics, including additional agents that are chemically based on the morphine molecule but have minimal abuse potential; nonsteroidal anti-inflammatory drugs (NSAIDs) including the salicylates; and acetaminophen. Other drugs, notably the tricyclic antidepressants and anti-epileptic agents such as gabapentin, have been used to relieve pain, particularly neurologic pain, but are not routinely classified as analgesics. Analgesics provide symptomatic relief, but have no effect on the cause, although clearly the NSAIDs, by virtue of their dual activity, may be beneficial in both regards.

The Oral Ocular Formulary includes the following Analgesics or their generic or therapeutic equivalents:

1. *Tramadol hydrochloride*
2. *Acetaminophen 300 mg with No. 3 codeine phosphate 30 mg*

The following sections will provide relevant clinical information about each of the agents listed above, including mechanism of action, indication, contraindications, adverse reactions, drug interactions, general dosing guides, special instructions, and most importantly, dosages and examples of use specifically for optometrists for the treatment of ocular conditions. This particular information for optometrists is included at the end of each drug section.

Tramadol

Drug Description

Tramadol is a centrally-acting analgesic with a unique, dual mechanism of action. It is a mu-opioid receptor agonist and a weak inhibitor of norepinephrine and serotonin reuptake. Tramadol exists as a racemic mixture of the trans isomer. Important differences in binding, activity, and metabolism are associated with the two enantiomers. Tramadol is a synthetic analog of codeine; however, tramadol has a lower affinity for opioid receptors than codeine. Tramadol has less potential for abuse or respiratory depression than other opiate agonists, but both may occur. Drug abuse and overdose, seizures, serotonin syndrome, suicides, and anaphylactoid reactions have been associated with tramadol use/misuse. Due to CYP2D6 and CYP3A4 dependent tramadol metabolism, potentially serious drug interactions are possible. Comparative studies with other analgesics for the treatment of postoperative pain indicate that tramadol is equivalent in analgesic relief to codeine but is less potent than acetaminophen; codeine and acetaminophen; hydrocodone combinations for the treatment of dental and acute musculoskeletal pain. Tramadol has been shown to be effective as an adjuvant to NSAID therapy in patients with osteoarthritis who experience breakthrough pain. The World Health Organization guidelines for cancer pain management classify tramadol as a step II agent. For patients with severe cancer pain, morphine is superior and most patients treated with tramadol require a change to a more potent opioid after a few weeks of

treatment. The lack of significant cardiac effects and no association with peptic ulcer disease make tramadol an alternative in some patients who may not tolerate NSAIDs. Tramadol has been effective in the control of post-operative pain when given intravenously but may not be suitable as an adjunct to anesthesia because of low sedative properties and a high incidence of postoperative respiratory depression. Tramadol has been widely used in Europe since the late 1970s where it is available as intravenous, rectal, and oral formulations. There are no plans to market intravenous tramadol in the United States. The FDA approved oral, immediate-release tramadol (Ultram) in March 1995; an orally disintegrating tablet (Rybix) in May 2005; a once-daily, oral, extended-release tablet (Ultram ER) in September 2005; a second once-daily, oral, extended-release tablet with a different release formulation (Ryzolt) in December 2008; and a once-daily, extended-release capsule (ConZip) in May 2010; the ConZip product provides an immediate release component of tramadol, along with an extended-release component.

Classifications:	
Analgesics Analgesic/Miscellaneous	
Brand Names:	
ConZip® Ralivia® ER Ralivia® Flash Rybix®	Ryzolt® Ultram® Dose Ultram® ER

Mechanism of Action

Tramadol has a unique dual mechanism of pain relief. It has central opiate receptor agonist activity and, thus, exerts an analgesic effect from binding of the parent drug and the O-desmethyiltramadol metabolite (M1) to mu-receptors. The relative contribution of tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound (see Pharmacokinetics). There are limited data available on the efficacy of tramadol for pain in poor versus extensive CYP2D6 metabolizers. Data from a randomized, double-blind, crossover study suggest that receipt of tramadol 2 mg/

kg orally produces a greater analgesic effect, especially after the first four hours after dosing in extensive metabolizers whereas the analgesic effect in poor metabolizers is more modest but is sustained up to 10 hours after dosing. The threshold for pressure pain detection, tolerance, nociceptive reflex, and peak pain as compared with placebo was greater in extensive metabolizers as compared with the difference between placebo and tramadol receipt in poor metabolizers.[29940] The affinity of tramadol for mu-receptors is 10-fold less than codeine, 60-fold less than propoxyphene, and 6000-fold less than morphine. The M1 metabolite has four to 200 times greater affinity for the μ -receptor than tramadol. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone (see Interactions). Opiate receptors are coupled with G-protein (guanine-nucleotide-binding protein) receptors and function as modulators, both positive and negative, of synaptic transmission via G-proteins that activate effector proteins. Opiate agonists decrease intracellular cAMP by inhibiting adenylate cyclase which modulates the release of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine and norepinephrine. The stimulatory effects of opioids are the result of 'disinhibition' as the release of inhibitory neurotransmitters such as GABA and acetylcholine is blocked. The exact mechanism how opioid agonists cause both inhibitory and stimulatory processes is not well understood. In addition to central opiate receptor agonist activity, tramadol exerts norepinephrine and serotonin reuptake inhibition in the CNS, which inhibits pain transmission in the spinal cord. The monoaminergic reuptake blockade, similar to MAOIs, is an important contribution to the analgesic and adverse event profile of tramadol. The inhibitory reuptake effects of tramadol on norepinephrine and serotonin are 100 TO 1000 times less than those of imipramine.

Indications

FOR THE TREATMENT OF MODERATE PAIN OR MODERATELY SEVERE PAIN INCLUDING ARTHRALGIA, HEADACHE, MYALGIA, DENTAL PAIN FOLLOWING ORAL SURGERY SUCH AS EXTRACTION OF IMPACTED MOLARS OR

CHRONIC CONDITIONS SUCH AS LOW-BACK PAIN, BONE PAIN AND CANCER-RELATED PAIN, AND FOR PATIENTS WITH MODERATE TO MODERATELY SEVERE CHRONIC PAIN NOT REQUIRING RAPID ONSET OF ANALGESIC EFFECT:

NOTE: The tolerability of tramadol may be improved (e.g., less drug-induced vertigo and dizziness) by titrating dosage upward as compared to initiating therapy at full strength.

Oral dosage (immediate-release tablets ONLY):

Adults, Geriatric ≤ 75 years, and Adolescents ≥ 17 years:

Initially, 25 mg PO once daily then titrated in 25 mg increments as separate doses every three days to reach a dose of 100 mg/day PO (i.e., 25 mg PO four times daily). Thereafter, the total daily dose may be increased by 50 mg as tolerated every three days to reach 200 mg/day PO (i.e., 50 mg PO four times daily). After titration, tramadol 50 to 100 mg PO every four to six hours as needed, not to exceed 400 mg/day PO. Use with caution in Elderly 65 years or older. The tolerability of tramadol may be improved by initiating therapy with this dosage titration.[28314]

Geriatric > 75 years:

Initially, 25 mg PO once daily and titrated in 25 mg increments as separate doses every 3 days to reach a dose of 100 mg/day PO (i.e., 25 mg PO four times daily). Thereafter the total daily dose may be increased by 50 mg as tolerated every three days to reach 200 mg/day PO (i.e., 50 mg PO four times daily). After titration, tramadol 50 to 100 mg PO every four to six hours as needed, not to exceed 300 mg/day PO.[28314]

Neonates, Infants, Children, and Adolescents < 17 years:

Safety and efficacy have not been established.

Oral dosage (orally disintegrating tablets [Rybix® ODT] ONLY):

NOTE: Do not chew, cut, or break tablets.

Adults, Geriatric ≤ 75 years, and Adolescents ≥ 17 years:

Initially, 50 mg PO once daily then titrated in 50 mg increments as separate doses every 3 days to reach a dose of 200 mg/day PO in divided doses (i.e., 50 mg PO four times daily). After titration, tramadol 50 to 100 mg PO every four to six hours as needed, not to exceed 400 mg/day PO. Use with caution in Elderly 65 years and older.[40255]

Oral dosage (orally disintegrating tablets [Rybix® ODT] ONLY) continued: <i>NOTE: Do not chew, cut, or break tablets.</i>
Geriatric > 75 years: <i>Initially, 50 mg PO once daily then titrated in 50 mg increments as separate doses every three days to reach a dose of 200 mg/day PO in divided doses (i.e., 50 mg PO four times daily). After titration, 50 to 100 mg PO every four to six hours as needed. Max: 300 mg/day PO. Cautious dosing is advised. [40255]</i>
Neonates, Infants, Children, and Adolescents < 17 years: <i>Safety and efficacy have not been established.</i>

FOR RAPID RELIEF OF MODERATE TO MODERATELY SEVERE PAIN IN PATIENTS FOR WHOM THE BENEFITS OUTWEIGH THE RISK OF INCREASED ADVERSE REACTIONS ASSOCIATED WITH HIGHER INITIAL DOSES: FOR MODERATE CHRONIC PAIN OR MODERATELY SEVERE CHRONIC PAIN IN PATIENTS REQUIRING CONTINUOUS, AROUND-THE-CLOCK TREATMENT FOR AN EXTENDED PERIOD OF TIME:

NOTE: Clinical benefit at a total daily dose exceeding 300 mg of extended-release tramadol has not demonstrated.

Oral dosage (immediate-release tablets ONLY):
Adults, Geriatric ≤ 75 years, and Adolescents ≥ 17 years: <i>50 to 100 mg PO every four to six hours as needed, not to exceed 400 mg/day PO. Use with caution in Elderly 65 years and older. [28314]</i>
Geriatric > 75 years: <i>50 to 100 mg PO every four to six hours as needed. Cautious use advised. Total doses should not exceed 300 mg/day PO. [28314]</i>
Neonates, Infants, Children, and Adolescents < 17 years: <i>Safety and efficacy have not been established.</i>

Oral dosage (orally disintegrating tablets [Rybix® ODT] ONLY):
Adults, Geriatric ≤ 75 years, and Adolescents ≥ 17 years: <i>50 to 100 mg PO every four to six hours as needed. Cautious use is advised in Elderly. Total doses should not exceed 400 mg/day PO. [40255]</i>
Geriatric > 75 years: <i>50 to 100 mg PO every four to six hours as needed; cautious dosing is advised, starting at the low end of the dosing regimen. Total doses should not exceed 300 mg/day PO. [40255]</i>
Neonates, Infants, Children, and Adolescents < 17 years: <i>Safety and efficacy have not been established.</i>

Oral dosage (coated extended-release tablets [Ultram® ER] ONLY): <i>NOTE: Different formulations of extended-release tramadol are NOT interchangeable; pharmacokinetics and dosage titration schedules differ.</i>
Adults: <i>For patients not currently treated with tramadol, initially, 100 mg PO once daily; titrate in 100 mg increments every five days, if needed, up to max 300 mg/day. Dose no more frequently than every 24 hours. For patients maintained on tramadol immediate-release tablets, calculate the 24-hour tramadol dose, and initiate a total daily dose of the extended-release tablets rounded down to the next lowest 100 mg increment. Individualize dose as needed; max 300 mg/day.</i> <i>Consider lower doses in Elderly > 65 years, particularly in Elderly > 75 years, no specific dosage adjustment recommendations are available. Conversion from tramadol immediate-release tablets to the extended-release tablets may not be possible because of the limited strength availability of the extended-release tablets. The concomitant use of the extended-release tablets with other tramadol products is not recommended. [32475]</i>
Neonates, Infants, Children, and Adolescents: <i>Safety and efficacy have not been established.</i>

Oral dosage (dual-matrix extended-release tablets [Ryzolt®] ONLY):

NOTE: Different formulations of extended-release tramadol are NOT interchangeable; pharmacokinetics and dosage titration schedules differ.

Adults and Adolescents ≥ 16 years:

For patients not currently treated with tramadol, initially, 100 mg PO once daily; titrate in 100 mg increments every two to three days up to a maximum of 300 mg/day. Dose no more frequently than every 24 hours. For patients maintained on tramadol immediate-release tablets, calculate the 24-hour tramadol dose, and initiate a total daily dose of the extended-release tablets rounded down to the next lowest 100 mg increment. Individualize the dose as needed up to a maximum of 300 mg/day.

Consider lower doses in Elderly > 65 years, particularly in Elderly > 75 years; no specific dosage adjustment recommendations are available. Conversion from tramadol immediate-release tablets to the extended-release tablets may not be possible because of the limited strength availability of the extended-release tablets. The concomitant use of the extended-release tablets with other tramadol products is not recommended. [43297]

Neonates, Infants, Children, and Adolescents < 16 years:

Safety and efficacy have not been established.

Oral dosage (extended-release capsules [ConZip®] ONLY):

NOTE: Different formulations of extended-release tramadol are NOT interchangeable; pharmacokinetics and dosage titration schedules differ.

Adults:

For patients not currently treated with tramadol, initiate at 100 mg PO once daily; titrate in 100 mg increments every 5 days, if needed, up to max 300 mg/day. Dose no more frequently than every 24 hours. For patients maintained on tramadol immediate-release tablets, calculate the 24-hour tramadol dose, and initiate a total daily dose of the extended-release capsules rounded down to the next lowest 100 mg increment; individualize dose as needed, up to a max 300 mg/day.

Consider lower doses in Elderly > 65 years, particularly in Elderly > 75 years; no specific dosage adjustment recommendations are available. Conversion from tramadol immediate-release products to the extended-release capsules may not be possible due to limited strength availability of the extended-release capsules. The concomitant use of the extended-release capsules with other tramadol products is not recommended. When the patient no longer requires tramadol, taper the dose gradually to prevent withdrawal. [51440]

Neonates, Infants, Children, and Adolescents:

Safety and efficacy have not been established.

FOR THE ADJUVANT TREATMENT OF OSTEOARTHRITIS:

Oral dosage (immediate-release tablets):

Adults:

50 to 100 mg PO every four to six hours as needed, not to exceed 400 mg/day PO. Dosage titration may improve tolerability. Tramadol has been shown to be effective in controlling breakthrough pain in patients receiving NSAIDs. A trial of tramadol versus diclofenac in patients with osteoarthritis of the hip and/or knee showed that the drugs were comparable. Tramadol may be an alternative to NSAIDs in patients who do not tolerate or have preexisting conditions that limit NSAID use or in patients with a limited inflammatory component to their osteoarthritis. [24325]

Geriatric patients ≥ 75 years:

50 to 100 mg PO every four to six hours as needed with a maximum total daily dose not to exceed 300 mg PO.

FOR THE TREATMENT OF NEUROPATHIC PAIN INCLUDING DIABETIC NEUROPATHY AND POSTHERPETIC NEURALGIA:

Oral dosage (immediate-release tablets):

Adults:

An average tramadol dose of 210 mg/day PO, in divided doses, provided significant relief of neuropathic pain in patients with diabetic neuropathy who participated in a placebo-controlled study. Patients receiving tramadol scored better in physical and social functioning ratings than placebo. [25881] In a study of patients with postherpetic neuralgia, tramadol 600 mg/day was compared to a control arm of clomipramine plus levomepromazine. Nine of 10 patients treated with tramadol and six of 11 control patients reported satisfactory results. A large number of randomized patients withdrew from both arms due to side effects. [25882]

Maximum Dosage Limits

- **Adults:** 400 mg/day PO for immediate-release and orally disintegrating tablets; 300 mg/day PO for extended-release formulations.
- **Geriatrics 65 to 75 years:** 400 mg/day PO for immediate-release and orally disintegrating tablets; 300 mg/day PO for extended-release formulations.
- **Geriatrics > 75 years:** 300 mg/day PO.

• **Adolescents ≥ 17 years:** 400 mg/day PO

for immediate-release and orally disintegrating tablets; 300 mg/day PO for dual-matrix extended-release tablets (Ryzolt®). Safety and efficacy of other formulations have not been established.

- **Adolescents 16 years:** 300 mg/day PO for dual-matrix extended-release tablets (Ryzolt®). Safety and efficacy of other formulations have not been established.
- **Adolescents < 16 years, Children, Infants & Neonates:** Safety and efficacy have not been established.

Patients with Hepatic Impairment Dosing

Do not use the extended-release tramadol formulations in patients with severe hepatic impairment (Child-Pugh Class C); specific guidelines for dosage adjustments in mild to moderate hepatic impairment are not available. For the immediate-release and orally disintegrating tablets, a dose of 50 mg PO every 12 hours is recommended in patients with cirrhosis.

Patients with Renal Impairment Dosing:
CrCl 30 to 80 ml/min: <i>Specific guidelines for dosage adjustments are not available; decreased rate and extent of drug and metabolite excretion is expected.</i>
CrCl < 30 ml/min: <i>Do not use the extended-release tramadol formulations. For the immediate-release and orally disintegrating tablets, increase dosage interval to 12 hours; maximum daily dose not to exceed 200 mg/day PO.</i>

Intermittent hemodialysis

Approximately 7% of a tramadol dose is removed during a standard hemodialysis session. Therefore, no additional dosing adjustments of immediate-release and orally disintegrating tablets are needed on the day of dialysis. Do not use extended-release tramadol formulations in patients with CrCl < 30 ml/min.

Route-Specific Administration

Oral Administration

- *Slow titration of tramadol to the effective analgesic dose may improve tolerability (see Dosage).*

Oral Solid Formulations

Immediate-release tablets (e.g., Ultram®)

- *Administer tramadol immediate-release tablets with or without food.[28314]*

Orally disintegrating tablets (Rybix® ODT)

- *Administer with or without food.*
- *Remove tablet from the blister pack by peeling back foil from the blister; do not attempt to push the tablet through the foil.*
- *Do not break, chew, split, or crush the tablets.*
- *Place tablet in the mouth on the tongue; it will dissolve within one minute.*
- *May be taken with or without water.[40255]*
- *Extended-release tablets and capsules (e.g., Ryzolt®, ConZip®, Ultram® ER)*

NOTE: Different formulations of extended-release tramadol are NOT interchangeable; pharmacokinetics and dosage titration schedules differ.

- *Administer tramadol dual-matrix extended-release tablets (Ryzolt®) and extended-release capsules (ConZip®) without regard for meals.*
- *Administer the coated extended-release tablets (Ultram® ER) in a consistent manner, taken regularly either with food or without food.*
- *Swallow whole; do not break, chew, dissolve, or crush. Taking broken, chewed, dissolved, or crushed extended-release products leads to rapid release and absorption of a potentially fatal dose of tramadol.[32475] [43297] [51440]*

Contraindications / Precautions

Tramadol immediate-release tablets contain lactose; patients with lactase deficiency should take appropriate precautions with use.

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol, including reports of anaphylactoid

reactions after the initial tramadol dose, particularly in patients with a history of codeine hypersensitivity. Tramadol is contraindicated in patients with known tramadol hypersensitivity, opiate agonist hypersensitivity, or hypersensitivity to any other ingredient of the specific product formulation.[28314] [32475] [40255] Some tramadol immediate-release tablets contain polysorbate 80; do not use in patients with polysorbate 80 hypersensitivity.[28314]

Do not prescribe tramadol for patients who have depression, suicidal ideation, or addiction problems such as patients with alcoholism. Consider use of non-narcotic analgesics in these patients. Use of tramadol is associated with a significant potential for overdose or poisoning. Tramadol in excessive doses, either alone or in combination with other CNS depressants such as alcohol, is a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. Many of the tramadol-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts, as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of tramadol alone or in combination with other drugs. The use of immediate-release tramadol, tramadol orally disintegrating tablets (Rybix®), and extended-release tablets (specifically Ultram® ER) is contraindicated in cases of acute intoxication of CNS depressants including ethanol intoxication and/or intoxication with opiate agonists, hypnotics, centrally-acting analgesics, or psychotropic drugs. Note that while Ryzolt® extended-release tablets and ConZip® extended-release capsules are not specifically contraindicated, use during acute intoxication is not recommended. Tramadol may worsen central nervous system depression and decrease the respiratory rate in these patients. Tell patients not to exceed the recommended tramadol dose and to avoid ethanol ingestion during tramadol therapy. Advise patients of the additive depressant effects of tramadol and alcohol. [28314][32475][40255][43297] [51440]

As tramadol use is contraindicated in any situation where opioid agonist are contraindicated, do not use in patients with severe respiratory depression.[28314] Further, the manufacturers of dual-matrix extended-release tablets (Ryzolt) and extended-release capsules (ConZip) specifically contraindicate use in patients with acute or severe asthma or hypercapnia in unmonitored care settings or in the absence of resuscitate equipment. [43297] [51440] Consider alternative non-opioid analgesics instead of tramadol. Respiratory depression is possible with large doses of tramadol, especially when given concurrently with ethanol and anesthetic agents. Concurrent administration with other respiratory depressants exacerbates this risk (see Drug Interactions). If respiratory depression occurs, treat as an overdose; however, administer naloxone cautiously in these situations due to an increased risk of seizures.

Seizures have been reported in patients receiving tramadol within the recommended dosage range (see Adverse Reactions). Tramadol should be used with caution in patients who are at risk of seizures including those who have a pre-existing seizure disorder or a history of seizures, are receiving medications that reduce the seizure threshold (see Drug Interactions), who have certain medical conditions (i.e., metabolic disorders, increased intracranial pressure, CNS infection, head trauma), or who are experiencing ethanol or illicit drug withdrawal. The risk of seizures may increase in these patients. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. In tramadol overdose, naloxone administration may increase the risk of seizure. In addition, administration of tramadol to patients with increased intracranial pressure or head trauma may obscure the existence, extent, or course of intracranial pathology because tramadol induces pupillary changes (miosis). Further, the respiratory depressant effects of opioids such as carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly

exaggerated in these patients. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving tramadol.

Tramadol should be used with caution in patients with GI disease. It may be difficult to assess the condition of patients with acute abdominal conditions such as an acute abdomen if they are taking tramadol.

Tramadol is an opioid agonist of the morphine-type and is not recommended in patients with a substance abuse problem associated with opiate agonists. Tramadol has been shown to reinitiate physical dependence in some patients who have been physically dependent on other opiate agonists. Patients who have recently taken substantial amounts of opiate agonists may experience withdrawal symptoms after treatment with tramadol. Tramadol is not recommended in patients with a tendency towards opiate agonist substance abuse, in patients who have been physically dependent on opiate agonists, or in patients chronically taking opiate agonists. Psychologic dependence similar to that of codeine or dextropropoxyphene is possible with tramadol. However, because some of tramadol's activity comes from the active metabolite, μ -opioid activity may be delayed, thus possibly reducing the potential for abuse. The extended-release tablets could be abused by crushing, chewing, snorting, or injecting the dissolved product, which would result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death. The proper usage of tramadol in individuals with active or past drug or alcohol dependence is for the management of pain requiring opioid analgesia. Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

To prevent withdrawal symptoms, avoid abrupt discontinuation of tramadol. Withdrawal symptoms may include anxiety, sweating, nausea, tremors, diarrhea, upper respiratory symptoms, insomnia, rigors, pain, piloerection, panic attacks, paresthesias, and hallucinations (rarely). Clinical experience suggests that withdrawal symptoms may be relieved by tapering the dosage of tramadol.

Tramadol should be administered with caution to patients with renal impairment. Impaired renal function affects the rate and extent of excretion of both tramadol and its active metabolite, M1. It may take several days for elevated plasma concentrations and toxicity to develop. Dosage reductions of the immediate-release tablets are recommended if creatinine clearance falls below 30 ml/min (see Dosage). The extended-release tablets are not recommended for use in patients with a creatinine clearance below 30 ml/min. The extended-release tablets have not been studied in patients with a creatinine clearance below 30 ml/min, and the limited availability of dose strengths and once daily dosing do not permit the dosing flexibility required for safe use in patients with severe renal impairment.

Dosage reductions and an increased dosage interval are recommended for patients with hepatic disease (see Dosage). Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. It may take several days for elevated plasma concentrations and toxicity to develop. The extended-release tablets are not recommended for use in patients with severe hepatic impairment. The pharmacokinetics of the extended-release tablets have not been studied in patients with severe hepatic impairment, and the limited availability of dose strengths and once daily dosing do not permit the dosing flexibility required for safe use in patients with severe hepatic impairment.

Tramadol is classified as FDA pregnancy category C. Safe use in pregnancy has not been established; there are no adequate and well-controlled studies in pregnant women. Only administer tramadol to a pregnant woman if the

need clearly outweighs the risk to the fetus. High dosage levels in animal studies show tramadol as embryotoxic and fetotoxic. No teratogenic effects have been noted in animal studies, and fetal problems only occur at high doses where maternal toxicity is more severe. Tramadol crosses the placenta, and the effects on postnatal growth, development, and functional maturation of the fetus are unknown. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women treated with tramadol HCl during labor. Tramadol should not be given to women prior to or during labor or obstetric delivery unless the benefits outweigh the risk. Chronic use of tramadol during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn. Tramadol has been used outside the U.S. for the management of pain associated with labor. The effect of tramadol on respiratory depression in the neonate has been studied and was not significantly different from that following the administration of morphine or meperidine. [24328] However, neonatal seizures, neonatal withdrawal syndrome, fetal death, and still birth have been reported during post-marketing reports with tramadol HCl immediate-release products. [28314]

According to the manufacturer, breast-feeding is not recommended during maternal tramadol use. Alternative analgesics are recommended for use in women who are breast-feeding.[28314] Further, tramadol is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because the safety of tramadol in the exposed infant has not been studied. Tramadol and its metabolites are excreted into human milk in small amounts. After a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours post-dose was 100 mcg of tramadol (0.1% of the maternal dose) and 27 mcg of M1.[28314] Samples of breast milk taken from 75 women two to four days postpartum after receiving at least 4 doses of tramadol indicated that an exclusively breastfed baby would receive 2.24% of the maternal weight adjusted dose of tramadol and 0.64% of its metabolite. Assessments of the

babies of these mothers using the Neurologic and Adaptive Capacity Score found no difference when compared to babies in a control group. Forty-nine percent of mothers in the tramadol group and 100% of mothers in the control group were also receiving other opiates (mostly oxycodone).[45706] Alternative analgesics considered to be usually compatible with breast-feeding by the American Academy of Pediatrics include acetaminophen, ibuprofen, and morphine. [27500] Consider the benefits of breast-feeding, the risk of potential drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding baby experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

Geriatric patients vary in their tolerance of tramadol. Use all forms of tramadol with caution in patients 65 years and older, with consideration of the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Age-based dosage adjustments are recommended in patients older than 75 years of age.[28314] [32475] [40255] [43297] In clinical trials, elderly patients at least 65 years of age (n= 901) received extended-release tablets (Ultram ER). In general, higher incidence rates of constipation, fatigue, weakness, postural hypotension, and dyspepsia were observed for these patients as compared with younger patients. Healthy elderly subjects aged 65 to 75 years were found to have similar tramadol pharmacokinetics as compared to healthy subjects less than 65 years of age. However, in study patients over 75 years, elevated maximum serum concentrations and prolonged elimination half-life have been reported.[28314] According to the Beers Criteria, tramadol is considered a potentially inappropriate medication (PIM) for use in geriatric patients with chronic seizures or epilepsy and should generally be avoided in these populations because tramadol lowers the seizure threshold. The Beers expert panel states that tramadol may be acceptable in geriatric patients with well-controlled seizures in whom alternative agents have not been effective.[50974]

In the U.S., the safety and efficacy of tramadol in neonates, infants, children, and adolescents < 16 years of age have not been established. Safety and efficacy have been established for dual-matrix extended-release tramadol (Ryzolt®) in adolescent patients 16 years of age and older, and for orally disintegrating tablets (Rybix®) and immediate-release tablets (Ultram®) in adolescent patients 17 years of age and older.[28314] [43297] [40255] The safety and efficacy of the coated extended-release tablets (Ultram® ER) and the extended-release capsule (ConZip®) have not been established in patients under 18 years of age, and use of these dosage forms in children is not recommended. [32475] [51440]

Patients should be warned against driving or operating machinery until they know how tramadol may affect them.

Use tramadol extremely cautiously, if at all, in patients also receiving MAOI therapy (see Drug Interactions). Concomitant usage of tramadol and MAOIs is associated with an increased risk of seizures and serotonin syndrome.

Orally disintegrating tablets contain phenylalanine; do not prescribe this dosage form for patients with phenylketonuria or other phenylketone-related sensitivity.

Adverse Reactions

Dizziness and vertigo are among the most common adverse reactions associated with tramadol use. Dizziness or vertigo was reported in 26% of patients receiving immediate-release tramadol at seven days of treatment and 33% of patients receiving immediate-release tramadol at 90 days of treatment. Dizziness (not vertigo) was reported in 15.9% to 28.2% of patients who received 100 to 400 mg daily doses of coated extended-release tramadol (e.g., Ultram® ER), in 7% to 10% of patients who received 100 to 300 mg daily doses of dual-matrix extended-release tramadol (e.g., Ryzolt), and in 9.6% to 13.6%

of patients who received 100 to 300 mg daily of extended-release capsules (e.g., ConZip®). Vertigo occurred in 0.5 to < 1% of study patients receiving extended-release dosage forms.[28314] [32475] [43297] [51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255]

Constipation is among the most common adverse reactions associated with tramadol use. Constipation was reported in 24% of patients receiving immediate-release tramadol at seven days of treatment and in 46% at 90 days of treatment. It was reported in 12.2 to 29.7% of patients who received 100 to 400 mg daily doses of extended-release coated tablets (e.g., Ultram® ER), in 10 to 12% of patients who received 100 to 300 mg daily doses of dual-matrix extended-release tablets (e.g., Ryzolt®), and in 9.3 to 21.3% of patients who received 100 to 300 mg daily doses of extended-release capsules (e.g., ConZip®).[28314] [32475] [43297] [51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255] Tramadol is less likely to cause constipation than equipotent doses of acetaminophen and codeine.

Gastrointestinal effects are among the most common adverse reactions associated with tramadol use. These effects may occur independently or may indicate tramadol-induced hyperserotonergic state; evaluate patients with GI symptoms as appropriate to rule out such a syndrome. In patients receiving immediate release tramadol, nausea was reported in 24% after seven days and in 40% after 90 days of use; the use of extended release preparations may decrease nausea, as reported rates were 15.1 to 26.2% with Ultram® ER, 13 to 14% with dual-matrix extended-release (i.e., Ryzolt®), and 16.1 to 25.1% with extended-release capsules (i.e., ConZip®). Vomiting was reported with immediate release tramadol in 9% after seven days and in 17% after 90 days of use; the use of extended release preparations may decrease vomiting, as reported rates were 5 to 9.4% with Ultram® ER, 3 to 6% with dual-matrix extended-release (i.e., Ryzolt®), and 6.5 to 10.4% with extended-release

capsules (i.e., ConZip®).[28314][32475][43297][51440] A slow oral dose titration (increasing immediate-release tramadol by 50 mg every 3 days) has been associated with a decreased incidence of nausea and vomiting.[28314] Concomitant administration of an antiemetic during the first few days of tramadol therapy or with dosage increases may be beneficial. Anorexia was reported in 0.7 to 5.9% of patients who received various forms of tramadol. Other GI effects reported in clinical trials include: abdominal pain (1 to < 5%), upper abdominal pain (1 to < 5%), flatulence (0.5 to < 5%), and sore throat (1 to < 5%). Symptoms reported in < 1% of study patients receiving some form of tramadol include: appendicitis, gastroenteritis, hepatic failure, hepatitis, pancreatitis, stomatitis, toothache (i.e., dental pain), abdominal discomfort, abdominal distension, abdominal tenderness, change in bowel habit, diverticulitis, diverticulum, dysphagia, fecal impaction, GI bleeding, GI irritation, gastroesophageal reflux disease, rectal hemorrhage, rectal prolapse, and retching.[28314][32475][43297][51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255]

Somnolence (drowsiness) is among the most common adverse reactions associated with tramadol use. In separate studies, somnolence was reported in 16 to 25% of patients receiving immediate-release tablets (incidence increasing with time up to 90 days), in 7.3 to 20.3% of patients receiving extended-release coated tablets (e.g., Ultram ER), in 5 to 7% of those receiving dual-matrix extended-release tablets (e.g., Ryzolt®), and in 11.7 to 16.1% of patients receiving extended-release capsules (e.g., ConZip®). Study patients experienced malaise at an incidence of 1 to < 5% with immediate-release tramadol and < 1% with two forms of extended-release tramadol. Lethargy was reported in 1 to < 5% of patients on extended-release tramadol, though not among those receiving immediate-release, dual-matrix extended-release, or extended-release capsule forms of tramadol. Similarly, 1 to < 5% of patients receiving extended-release or dual-matrix extended-

release tramadol experienced fatigue and/or weakness; this effect was not reported in patients on the immediate-release product or extended-release capsules.[28314][32475][43297][51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255]

Pruritus is a common adverse reactions associated with tramadol use. This effect may occur independently or may indicate a hypersensitivity reaction; monitor as appropriate. In patients receiving immediate release tramadol, pruritus was reported in 8% after seven days and in 11% after 90 days of use. Pruritus was reported in 6.2 to 11.9% of patients who received Ultram® ER, in 3 to 5% who received dual-matrix extended-release tramadol (e.g., Ryzolt®), and in 3 to 7.3% of patients who received extended-release tramadol capsules (e.g., ConZip®).[28314][32475][43297][51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255]

Asthenia is a common adverse reactions associated with tramadol use. In patients receiving immediate release tramadol, asthenia was reported in 6% after seven days and in 12% after 90 days of use. Asthenia was reported in 3.5 to 6.5% of patients who received Ultram® ER, in < 1% who received dual-matrix extended-release tramadol (e.g., Ryzolt®), and in 3.5 to 8.6% of those who received extended-release tramadol capsules (e.g., ConZip®).[28314][32475][43297][51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255]

Diaphoresis (increased sweating) is a common adverse reactions associated with tramadol use. This effect may occur independently or may indicate a hyperserotonergic state; monitor as appropriate. In patients receiving immediate release tramadol, diaphoresis was reported in 6% after seven days and in 9% after 90 days of use. Diaphoresis was reported in 1.5 to 6.4% of patients who received Ultram® ER, in 0 to

3% who received dual-matrix extended-release tramadol (e.g., Ryzolt®), and in 4.2 to 6.7% who received extended-release tramadol capsules (e.g., ConZip®).[28314] [32475] [43297] [51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255]

Dyspepsia is a common adverse reactions associated with tramadol use. In patients receiving immediate release tramadol, dyspepsia was reported in 5% after seven days and in 13% after 90 days of use. Dyspepsia was reported in 1% to < 5% of patients who received any form of extended-release tramadol.[28314] [32475] [43297] [51440] Dosage form-specific adverse events of the orally disintegrating formulation are not reported.[40255]

Diarrhea is a common adverse reactions associated with tramadol use. This effect may occur independently or may indicate a hyperserotonergic state; monitor as appropriate. In patients receiving immediate release tramadol, diarrhea was reported in 5% after 7 days and in 10% after 90 days of use. Diarrhea was reported in 3.7 to 8.5% of patients who received Ultram® ER, in 1 to < 5% who received Ryzolt®, and was not specifically reported in study patients who received ConZip®.[28314] [32475] [43297] [51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255]

Mouth, nose, or throat related adverse reactions have been reported with tramadol use. In patients receiving immediate release tramadol, xerostomia (dry mouth) was reported in 5% after 7 days and in 10% after 90 days of use. Dry mouth was reported in 5 to 9.8% of patients who received Ultram ER, in 1 to 4% who received Ryzolt®, and in 4.7 to 13.1% who received ConZip® formulations of extended-release tramadol.[28314] [32475] [43297] [51440] Other mouth, nose, and throat effects, such as sneezing, cough, rhinorrhea, nasal congestion, and sinus congestion, have been reported in 1 to < 5% of patients on extended-release tramadol in clinical trials; yawning has been reported in < 1%

of study patients.[32475] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255]

Cardiovascular adverse events have been reported with tramadol use. At therapeutic doses, tramadol has no effect on heart rate, left-ventricular function, or cardiac index. Labile blood pressure and/or tachycardia may indicate a tramadol-induced hyperserotonergic state; evaluate any patient with cardiovascular changes as appropriate to rule out this syndrome. Abnormal ECG (0.5% to <1%), bradycardia (< 1%), hypertension (< 5%), hypertension aggravated, hypotension (< 1%), sinus tachycardia (0.5% to <1%), hot flashes (or feeling hot; 1% to < 5%), myocardial ischemia, myocardial infarction (0.5% to < 1%), palpitations (0.5% to < 1%), peripheral ischemia (0.5% to < 1%), peripheral edema (1% to < 5%), pulmonary edema, and pulmonary embolism were reported in clinical trials and/or in post-marketing experience; causal relationships are unknown. Adverse events that occurred in clinical trials with immediate-release, extended-release, and dual-matrix extended-release tramadol: flushing (< 1 to 15.8%), orthostatic hypotension (< 1 to 5.4%), syncope (< 5%), and peripheral vasodilation (1 to < 5%).[28314] [32475] [43297] [51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255]

CNS stimulation (consisting of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional lability, and hallucinations) has been reported in 7% of patients receiving oral, immediate-release tramadol for seven days and in 14% after 90 days. Individual symptoms of CNS stimulation have been noted in trials for extended-release formulations of tramadol (e.g., Ultram® ER, Ryzolt®, ConZip®), including: nervousness (< 5%), anxiety (1 to < 5%), agitation (< 5%), depression (< 5%), tremor (1 to < 5%), euphoria (< 5%), emotional disturbance (< 1%), paresthesias (< 5%), and hypertonia (< 5%). As CNS changes may occur as part of the constellation of symptoms of tramadol-induced hyperserotonergic state, evaluate any patient

with such symptoms as appropriate to rule out this syndrome. Insomnia or sleep disorder occurred in 1 to 10.9% of patients receiving immediate-release or extended-release forms of tramadol. Other CNS effects reported in 1% to less than 5% of patients in pre-marketing trials of one or more tramadol dosage formulations include: blurred vision, confusion, coordination disturbance, depersonalization, hypoesthesia, indifference or apathy, miosis, restlessness, and visual impairment. Those reported in less than 1% of tramadol study patients include: abnormal dreams, abnormal gait or ataxia, abnormal thinking, amnesia, clamminess, impaired cognition or difficulty in concentration, disorientation, hyperkinesia, irritability, night sweats, pallor, sedation, sleep apnea syndrome, suicidal ideation or tendency, and twitching. Dysphonia (speech disorders) has also been reported.[28314] [32475] [43297] [51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255] Seizures have been reported (< 1%) and have occurred with recommended doses and with high doses. Concomitant treatment with antidepressants, especially tricyclic antidepressants or SSRIs, or opiate agonists may increase the risk of seizures.[25884] Patients with an existing seizure disorder are most at risk (see Contraindications). In a post-marketing surveillance case-control study (n=10,916) in the United Kingdom, patient exposure to tramadol alone at usual therapeutic dosages was not associated with an increased risk of idiopathic incident seizures.[25158] In overdose situations, tramadol's neurotoxicity due to monoamine uptake inhibition appears to be a major problem as opposed to the opioid effects.

Some evidence of respiratory depression exists, and the respiratory effects of tramadol have been compared to other opiate agonists. Tramadol produces less respiratory depression than morphine. At recommended doses, respiratory depression is not likely to be significant. In tramadol overdose or in combination with anesthetic agents or ethanol, significant respiratory depression may occur. In a prospective case study of reports made to poison control centers of overdose, the lowest dose of

tramadol associated with coma or respiratory depression was 800 mg.[25885] Dyspnea has been reported in 1% to < 5% of patients on immediate-release (e.g., Ultram) and extended-release tramadol (e.g., Ultram ER) and in < 1% on immediate-release or dual-matrix extended-release tramadol (e.g., Ryzolt) in separate clinical trials; though occurrence cannot be ruled out, this effect has not been specifically reported in study patients on extended-release tramadol capsules (e.g., ConZip).[28314] [32475] [43297] [40255] [51440]

Serious, and rarely fatal, anaphylactoid reactions have been reported in patients receiving tramadol. According to documented case reports on file with the manufacturer, patients with an allergy to codeine are at increased risk. Use of tramadol is contraindicated in patients with a history of hypersensitivity to tramadol or opioids. Other allergic manifestations of tramadol include urticaria (reported in < 1% of tramadol study patients), bronchospasm, angioedema, rash, vesicles (< 1%), Stevens-Johnson syndrome (< 1%), and toxic epidermal necrolysis (< 1%). Dermatitis and rash (unspecified) have been reported in 1% to < 5% of study patients receiving a form of extended-release tramadol and allergic dermatitis, undefined hair disorder, and undefined skin disorder in < 1% of patients. In contrast to morphine, tramadol has not been shown to cause histamine release.[28314] [32475] [43297] [51440]

Physiological dependence, tolerance, and a withdrawal syndrome (1 to < 5%) have been reported during tramadol therapy. Tramadol has also been associated with psychological dependence including drug craving and drug seeking behavior. Withdrawal reactions have been reported in patients receiving tramadol following naloxone administration. Tramadol can reinstate physical dependence in patients who have been previously dependent or chronically taking opiate agonists. In patients with a tendency to drug abuse, a history of drug dependence, or who are taking chronic opiate agonists, treatment with tramadol is not recommended. [28314] [32475] [43297] [40255] [51440] With parenteral abuse, the tablet excipients can

be expected to result in local tissue necrosis, infections, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Headache was reported in 18% and 32% of patients treated with immediate-release tramadol for seven and 90 days, respectively. It has also been reported in 11.5 to 15.8% of patients on extended-release tramadol coated tablets (e.g., Ultram® ER), in 3 to 5% of patients on dual-matrix extended-release tramadol (e.g., Ryzolt®), and in 19 to 23.1% of patients on extended-release tramadol capsules (e.g., ConZip®). Migraine has been reported infrequently in clinical trials and/or in post-marketing experience of immediate-release tramadol and in 0.5% to < 1% of patients on some forms of extended-release tramadol.[28314] [32475] [43297] [51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255] Overuse of analgesics such as tramadol products by headache-prone patients frequently produces drug-induced rebound headache accompanied by dependence on symptomatic medication, tolerance (refractoriness to prophylactic medication), and withdrawal symptoms. In this case, overuse of tramadol products has been defined as taking three or more doses per day more often than three to five days per week.[27347] The frequency of use may be more important than the dose. Features of a rebound headache include morning headache, end-of-dosing interval headache, or headache improvement with discontinuation of overused medication. Stopping the symptomatic medication may result in a period of increased headache and then headache improvement. Analgesic overuse may be responsible for the transformation of episodic migraine or episodic tension headache into daily headache and may perpetuate the syndrome.[27347]

Urogenital effects have been reported during tramadol use. In separate clinical studies, immediate-release tramadol, extended-release tramadol (e.g., Ultram® ER), and dual-matrix extended-release tramadol (e.g., Ryzolt®),

have been associated with increased urinary frequency (< 1 to < 5%) and urinary retention (< 1 to < 5%); urinary retention was also reported in 0.5 to < 1% of patients on extended-release tramadol capsules (e.g., ConZip®). Unspecified urine abnormalities were reported in < 5% of patients taking ConZip®. Other urogenital disorders that have been reported at an incidence of < 1% with at least one form of tramadol include: dysuria, difficulty in micturition, urinary hesitation, hematuria, proteinuria, and menstrual irregularity.[28314] [32475] [43297] [51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255]

Serotonin syndrome may occur with tramadol within the recommended doses (< 1%), especially when used with serotonergic drugs (see Drug Interactions). Serotonin syndrome may be life-threatening. Symptoms include agitation, hallucinations, coma, tachycardia, labile blood pressure, hyperthermia, hyperreflexia, incoordination, nausea, vomiting, and/or diarrhea. [28314] [32475] [43297] [51440]

Neonatal seizures, neonatal abstinence syndrome, fetal death, and still birth have been reported with tramadol in post-marketing experience.[28314] [32475] [43297] [51440]

Although no causal relationships have been established, infection and infestations have been reported during clinical trials with tramadol. Among study patients receiving either immediate-release or extended-release forms of tramadol in separate study, 1 to < 5% experienced influenza-like illness, pharyngitis (reported as nasopharyngitis), respiratory tract infection, chills, rhinitis, sinusitis, influenza, gastroenteritis viral, urinary tract infections, or bronchitis and less than 1% of patients experienced cellulitis, cystitis, ear infection, gastroenteritis, pneumonia, or viral infection. Fever was reported at a rate of either < 1% or 1 to < 5% in various studies.[28314] [32475] [43297] [51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255] Laboratory abnormalities have been reported rarely with tramadol use; no causal relationships

are established. In separate clinical studies, 1% to less than 5% of patients receiving some form of either immediate-release or extended-release tramadol have experienced increased blood creatine phosphokinase; < 1% were noted to have abnormal blood potassium, anemia, thrombocytopenia, lowered or elevated hepatic enzymes (including decreased or increased alanine aminotransferase [ALT or SGPT], decreased or increased aspartate aminotransferase [AST or SGOT], and increased gamma glutamyltransferase [GGT]), increased blood amylase, increased serum creatinine, or increased blood urea nitrogen (BUN). Increased blood glucose or hyperglycemia was noted in 0.5 to < 1% of patients on extended-release tablet (Ultram ER) and in 1 to < 5% of those on extended-release capsule (ConZip) in separate trials.[28314] [32475] [43297] [51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255]

Unquantified weight loss has been reported during tramadol use. In separate trials, weight loss was noted in < 1% of patients receiving immediate-release tramadol and in 1 to < 5% of patients receiving extended-release formulations.[28314] [32475] [43297] [51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255]

Hepatobiliary disorders have been reported infrequently during tramadol use. Cholelithiasis (< 1%), cholecystitis (0.5 to 1%), or other biliary tract disorders (< 1%) have been reported in patients receiving extended-release tramadol tablets; these effects were not noted in patients on immediate-release tramadol or on extended-release tramadol capsules during clinical trials. [28314] [32475] [43297] [51440]

Cataracts (< 1%), lacrimation disorder (0.5 to < 1%), undefined eye disorder (0.5 to < 1%), hearing loss or deafness (< 1%), and tinnitus (0.5 to 1% and < 1%) have been reported during clinical trials or in post-marketing experience with various dosage forms of tramadol.[28314]

[32475] [43297] [51440]

Musculoskeletal adverse events have been noted during tramadol use. Arthralgia has been reported in 1 to 5.4% of patients using extended-release dosage forms. Pain, falls, rigors, back pain, pain in limb, pelvic pain, and neck pain have been reported in 1% to < 5% of patients receiving various forms of extended-release tramadol during clinical trials; 0.5% to < 1% reported ecchymosis, gout, arthrosis, neck rigidity, joint swelling, joint disorder, leg or muscle cramps, muscle spasms, joint stiffness, muscle twitching, and arthritis or aggravation of osteoarthritis. Accidental injury and myalgia were reported in either 0.5% to < 1% or 1 to < 5% of study patients in different trials. Contusion, joint sprain, and muscle injury was reported in < 1% of patients on immediate-release tramadol.[28314] [32475] [43297] [51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255]

Sexual dysfunction, including impotence (erectile dysfunction) and libido decrease, have been reported in less than 1% of patients receiving extended-release tramadol in clinical trials; these effects were not noted with immediate-release tramadol. In those taking extended-release tramadol capsules (e.g., ConZip®), unspecified prostatic disorders and sexual function abnormalities were reported in < 5% and < 1% of patients, respectively.[28314] [32475] [43297] [51440] Dosage form-specific adverse events of the orally disintegrating tramadol formulation are not reported.[40255]

Tramadol hydrochloride Specific Ocular Use

Adult dose: 50 mg 1-2 tablets every 6 hours for pain (400 mg/day max) up to 72 hours.

Children: not recommended for use in patients < 18 years of age

Example for use: severe corneal abrasion in an adult patient 50 mg QID x 72 hours

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Acetaminophen with codeine 300/30mg

Drug Description

Acetaminophen with codeine 300/30mg is a schedule C-III controlled substance.

Acetaminophen and codeine are used together to treat moderate to severe pain due to cancer, dental procedures, headache, back pain, and arthralgias and myalgias. Acetaminophen is a non-salicylate analgesic with similar analgesic potency as NSAIDs, and codeine is an oral semisynthetic opiate agonist derived from the opioid alkaloid, thebaine. The combination of acetaminophen and codeine produces additive analgesia as compared to the same doses of either agent alone. Combinations containing higher doses of one or both components give progressively increasing analgesia. However, dosage escalation of this combination is limited by the maximum dose and “ceiling effect” of acetaminophen. The combination of acetaminophen and opioid analgesics may achieve a “dose-sparing” effect such that lower doses of the both agents produce pain relief with fewer side effects.[25417] The acetaminophen-codeine combination is available as tablets and liquid dosage forms.

Classifications:
Analgesics Acetaminophen/Opiate Agonist Combinations
Brand Names:
Tylenol with Codeine #3

Mechanism of Action

Acetaminophen-codeine combination produced analgesia through two different mechanisms of action leading to a synergistic analgesic affect.

- **Codeine:** Codeine is a weak μ -opiate receptor agonist and the majority of its analgesic affect is due to metabolism to morphine. Opiate analgesia is mediated through changes in the perception of pain at the spinal cord and higher levels in the CNS. Opiate analgesics also alter the emotional response to pain. The stimulatory effects of opioids are the result of ‘disinhibition’ as the release of inhibitory neurotransmitters such as GABA and acetylcholine is blocked. The antitussive effect of codeine is due to direct action of codeine in the cough center of the medulla.

- **Acetaminophen:** Acetaminophen acts primarily in the CNS and increases the pain threshold by inhibiting cyclooxygenase, an enzyme involved in prostaglandin (PG) synthesis. Acetaminophen inhibits both isoforms of central cyclooxygenase, COX-1 and COX-2. Acetaminophen weakly inhibits PG synthesis in peripheral tissues, which is the reason for its lack of clinical useful peripheral anti-inflammatory effects. The antipyretic activity of acetaminophen is exerted by blocking the effects of endogenous pyrogen on the hypothalamic heat-regulating center by inhibiting PG synthesis.

Indications

NOTE: In January 2011, the FDA mandated that all acetaminophen-containing combination prescription medications will have a maximum of 325 mg of acetaminophen per dosage unit (i.e., capsule, tablet, or other dose unit).

This action has been taken to reduce the risk of liver damage and severe hypersensitivity reactions associated with acetaminophen. Manufacturers will have three years to comply. In the interim, healthcare providers are encouraged

to instruct patients to limit acetaminophen use to no more than 4 grams daily and to avoid alcohol while taking acetaminophen. Further, advise patients to check all over-the-counter and prescription medications for acetaminophen content and to consult their healthcare provider with any questions. Patients may continue current medications as prescribed and should seek medical help if excess acetaminophen is consumed or if symptoms of hypersensitivity or other adverse events occur.[43086]

FOR THE TREATMENT OF MILD PAIN TO MODERATE PAIN INCLUDING THE RELIEF OF DENTAL PAIN (E.G., TOOTHACHE), HEADACHE, MIGRAINE, BACK PAIN, BONE PAIN, ARTHRALGIA AND MYALGIA:

Oral dosage (tablets or capsules): Adults: 1 to 2 tablets PO every 4 hours as needed. Maximum single dose of codeine is 60 mg/dose. Maximum dose of acetaminophen is 4 g/day. Children: 0.5 to 1 mg codeine/kg PO every four to six hours. Dosage should be titrated to appropriate analgesic effect. Maximum acetaminophen dose is 75 mg/kg/day PO or 4 g/day PO, whichever is less.	Maximum Dosage Limits: <i>NOTE: For combination products containing acetaminophen, total daily intake of acetaminophen from all sources should be considered and may be the dose-limiting consideration for acetaminophen; codeine products.</i> Adults: Acetaminophen 4 g/day PO; codeine 60 mg/dose PO; some clinicians have recommended the following maximum dosages: for pain, codeine 360 mg/24 hours PO; as an antitussive, codeine 120 mg/day PO.. Elderly: Acetaminophen 4 g/day PO; codeine 60 mg/dose PO; some clinicians have recommended the following maximum dosages: for pain, codeine 360 mg/24 hours PO; as an antitussive, codeine 120 mg/day PO.
Oral dosage (elixir or suspension): Adults, Adolescents, and Children >= 12 years: 15 ml PO every four hours as needed. Maximum single dose of codeine is 60 mg/dose. Maximum dose of acetaminophen is 4 g/day. Children: 7 to 11 years: 10 ml PO three to four times per day as needed. Maximum acetaminophen dose is 75 mg/kg/day PO or 4 g/day PO, whichever is less. 4 to 6 years: 5 ml PO three to four times per day as needed. Maximum acetaminophen dose is 75 mg/kg/day PO or 4 g/day PO, whichever is less. <= 3 years: Safety and efficacy have not been established.	Adolescents: Acetaminophen 4 g/day PO; codeine 60 mg/dose PO; some clinicians have recommended the following maximum dosages: for pain, codeine 360 mg/24 hours PO; as an antitussive, codeine 120 mg/day PO. Children: 6 to 12 years: Acetaminophen 75 mg/kg/day PO or 4 g/day PO, whichever is less; codeine 60 mg/dose PO; some clinicians have recommended a maximum dosage for codeine as an antitussive of 60 mg/day PO. < 5 years: Acetaminophen 75 mg/kg/day PO or 4 g/day PO, whichever is less; as an antitussive, some clinicians have recommended a maximum dosage for codeine as an antitussive of 30 mg/day PO.

Patients with Hepatic Impairment Dosing

Dosage should be modified depending upon the clinical response and degree of hepatic impairment. No quantitative recommendations are available.

Patients with Renal Impairment Dosing

Dosage should be modified depending upon the clinical response and degree of renal impairment. No quantitative recommendations are available.

Route-Specific Administration

Oral Administration

Administer with a full glass of water. May be taken with food or milk to minimize GI irritation.

Acetaminophen; codeine should be titrated to the dose required to relieve the patient's pain keeping in mind the maximum daily dose of acetaminophen. Careful titration in opioid-naïve patients is required until tolerance develops to some of the side effects (i.e., drowsiness, respiratory depression).

Contraindications/Precautions

Acetaminophen; codeine combinations are contraindicated in patients with known acetaminophen hypersensitivity. Acetaminophen hypersensitivity reactions are rare, but severe sensitivity reactions are possible. Although true opiate agonist hypersensitivity is rare, use of acetaminophen; codeine is contraindicated in patients who have demonstrated a prior codeine hypersensitivity reaction.[43287] [43288] Such patients should not receive other opioid agonists of the phenanthrene subclass including morphine, oxycodone, and hydromorphone. Use caution in patients with sulfite hypersensitivity, as some acetaminophen; codeine tablets contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible patients. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.[43287]

Due to the effects of opiate agonists on the gastrointestinal tract, acetaminophen; codeine should be used cautiously in patients with GI disease including GI obstruction or ileus, ulcerative colitis, or pre-existing constipation. Opiate agonists may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Use acetaminophen; codeine with caution in patients who have or are suspected of having a paralytic ileus. Patients with

acute ulcerative colitis or other inflammatory bowel disease may be more sensitive to the constipating effects of opiate agonists. Although opiate agonists may worsen systemic symptoms and/or lengthen disease course in cases of diarrhea secondary to poisoning or infectious diarrhea, antimotility agents have been used successfully in these patients. If possible, opiate agonists should not be given until the toxic substance has been eliminated.

Acetaminophen; codeine should be used cautiously in patients with asthma. In addition, codeine should be avoided in patients with severe pulmonary disease such as acute or severe bronchial asthma, chronic obstructive pulmonary disease (COPD), or upper airway obstruction, patients with decreased respiratory reserve or in patients with significant respiratory depression due to potential additive effects.

Abrupt discontinuation of prolonged acetaminophen; codeine therapy can result in withdrawal symptoms (see Adverse Reactions). Patients should be gradually tapered off acetaminophen; codeine to avoid a withdrawal reaction. Generally, a 50% decrease every one to two days of the daily acetaminophen; codeine dose will prevent withdrawal symptoms in patients who have been receiving large daily doses of codeine.

Due to potential toxicities and increased side effects, acetaminophen; codeine should be used cautiously in patients with hepatic disease. Patients with viral hepatitis or alcoholism may be at risk for acetaminophen-induced hepatotoxicity due to decreased conjugation with glucuronide or sulfate. Acetaminophen should not be used in patients who consume more than three alcoholic beverages per day. The maximum daily dose of acetaminophen is 4 g/day in patients with normal hepatic function. Health care providers need to consider other potential sources of acetaminophen in addition to acetaminophen; codeine products. Codeine may accumulate leading to a prolonged duration of action in patients with decreased liver function. In acute situations, patients require close monitoring to

avoid excessive toxicity. Patients with chronic liver or renal disease may require less frequent dosing intervals. Short courses of normal adult doses of acetaminophen have been administered safely in patients with stable chronic liver disease.[23562]

Because codeine is an opiate agonist, acetaminophen; codeine is subject to substance abuse and psychologic dependence (i.e., drug addiction) or criminal diversion. Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk for harm. Patients with a previous history of substance abuse may be at increased risk of relapse if treated with acetaminophen; codeine. Abuse and addiction are separate and distinct from physiologic dependence and tolerance. Physicians should be aware that psychologic dependence may not be accompanied by concurrent tolerance and symptoms of physiologic dependence. In addition, abuse of opiate agonists can occur in the absence of true psychologic dependence and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Health care professionals should not let concerns over psychologic dependence deter them from using adequate amounts of opiate agonists in the management of severe pain. Patients should also be counseled regarding misconceptions regarding the use of opiate agonists for pain management. Acetaminophen; codeine is not approved for the management of substance abuse (alcohol or drug dependence). The use of acetaminophen; codeine in patients with alcohol or drug dependence, either active or in remission, is for the treatment of pain requiring opiate agonist analgesia. Patients receiving opiate substitution therapy for opiate substance abuse will have increased tolerance to the analgesic effects of opiate agonists used for acute pain, and will require higher and more frequent dosing to control their pain. Opiate substitution therapy does not adequately treat pain.

Patients with head trauma or with increased intracranial pressure should be given

acetaminophen; codeine with extreme caution, because these drugs can make it difficult to evaluate neurologic parameters. Hypoventilation due to the codeine component can produce cerebral hypoxia and raise CSF pressure, exaggerating the injury.

Opiate agonists, such as codeine, produce cholinergic side effects (by stimulating medullary vagal nuclei) causing bradycardia and vasovagal syncope, and induce the release of histamine, causing peripheral vasodilatation and orthostatic hypotension. These effects can cause problems in patients with cardiac disease. Acetaminophen; codeine should be used with caution in patients with cardiac arrhythmias, hypotension, or hypovolemia.

Acetaminophen; codeine is classified as FDA pregnancy risk category C drug. No well-controlled studies in pregnant women have been performed. Some experts suggest increased risk of codeine if used for prolonged periods or at high doses near term.[45806] Newborns whose mothers have been taking acetaminophen; codeine chronically may show some respiratory depression and/or withdrawal symptoms at birth or within a few days. Higher doses and doses administered close to obstetric delivery may also increase the risk for respiratory depression in the newborn. Newborns of mothers who receive acetaminophen; codeine during labor or delivery should be observed for signs of respiratory depression. Acetaminophen; codeine should be avoided during labor if delivery of a premature newborn is expected.[43287] No overall increase in fetal mortality, as determined by pregnancy outcomes of mothers that overdosed on various amounts of acetaminophen, was apparent amongst 300 women.[27731] Treatment with acetylcysteine or methionine did not appear to affect fetal or neonatal toxicity. Of 235 babies exposed to an overdose of only acetaminophen, 168 were normal, 8 had malformations, 16 were spontaneously aborted, and 43 were electively terminated. Of 67 babies exposed to an overdose of a combination acetaminophen product, 51 were normal, three had malformations, two were spontaneously aborted (late fetal deaths), and 11

were electively terminated. None of the babies with malformations were exposed during the first trimester, but all of the spontaneous abortions and one of the late fetal deaths were subsequent to first trimester exposure.

Acetaminophen; codeine should be used with caution in breast-feeding women, as codeine is distributed into breast milk at varying degrees depending upon the dose. Codeine is metabolized to morphine, which is also distributed into breast milk (see Pharmacokinetics). Breast-fed babies of women who quickly metabolize codeine (ultra-rapid metabolizer) may ingest dangerous amounts of morphine.[43287] A healthy, 13-day-old breastfed baby died from a morphine overdose; the baby's blood morphine concentration was 70 ng/ml. The mother was taking codeine 30 mg and acetaminophen 500 mg tablets. The mother initially took two tablets every 12 hours, but she took half of this dose from day two to 14 because of somnolence and constipation. She stored her milk on day 10 because of poor neonatal feeding; the morphine concentration in the milk was 87 ng/ml. She was determined by genetic testing to be an ultra-rapid metabolizer of codeine (heterozygous for a CYP2D6*2A allele with CYP2D6*2x2 gene duplication). [33434] Ultra-rapid metabolizers have a specific CYP2D6 genotype and may change codeine to morphine more rapidly and completely than other people. Ultra-rapid metabolizers are more likely to have higher than normal blood and breast milk morphine concentrations after taking codeine. Ultra-rapid metabolism has only been reported as a problem with codeine, although ultra-rapid metabolism has the potential to affect other narcotics. Too much of any narcotic in breast milk can be fatal to a nursing baby. The estimated number of ultra-rapid metabolizers varies among different population groups from less than 1 per 100 people up to 28 per 100 people. Although a genetic test to identify ultra-metabolizers is available, the risk of having an adverse event when taking codeine is not known. The test result alone may not correctly predict if a mother's milk will have too much morphine if she ingests codeine. Acetaminophen also crosses into

breast milk, with a concentration ranging from 0.1 to 1.85% of the maternal dose. According to the American Academy of Pediatrics (AAP), acetaminophen has not been associated with any observable changes in nursing babies of mothers that took acetaminophen while breast feeding. The AAP regards acetaminophen and codeine as maternal medicines that are usually compatible with breast feeding. Other alternative analgesics considered to be usually compatible with breast-feeding by the AAP include ibuprofen and morphine.[27500] According to the manufacturer, because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing babies, a decision should be made whether to discontinue nursing or to discontinue the drug. If acetaminophen; codeine use by a breast-feeding mother is desired, prescribe the lowest dose for the shortest amount of time to relieve pain or cough. Also, educate nursing patients about the potential risks and the signs of morphine overdose in themselves and in their babies. Instruct patients to immediately call their physician or get emergency help if they are extremely sleepy, confused, or have shallow breathing or severe constipation or if the baby shows signs of increased sleepiness (more than usual), difficulty breast-feeding, difficulty breathing, or limpness. Acetaminophen; codeine should not be used chronically during breast-feeding, as withdrawal symptoms may occur in the baby when the mother stops chronic acetaminophen; codeine therapy.[43287] Healthcare providers and other individuals are encouraged to report any acetaminophen; codeine side effects to the FDA by calling (800) 332-1088.

Acetaminophen; codeine should be used cautiously in patients with renal impairment and renal failure; dosage adjustments may be required. Codeine can cause urinary retention and oliguria, due to increasing the tension of the detrusor muscle. Patients more prone to these effects include those with prostatic hypertrophy, urethral stricture, bladder obstruction or pelvic tumors. In addition, codeine may accumulate in these patients leading to a prolonged duration of action and potential increase in side effects.

Chronic acetaminophen administration should be avoided in patients with underlying renal disease; however it may be used for episodic pain.

Geriatric patients are more sensitive to the analgesic effects of opiate agonists as they experience higher peak serum levels and a longer duration of pain relief. In addition, elderly patients are more susceptible to adverse reactions from opiate agonists; especially sedation and respiratory depression probably as a result of altered distribution of the drug and decreased elimination. Initial doses of opiate agonists may need to be reduced and doses should be carefully titrated taking into account analgesic effects and adverse reactions.

Opiate agonists, including acetaminophen; codeine products, are used in children for moderate to severe pain. Acetaminophen; codeine oral liquid formulations are not indicated for neonates, infants, and children < 3 years of age. The safety and efficacy of oral tablet formulations have not been established in pediatric patients, including neonates, infants, children, and adolescents.[43287] [43288] It is also important to note that children weighing < 50 kg may be more sensitive to the effects of opiate agonists and require body weight dosing of opiate agonists. Whenever possible analgesia should be administered to a pediatric patient through a noninvasive route (i.e., orally or through an existing IV line). Intramuscular administration of analgesic medications, including opiate agonists, to children sends them the message that to achieve pain relief more pain must be given. This can lead to denial of pain by fearful children.

Patients with G6PD deficiency who overdose with acetaminophen; codeine may be at increased risk for drug-induced hemolysis due to the acetaminophen component. During acetaminophen overdose, cyanosis may not be apparent in patients with pre-existing anemia, in spite of dangerously high blood concentrations of methemoglobin.

Symptoms of acute infection (e.g., fever, pain) can be masked during treatment with acetaminophen; codeine in patients

who have bone marrow suppression or immunosuppression.

Any patient receiving acetaminophen; codeine should be warned about the possibility of sedation and to use caution when driving or operating machinery.

Adverse Reactions

Pharmacologic tolerance to the analgesic effects of opiate agonists including acetaminophen; codeine combinations may occur in some patients.[43287] Tolerance is the need for increasing doses to maintain initial pain relief. Typically, tolerance presents as a decrease in the duration of analgesia and can be managed by increasing the dose or frequency; however, dosage increases in patients receiving acetaminophen and opiate agonist combination therapy will be limited by the total daily dose of acetaminophen. Some patients may require changing to a pure opiate agonist, such as morphine or oxycodone, which is not limited by a maximum daily dose as is the acetaminophen; codeine combination. When increasing doses of analgesia are required causes may be multifactorial including tolerance, progression of disease or psychologic distress.

The most significant adverse effect associated with opiate agonist use is respiratory depression and dyspnea (shortness of breath).[43287] Respiratory depression is more common in elderly or debilitated patients, following large initial doses in non-opioid tolerant patients or when opioids are given with other agents which cause CNS depression. Routine use of opiate agonists by an expectant mother can lead to respiratory depression.[43287] When acetaminophen; codeine is appropriately titrated, the risk of respiratory depression is generally small as tolerance rapidly develops to this effect. Caution needs to be employed in patients with chronic obstructive pulmonary disease or decreased pulmonary reserve, cardiovascular disease, or who are taking other CNS depressants. Severe symptomatic respiratory depression should be treated cautiously with an opioid antagonist such as naloxone.[33654]

Patients may experience adverse GI effects while taking acetaminophen; codeine. Although incidences of these adverse effects vary by population and study, nausea (19 to 25%), vomiting (7 to 24%), and abdominal pain (5%) are among the most frequently reported.[43287] [44216] [44217] [26672] Nausea and vomiting are more commonly seen at the initiation of opioid therapy or when switching agents. Opiate agonists affect the vestibular system and may cause more nausea and vomiting in ambulatory patients than bedridden patients. [43287] Scheduled treatment with an antiemetic during the first one to two days, then as needed during opiate therapy may minimize these symptoms until tolerance develops. If patients have nausea associated with movement, an antivertigo agent such as meclizine may be appropriate. Metoclopramide may be helpful in treating the symptoms of early satiety or fullness. Constipation due to decreased GI motility and secretions is common during opiate agonist therapy, occurring in an estimated 15 to 90% of opioid-treated patients depending on underlying disease, medication potency, and study design. [44213] Tolerance rarely develops to this effect, therefore, patients require a bowel regimen consisting of a stool softener and mild stimulant throughout chronic acetaminophen; codeine therapy. If constipation persists, an enema or suppository may be needed to prevent impaction.

Acetaminophen can be hepatotoxic and acute hepatic failure may occur which can result in liver transplant and death. In most cases, acetaminophen-induced hepatotoxicity occurs as a result of an acute overdose; however, moderately excessive doses, if taken chronically, may also produce hepatotoxicity. [43287] Acetaminophen-induced hepatotoxicity is manifested as hepatic necrosis, jaundice, bleeding and encephalopathy. After acute overdose, two or three days pass before maximum liver damage becomes apparent. Nausea, vomiting, anorexia, and abdominal pain usually occur within two to three hours of ingestion of toxic doses. Elevated hepatic enzymes and hypoprothrombinemia are also seen with acetaminophen overdose. Both

cimetidine and ethanol can affect the severity of acetaminophen-induced hepatotoxicity (see Drug Interactions). The exact incidence of acetaminophen-induced hepatotoxicity seen with acetaminophen; codeine is not known and may be limited by the respiratory depression effects of codeine.

The acetaminophen component of acetaminophen; codeine can cause acute renal tubular necrosis and chronic analgesic nephropathy, which is characterized by interstitial nephritis and renal papillary necrosis, in patients receiving high doses (e.g., 2.5 to 10 g/day) chronically or after acute overdose. Acute renal failure may occur in 25 to 30% of patients secondary to liver dysfunction. Rarely, acute renal failure (unspecified) may occur without severe hepatic toxicity. The risk of renal complications appears to be higher in patients with alcoholism. Chronic acetaminophen use has been implicated as a contributing factor in the decline of renal function in patients with underlying renal disease, including diabetic nephropathy.[23977]

Patients receiving acetaminophen; codeine may experience rebound or new-onset headache during therapy. Although the incidence may vary by population and study design, headache has been reported in 7% of study patients receiving acetaminophen; codeine for chronic non-malignant pain.[26672] Further, overuse of combination analgesics such as acetaminophen; codeine products by headache-prone patients frequently produces drug-induced rebound headache accompanied by dependence on symptomatic medication and tolerance (refractoriness to prophylactic medication). In this case, overuse of acetaminophen; codeine products has been defined as taking 3 or more doses per day more often than two days per week.[27347] The frequency of use may be more important than the dose. Features of a rebound headache include morning headache, end-of-dosing interval headache, or headache improvement with discontinuation of overused medication. Stopping the symptomatic medication may result in a period of increased headache and then headache improvement. Analgesic overuse

may be responsible for the transformation of episodic migraine or episodic tension headache into daily headache and may perpetuate the syndrome.[27347]

Codeine's effect on opiate receptors in the reticular activating system and striatum produces sedation. Although the incidence may vary by dose, population, and study design, lightheadedness or dizziness and drowsiness or sedation are among the most frequently reported adverse events associated with acetaminophen; codeine use.[44246] [26672] Patients should be warned that activity requiring mental alertness can be affected during acetaminophen; codeine treatment because CNS depression, including drowsiness, lightheadedness, sedation, confusion, and dizziness, can occur. [33654] [43287] Nervousness, restlessness, sleep disturbances and anxiety have been reported. Depending upon the individual patient tolerance, hallucinations may be reported in patients undergoing rapid dose escalation of acetaminophen; codeine.

Hematologic adverse events reported by the manufacturer include thrombocytopenia and agranulocytosis.[43287] Other hematologic reactions reported with acetaminophen include neutropenia, thrombocytosis, and pancytopenia. Acetaminophen sulfate, a metabolite of acetaminophen, may cause immune-mediated thrombocytopenia. Two adults had improvement in their platelet counts from 45 to 50 x10⁹/L to 165 to 325 x10⁹/L within seven to 10 days of acetaminophen discontinuation. The sera from each patient had antibodies against platelets in the presence of acetaminophen sulfate. [31419] Agranulocytosis, thrombocytosis, and pancytopenia have only been documented in the literature after acetaminophen overdose. Symptoms such as unusual tiredness or weakness, unusual bleeding or bruising, and unexplained sore throat or fever should be investigated promptly.

As a case of acquired purpura fulminans developed in a 32 year old woman who was instructed to take acetaminophen 1000 mg every

four to six hours as needed for pain [27733], such a reaction may be possible in patients taking acetaminophen; codeine. The patient noted rapidly spreading purpuric lesions and edema. Her lesions were nonblanchable and enlarging, and she had multiple purplish-black hemorrhagic and necrotic areas. Purpura fulminans is usually associated with disseminated intravascular coagulation and can occur in patients with inherited or acquired deficiencies of the protein C anticoagulant pathway. The patient developed acquired protein C deficiency from alcohol-induced hepatotoxicity. Fibrin thrombi in the dermal blood vessels, a characteristic finding of purpura fulminans, were present. Discontinuation of alcohol and acetaminophen and administration of vitamin K, heparin, and a systemic antibiotic led to almost complete purpuric lesion and hepatotoxicity resolution in 6 days.

Acetaminophen; codeine use may result in histaminic and hypersensitivity reactions. Pruritus has been reported in less than 5% of study patients receiving acetaminophen; codeine for chronic non-malignant pain.[26672] In the absence of other symptoms, pruritus, particularly of the nose or face, is typically attributable to opioid activity rather than drug hypersensitivity. [44146] [44147] Hypersensitivity, however, is typified by a constellation of dermal and systemic symptoms. Hypersensitivity reactions to acetaminophen may be manifested by urticaria, erythema, generalized pruritus, rash (unspecified), maculopapular rash, respiratory distress, and vomiting. Anaphylactic shock, angioedema, and anaphylactoid reactions have been infrequently reported with acetaminophen. [43287] Toxic epidermal necrolysis (TEN) consisting of generalized erythematous rash, fever, low blood pressure, elevated erythrocyte sedimentation rate, elevated liver function tests, full-thickness necrolysis of the epidermis, and sparse upper dermal lymphocytic infiltrate with a positive re-challenge has been reported following oral acetaminophen use.[27732] In addition, cases of allergic contact dermatitis (delayed hypersensitivity type) have been reported in the literature.[27734] [27735] Various reactions including generalized pruriginous micropapular

eruption, facial edema, generalized pruriginous exanthem, exfoliative dermatitis, and generalized exanthema occurred within several hours after acetaminophen ingestion. Acetaminophen has also been associated with acute generalized exanthematous pustulosis (AGEP). The nonfollicular, pustular, erythematous rash starts suddenly, is associated with fever above 38 degrees C, and is distinct from pustular psoriasis, although biopsy results in each reveal spongiform subcorneal pustules. Drugs are the main cause of AGEP. A period of 2 to 3 weeks after an inciting drug exposure appears necessary for a first episode of AGEP. Unintentional reexposure may cause a second episode within two days. Clinical presentation is diverse with cutaneous lesions beyond erythema and pustules present in half of the cases. For example, bullous lesions, edema, purpura, pruritus, and mucosal erosions are possible. The mean duration of the pustules is 9.7 days followed by an annular desquamation, as long as the causative drug or factor is discontinued. The physiopathological mechanisms of AGEP have not been determined but the pathological criteria of edema, leukocytoclastic vasculitis, eosinophil exocytosis, and keratinocyte focal necrosis are distinctive. Pustule confluence or very small pustules may lead a clinician to make an incorrect diagnosis of TEN, of drug-induced erythroderma, or of staphylococcal scalded skin syndrome.[27736]

As codeine can cause cardiovascular adverse reactions due to its anticholinergic effects and ability to release histamine, such effects may be seen in patients after the administration of acetaminophen; codeine. These reactions include flushing, faintness, palpitations, hypotension, orthostatic hypotension, and syncope. In cases of severe respiratory and/or circulatory depression, shock and cardiac arrest may occur.[33654]

Codeine, like other opiate agonists, can cause miosis.[33654] Therapeutic doses can increase accommodation and sensitivity to light reflex and decrease intraocular tension in both normal and glaucomatous eyes. The incidence of these effects during acetaminophen; codeine therapy is not known.

Acetaminophen; codeine may cause euphoria and dysphoria.[43287]

Acetaminophen; codeine may cause hyperamylasemia.[43287]

Opiate agonists present the potential for abuse or psychological dependence, and although the true risk of this phenomenon is extremely low, these effects have been reported in association with acetaminophen; codeine use.[24361] [43287] Physiological dependence, however, should be expected with chronic acetaminophen; codeine therapy as evidenced by a withdrawal syndrome occurring after abrupt discontinuation of the drug. Dosage tapers ranging from 10% reductions every week to 25 to 50% reductions every few days have been used to minimize withdrawal symptoms upon opioid therapy cessation; the rate of dose reductions may be guided by occurrence of withdrawal symptoms. [36122] Symptoms of withdrawal include nausea and diarrhea, coughing, lacrimation, yawning, sneezing, rhinorrhea, profuse sweating, twitching muscles, abdominal and muscles pain/cramps, hot and cold flashes, and piloerection. Elevations in body temperature, respiratory rate, heart rate, and blood pressure may also occur.[33654] Routine use of opiate agonists by an expectant mother can lead to depressed respiration in the newborn and a neonatal abstinence syndrome (NAS); NAS is estimated to occur in up to 50% of neonates born to opioid-dependent mothers. [36122] [43287] Withdrawal symptoms in a newborn occur one to four days after birth and include generalized tremors, hypertonicity with any form of tactile stimuli, hyperalertness, sleeplessness, excessive crying, vomiting, diarrhea, yawning and fever. It is important to differentiate physiological dependence, the onset of a withdrawal syndrome upon abrupt discontinuation of the drug from psychologic dependence. Psychological dependence is a behavioral syndrome characterized by drug craving, overwhelming concern with acquisition of the drug and other drug-related behaviors such as drug selling and seeking the drug from multiple sources.[33654]

Acetaminophen 300 mg with No. 3 Codeine Phosphate 30 mg Specific Occular Use

Adult dose: 1-2 tablets every 4-6 hours for severe eye pain up to 72 hours

Children: For corneal abrasions or other causes of pain in children, acetaminophen with codeine is available in a elixir of 120 mg acetaminophen/12 mg codeine per teaspoon, which can be dosed as follows: one teaspoonful three or four times daily for ages three to six; two teaspoonfuls three or four times daily for ages seven to 12; and three teaspoonfuls every four hours for children older than 12.

Maximum duration for use is 72 hours as all pain medications can cause sedation and other central nervous system disturbances.

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Overview of Antibiotics

An antibacterial is an agent that inhibits bacterial growth or kills bacteria.[1] The term is often used synonymously with the term *antibiotic(s)*. Today, however, with increased knowledge of the causative agents of various infectious diseases, *antibiotic(s)* has come to denote a broader range of antimicrobial compounds, including anti-fungal and other compounds.[2]

The term *antibiotic* was first used in 1942 by Selman Waksman and his collaborators in journal articles to describe any substance produced by a microorganism that is antagonistic to the growth of other microorganisms in high dilution.[3] This definition excluded substances that kill bacteria, but are not produced by microorganisms (such as gastric juices and hydrogen peroxide). It also excluded synthetic antibacterial compounds such as the sulfonamides. Many antibacterial compounds are relatively small molecules with a molecular weight of less than 2000 atomic mass units.

With advances in medicinal chemistry, most of today's antibacterials chemically are semisynthetic modifications of various natural compounds.[4] These include, for example, the beta-lactam antibacterials, which include the penicillins (produced by fungi in the genus *Penicillium*), the cephalosporins, and the carbapenems. Compounds that are still isolated from living organisms are the aminoglycosides, whereas other antibacterials—for example, the sulfonamides, the quinolones, and the oxazolidinones—are produced solely by chemical synthesis. In accordance with this, many antibacterial compounds are classified on the basis of chemical/biosynthetic origin into natural, semisynthetic, and synthetic. Another classification system is based on biological activity; in this classification, antibacterials are divided into two broad groups according to their biological effect on microorganisms: bactericidal agents kill bacteria, and bacteriostatic agents slow down or stall bacterial growth. (Wikipedia)

The Oral Ocular Formulary includes the following Antibiotics or their generic or therapeutic equivalents:

- | | |
|---|------------------------------------|
| 1. <i>Amoxicillin with or without clavulanic acid</i> | 5. <i>Doxycycline/Tetracycline</i> |
| 2. <i>Azithromycin</i> | 6. <i>Cephalexin (Keflex®)</i> |
| 3. <i>Erythromycin</i> | 7. <i>Minocycline</i> |
| 4. <i>Dicloxacillin</i> | |

The following sections will provide relevant clinical information about each of the agents listed above, including mechanism of action, indication, contraindications, adverse reactions, drug interactions, general dosing guides, special instructions, and most importantly, dosages and examples of use specifically for optometrists for the treatment of ocular conditions. This particular information for optometrists is included at the end of each drug section.

Amoxicillin Without Clavulanic acid

Drug Description

Amoxicillin is an oral semisynthetic aminopenicillin similar to ampicillin. The aminopenicillins are not stable to beta-lactamases of either gram-positive or gram-negative bacteria. Amoxicillin is more stable to gastric acid than is penicillin and more bioavailable than oral ampicillin. Because of greater bioavailability, amoxicillin is associated with a lower incidence of diarrhea versus orally-administered ampicillin. Like ampicillin, amoxicillin has a broader spectrum of activity than penicillin, although the carboxy- and ureidopenicillins are much more active against gram-negative rods. Amoxicillin is commonly used to treat infections such as otitis media, bronchitis, sinusitis, and bacterial cystitis caused by susceptible

organisms. To increase the efficacy of amoxicillin against penicillin-resistant *S. pneumoniae* in otitis or respiratory infections, higher dosage regimens have been recommended

Mechanism of Action

Beta-lactam antibiotics such as amoxicillin are mainly bactericidal. Like other penicillins, amoxicillin inhibits the third and final stage of bacterial cell wall synthesis by preferentially binding to specific penicillin-binding proteins (PBPs) that are located inside the bacterial cell wall. Penicillin-binding proteins are responsible for several steps in the synthesis of the cell wall and are found in quantities of several hundred to several thousand molecules per bacterial cell.

Penicillin-binding proteins vary among different bacterial species. Thus, the intrinsic activity of amoxicillin, as well as the other penicillins, against a particular organism depends on their ability to gain access to and bind with the necessary PBP. The aminopenicillins are able to penetrate gram-negative bacteria more readily than are the natural penicillins or penicillinase-resistant penicillins due to the presence of a free amino group within the structure. Like all beta-lactam antibiotics, amoxicillin's ability to interfere with PBP-mediated cell wall synthesis ultimately leads to cell lysis. Lysis is mediated by bacterial cell wall autolytic enzymes (i.e., autolysins). The relationship between PBPs and autolysins is unclear, but it is possible that the beta-lactam antibiotic interferes with an autolysin inhibitor.

Penicillin-resistant strains of *S. pneumoniae* are increasing in number. The mechanism of resistance is mediated via the development of altered PBPs and the penicillin-resistant strains will generally be resistant to amoxicillin. The addition of clavulanic acid does not overcome this type of resistance. Increased dosages of amoxicillin may be necessary to overcome resistant *S. pneumoniae*. Community resistance patterns may determine the likelihood of amoxicillin efficacy against *S. pneumoniae*.

Indication

Per the manufacturer, this drug has been shown to be active against most strains of the following microorganisms either in vitro and/or in clinical infections:

- *Enterococcus faecalis*
- *Escherichia coli*
- *Haemophilus influenzae* (beta-lactamase negative)
- *Helicobacter pylori*
- *Neisseria gonorrhoeae*
- *Proteus mirabilis*, *Staphylococcus sp.*
- *Streptococcus agalactiae* (group B streptococci)
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes* (group A beta-hemolytic streptococci)
- *Streptococcus sp.*

NOTE: The safety and effectiveness in treating clinical infections due to organisms with in vitro

data only have not been established in adequate and well-controlled clinical trials.

This drug may also have activity against the following microorganisms:

- | | |
|--|---|
| <ul style="list-style-type: none"> • <i>Actinomyces sp.</i> • <i>Bacillus anthracis</i> • <i>Bifidobacterium sp.</i> • <i>Bordetella pertussis</i> • <i>Borrelia burgdorferi</i> • <i>Brucella sp.</i> • <i>Clostridium perfringens</i> • <i>Clostridium tetani</i> • <i>Corynebacterium diphtheriae</i> • <i>Eikenella corrodens</i> • <i>Erysipelothrix rhusiopathiae</i> • <i>Eubacterium sp.</i> • <i>Lactobacillus sp.</i> | <ul style="list-style-type: none"> • <i>Listeria monocytogenes</i> • <i>Neisseria meningitidis</i> • <i>Peptococcus sp.</i> • <i>Peptostreptococcus sp.</i> • <i>Prevotella melaninogenica</i> • <i>Propionibacterium sp.</i> • <i>Salmonella enteritidis</i> • <i>Salmonella sp.</i> • <i>Salmonella typhi</i> • <i>Shigella sp.</i> • <i>Streptococcus dysgalactiae</i> • <i>Treponema pallidum</i> • <i>Vibrio cholerae</i> • <i>Viridans streptococci</i> |
|--|---|

NOTE: Some organisms may not have been adequately studied during clinical trials; therefore, exclusion from this list does not necessarily negate the drug's activity against the organism

Maximum Dosage Limits

Adults:

1750 mg/day PO for most labeled indications; up to 3000 mg/day PO is recommended off-label for community-acquired pneumonia.

Geriatric:

1750 mg/day PO for most labeled indications; up to 3000 mg/day PO is recommended off-label for community-acquired pneumonia.

Adolescents:

1750 mg/day PO for most indications; however, doses up to 4 g/day PO have been used off-label for community-acquired pneumonia.

Children:

45 mg/kg/day PO for most indications; however, doses up to 90 mg/kg/day have been used off-label for acute otitis media (Max: 1750 mg/day) and community-acquired pneumonia (Max: 4 g/day).

Maximum Dosage Limits continued

Infants:

3 months: 45 mg/kg/day PO for most indications; however, doses up to 90 mg/kg/day have been used off-label for acute otitis media and community-acquired pneumonia.

2 to 3 months: 30 mg/kg/day PO for most indications; however, doses up to 90 mg/kg/day have been used off-label for acute otitis media.

< 2 months: 30 mg/kg/day PO.

Neonates:

30 mg/kg/day PO.

Patients with Hepatic Impairment Dosing

No dosage adjustment needed; amoxicillin is not appreciably metabolized in the liver and does not undergo biliary secretion.

Patients with Renal Impairment Dosing

The following dosing recommendations pertain to adults. No specific dosage adjustments for pediatric patients with renal impairment are available at this time; however, dosage intervals should be adjusted.

CrCl > 30 ml/min:

No dosage adjustment needed.

CrCl 10 to 30 ml/min:

250 to 500 mg PO every 12 hours, depending on the severity of the infection. Do not use the 875 mg-tablet strength or the extended-release tablet for dosing.

CrCl < 10 ml/min:

250 to 500 mg PO every 24 hours, depending on the severity of the infection. Do not use the 875 mg-tablet strength or the extended-release tablet for dosing.

Intermittent hemodialysis

For adults, 250 to 500 mg PO every 24 hours, depending on the severity of the infection. According to the manufacturer, an additional dose should be given both during and at the end of a

dialysis session. Do not use the 875 mg-tablet strength or the extended-release tablet for dosing.

Peritoneal dialysis

Follow dosage recommendations as for renal impairment for CrCl < 10 ml/min for those adults receiving continuous ambulatory peritoneal dialysis (CAPD). Do not use the 875 mg-tablet strength or the extended-release tablet for dosing.

Continuous hemodialysis (CAVHD, CVVHD)

Amoxicillin is removed by CAVHD or CVVHD.

Contraindications / Precautions

Amoxicillin is a penicillin and is contraindicated in patients with a penicillin hypersensitivity.[43844] In general, amoxicillin should be used cautiously in patients with cephalosporin hypersensitivity or carbapenem hypersensitivity. These patients are more susceptible to hypersensitivity reactions during therapy with amoxicillin; the incidence of true cross-sensitivity has been estimated at roughly 3 to 5%. Amoxicillin is contraindicated in patients with a known serious hypersensitivity reaction (i.e., anaphylaxis) to other beta-lactams.[43844] Patients with allergies or atopic conditions including asthma, eczema, hives (urticaria), or hay fever may have a greater risk for hypersensitivity reactions to penicillin.[43844]

Use amoxicillin with caution in patients with renal impairment as the drug is substantially eliminated via renal mechanisms. Adjust dosage intervals in patients with CrCl ≤ 30 ml/min and in patients with renal failure. Dosage adjustments are also recommended for patients receiving dialysis (see Dosage). Do not use the extended release tablet in patients with CrCl ≤ 30 ml/min.[43096]

Almost all antibacterial agents have been associated with pseudomembranous colitis (antibiotic-associated colitis) which may range in severity from mild to life-threatening.

In the colon, overgrowth of Clostridia may exist when normal flora is altered subsequent to antibacterial administration. The toxin produced by Clostridium difficile is a primary cause of

pseudomembranous colitis. It is known that systemic use of antibiotics predisposes patients to development of pseudomembranous colitis. Consideration should be given to the diagnosis of pseudomembranous colitis in patients presenting with diarrhea following antibacterial administration. Systemic antibiotics should be prescribed with caution to patients with inflammatory bowel disease such as ulcerative colitis or other GI disease. If diarrhea develops during therapy, the drug should be discontinued. Following diagnosis of pseudomembranous colitis, therapeutic measures should be instituted. In milder cases, the colitis may respond to discontinuation of the offending agent. In moderate to severe cases, fluids and electrolytes, protein supplementation, and treatment with an antibacterial effective against *Clostridium difficile* may be warranted. Products inhibiting peristalsis are contraindicated in this clinical situation. Practitioners should be aware that antibiotic-associated colitis has been observed to occur over two months or more following discontinuation of systemic antibiotic therapy; a careful medical history should be taken.

Amoxicillin has been used to treat infections in infants ≤ 3 months of age, including neonates and premature neonates. However, dosages must be modified for these age groups compared to infants > 3 months of age because of incompletely developed renal function (see Dosage). Safety and effectiveness of Moxatag extended-release tablets has not been established in neonates, infants, or children < 12 years of age.[43096]

Based on manufacturer data, geriatric patients (age > 65 years) do not respond differently to amoxicillin treatment than younger patients. However, a greater sensitivity to amoxicillin in elderly patients could not be ruled out. Amoxicillin is known to be substantially excreted via the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection for elderly patients; renal function monitoring may be useful.

Amoxicillin is classified in FDA pregnancy risk

category B. Animal data reveal no teratogenic effects, however, there are no adequate and well-controlled studies in pregnant women. While amoxicillin should be used with caution in pregnancy, penicillins are usually considered safe during pregnancy when clearly needed.[43844]

According to the manufacturer, amoxicillin should be used cautiously during breast-feeding due to the potential for sensitization of the infant. [43844] Unless the infant is allergic to penicillins, breast-feeding is generally safe during maternal penicillin therapy. The American Academy of Pediatrics considers amoxicillin a medication that is usually compatible with breast-feeding. [27500] Amoxicillin is excreted in breast milk in small amounts. Penicillins may cause diarrhea (due to disruption of GI flora), candidiasis, and skin rash in breast-feeding infants. Small studies assessing adverse events in breast fed infants exposed to antibiotics have found adverse event rates of 7.5—8.3% after exposure to amoxicillin. The adverse events reported included diarrhea, rash, and somnolence.[45767] [45768]The infant should be observed for potential effects. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

Patients with phenylketonuria should be warned that the chewable tablets and the tablets for oral suspension (DisperMox) contain phenylalanine. Amoxicillin chewable tablets contain phenylalanine in the amount of 1.4 mg per 125 mg tablet, 4.5 mg per 200 mg tablet, 2.8 mg per 250 mg tablet, and 9 mg per 400 mg tablet. Each 200 mg and 400 mg DisperMox Tablet for oral suspension contains 5.6 mg phenylalanine and each 600 mg tablet contains 11.23 mg phenylalanine. The oral suspensions do not contain phenylalanine.

A false-positive reaction for glucose in the urine has been observed in patients receiving penicillins and using Benedict's solution,

Fehling's solution, or Clinitest tablets for urine glucose testing. However, this reaction has not been observed with Tes-tape (glucose Enzymatic Test Strip, USP, Lilly) or Clinistix. Patients with diabetes mellitus who test their urine for glucose should use glucose tests based on enzymatic glucose oxidase reactions while on amoxicillin treatment.

According to the manufacturer, amoxicillin should not be used in patients with mononucleosis as a high incidence of skin rashes have been reported in these patients.[43844]

Antimicrobial agents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with amoxicillin should have a follow-up serologic test for syphilis 3 months after treatment for gonorrhea.

Adverse Reactions

Hypersensitivity reactions are among the most frequently reported side effects of the penicillins, including with amoxicillin. Penicillin allergy has been reported in up to 20% of patients; however, around 90% of reported allergies are incorrectly reported and patients lack penicillin-specific IgE antibodies. The actual prevalence of penicillin allergy is likely no greater than 5%.[44466] [44468] These reactions may include serum sickness, hypersensitivity-related rashes, and/or anaphylactoid reactions including anaphylactic shock.[28047] [43096] [43843] [43844] Angioedema has also been reported with penicillins.[32975] Hypersensitivity-related rashes include bullous rash, erythema multiforme, exfoliative dermatitis, maculopapular rash with erythema, toxic epidermal necrolysis, Stevens-Johnson syndrome, hypersensitivity vasculitis, and urticaria.[28047] [43096] [43843] [43844] Contact dermatitis and rash (unspecified) may occur in 4 to 8% of patients receiving penicillins and may be idiopathic in nature.[44469] The incidence of rash secondary to amoxicillin seems to be higher in patients with a history of allergy, asthma, hay fever, or urticaria. If a

hypersensitivity reaction occurs, discontinue amoxicillin (unless the condition being treated is life threatening and amenable only to amoxicillin therapy) and institute appropriate therapy, such as antihistamines and, if necessary, systemic corticosteroids.[28047] [43096] [43843] [43844]

Hematologic effects seen with penicillins, such as amoxicillin, include eosinophilia and are associated with hypersensitivity reactions. Other reactions seen include anemia (including hemolytic anemia), thrombocytopenia, thrombotic thrombocytopenic purpura (TTP), agranulocytosis, and leukopenia. These adverse hematologic effects are generally reversible after discontinuation of the penicillin.[28047] [43096] [43843] [43844] Platelet dysfunction, prolonged bleeding time, and prolongation of APTT have been reported in patients receiving beta-lactams.

Amoxicillin has been associated with acute generalized exanthematous pustulosis (AGEP). [28047] [43096] [43843] [43844] The nonfollicular, pustular, erythematous rash starts suddenly, is associated with fever above 38 degrees C, and is distinct from pustular psoriasis, although biopsy results in each reveal spongiform subcorneal pustules. Drugs are the main cause of AGEP. A period of two to three weeks after an inciting drug exposure appears necessary for a first episode of AGEP. Unintentional reexposure may cause a second episode within two days. Clinical presentation is diverse with cutaneous lesions beyond erythema and pustules present in half of the cases. For example, bullous lesions, edema, purpura, pruritus, and mucosal erosions are possible. The mean duration of the pustules is 9.7 days followed by an annular desquamation, as long as the causative drug or factor is discontinued. The physiopathological mechanisms of AGEP have not been determined but the pathological criteria of edema, leukocytoclastic vasculitis, eosinophil exocytosis, and keratinocyte focal necrosis are distinctive. Pustule confluence or very small pustules may lead a clinician to make an incorrect diagnosis of TEN, of drug-induced erythroderma, or of staphylococcal scalded skin syndrome.[27736]

Nausea, vomiting, and diarrhea have been reported with penicillins, such as amoxicillin. In a tonsillitis and pharyngitis study, 302 adults and pediatrics (≥ 12 years) were treated with the extended release oral tablet. Reports of diarrhea (1.7%), nausea (1.3%), vomiting (0.7%), and abdominal pain (0.3%) were all similar to those reported with the comparator drug. Additionally, in clinical trials using combination therapy of amoxicillin plus lansoprazole, diarrhea was reported in 8% of patients. In trials with the combination of amoxicillin, lansoprazole, and clarithromycin, diarrhea was reported in 7% of patients and taste perversion (e.g., dysgeusia) was reported in 5% of patients. Antibiotic-associated colitis, also known as pseudomembranous colitis can occur during use of or after discontinuance of amoxicillin, but this effect is rare. Tongue discoloration (black hairy tongue) has also been reported with amoxicillin. [28047] [43096] [43843] [43844] Amoxicillin has been rarely reported to cause esophagitis in some patients. Amoxicillin may be irritating to the esophagus if transit of an oral solid dosage form through the esophagus is delayed. Odynophagia, mid-chest pain, and dysphagia may be symptoms of esophagitis.

Superinfection can occur with amoxicillin therapy. Prolonged or repeated therapy in particular can result in overgrowth by nonsusceptible bacteria or fungi. If superinfections occur, discontinue amoxicillin and institute appropriate therapy. Mucocutaneous candidiasis may occur as oral candidiasis (rare) or vaginal candidiasis. Vulvovaginal mycotic infections were reported in 2% ($n = 302$) of adult and pediatric (≥ 12 years) patients receiving the extended release oral tablet during a tonsillitis and pharyngitis study. [28047] [43096] [43843] [43844]

Central nervous system reactions associated with amoxicillin include headache. In a study of adults and pediatric (≥ 12 years) receiving extended-release amoxicillin tablets for tonsillitis and pharyngitis ($n = 302$), 1% of patients reported headache. In clinical trials using the combination of amoxicillin plus lansoprazole or amoxicillin, lansoprazole, and clarithromycin, headache was

reported in 6—7% of patients. Other adverse events such as agitation, reversible hyperactivity, anxiety, convulsions (seizures), confusion, dizziness, insomnia, or other behavioral changes have been reported rarely.[28047] [43096] [43843] [43844] Seizures have been reported when large doses of penicillins were administered to patients with renal impairment. [23981] Appropriate dosage adjustments should be observed in these patients.

Hepatic dysfunction has been reported as cholestatic jaundice, cholestasis, or acute cytolytic hepatitis. Other reported side effects of amoxicillin include elevated hepatic enzymes (e.g., moderate rises in AST and/or ALT); however, the clinical significance is not known. [28047] [43096] [43843] [43844]

Tooth discoloration (brown, yellow, or gray staining) has been rarely reported with amoxicillin therapy. The majority of reports have been in children. In most cases, discoloration was reduced or eliminated by brushing or dental cleaning.[28047] [43096] [43843] [43844] A follow-up study assessing fluoride intake and amoxicillin use reported a possible link to amoxicillin-associated dental fluorosis affecting permanent teeth. After adjusting for fluoride intake and otitis media, the study noted a significant increase in the risk of fluorosis with amoxicillin therapy.[31599]

Crystalluria has also been reported.[28047] [43096] [43843] [43844]

Amoxicillin with Clavulanic acid

Drug Description

Amoxicillin-clavulanic acid is a combination drug marketed under the trade name Augmentin®. Clavulanic acid is a beta-lactamase inhibitor that possesses weak antibacterial activity. Combination with clavulanic acid reestablishes amoxicillin's activity against beta-lactamase-producing bacteria. This makes Augmentin® an excellent drug for treating infections due to

beta-lactamase-producing *H. influenzae* and penicillinase-producing anaerobes. The drug is commonly used to treat infections such as acute otitis media, acute sinusitis, acute bacterial cystitis, uncomplicated gonorrhea, and chancroid caused by susceptible organisms. Augmentin® was approved by the FDA in August 1984 and is off patent as of December 2002. An extended release dosage form, Augmentin® XR, was approved in September 2002 for the treatment of acute bacterial sinusitis or community-acquired pneumonia.

Mechanism of Action: As a beta-lactam antibiotic, amoxicillin is mainly bactericidal. It inhibits the third and final stage of bacterial cell wall synthesis by preferentially binding to specific penicillin-binding proteins (PBPs) that are located inside the bacterial cell wall. Like all beta-lactam antibiotics, amoxicillin's ability to interfere with PBP-mediated cell wall synthesis ultimately leads to cell lysis. Lysis is mediated by bacterial cell wall autolytic enzymes (i.e., autolysins). The relationship between PBPs and autolysins is unclear, but it is possible that the beta-lactam antibiotic interferes with an autolysin inhibitor.

Clavulanic acid is a beta-lactam drug that acts as a competitive "suicide" inhibitor of many plasmid-mediated and chromosomally mediated bacterial beta-lactamases. Like sulbactam, clavulanic acid inhibits the activity of beta-lactamase Richmond types II, III, IV, V, and VI. It will not inhibit chromosomal type I, however, found in some Enterobacteriaceae. Clavulanic acid binds to the enzyme's active site, inactivating the beta-lactamase. Clavulanic acid can penetrate the cell wall and inactivate bound, as well as extracellular, beta-lactamases. It does not, however, overcome methicillin-resistance in staphylococci since this is mediated via a different mechanism. Clavulanic acid does not alter the actions of the beta-lactam antibiotics. It exhibits weak antibacterial effects.

Organisms that are susceptible to ampicillin and plain amoxicillin are also susceptible to Augmentin®. Augmentin® has an expanded gram-positive spectrum that includes the beta-lactamase-producing staphylococci and

most streptococci including enterococcus. Methicillin-resistant staphylococci (MRSA) are not susceptible. Penicillin-resistant strains of *S. pneumoniae* are increasing in number. The mechanism of resistance is mediated via the development of altered PBPs and the penicillin-resistant strains will generally be resistant to amoxicillin. The addition of clavulanic acid does not overcome this type of resistance. Increased dosages of amoxicillin may be necessary to overcome penicillin-resistant *S. pneumoniae*. The gram-negative spectrum of Augmentin® includes *N. gonorrhoeae*, *N. meningitidis*, *Moraxella* (*Branhamella*) *catarrhalis*, *H. influenzae*, *H. ducreyi*, *Gardnerella vaginalis*, *Bordetella pertussis*, and some enteric bacilli including *E. coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Salmonella*. Augmentin® is extremely active against many anaerobic bacteria since many of these organisms liberate beta-lactamases. Clinicians are advised to consult individual organism susceptibility data prior to prescribing Augmentin®.

Indication

Per the manufacturer, this drug has been shown to be active against most strains of the following microorganisms either in vitro and/or in clinical infections:

Bacteroides fragilis, *Bacteroides* sp., *Eikenella corrodens*, *Enterobacter* sp., *Enterococcus faecalis*, *Escherichia coli*, *Fusobacterium nucleatum*, *Fusobacterium* sp., *Haemophilus influenzae* (beta-lactamase negative), *Haemophilus influenzae* (beta-lactamase positive), *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Klebsiella* sp., *Moraxella catarrhalis*, *Neisseria gonorrhoeae*, *Peptostreptococcus magnus*, *Peptostreptococcus micros*, *Peptostreptococcus* sp., *Proteus mirabilis*, *Staphylococcus aureus* (MSSA), *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* (group A beta-hemolytic streptococci), *Viridans streptococci*

NOTE: The safety and effectiveness in treating clinical infections due to organisms with in vitro

data only have not been established in adequate and well-controlled clinical trials.

This drug may also have activity against the following microorganisms:
Actinomyces sp., Bacillus anthracis, Bifidobacterium sp., Bordetella pertussis, Borrelia burgdorferi, Brucella sp., Burkholderia pseudomallei, Clostridium perfringens, Clostridium tetani, Corynebacterium diphtheriae, Erysipelothrix rhusiopathiae, Eubacterium sp., Haemophilus ducreyi, Helicobacter pylori, Lactobacillus sp., Listeria monocytogenes, Neisseria meningitidis, Nocardia brasiliensis, Peptococcus sp., Prevotella melaninogenica, Propionibacterium sp., Salmonella enteritidis, Salmonella sp., Salmonella typhi, Shigella sp., Streptococcus agalactiae (group B streptococci), Streptococcus dysgalactiae, Treponema pallidum, Vibrio cholerae

NOTE: Some organisms may not have been adequately studied during clinical trials; therefore, exclusion from this list does not necessarily negate the drug’s activity against the organism.

Route-Specific Administration

Oral Administration

NOTE: The ratio of amoxicillin; clavulanic acid is not equivalent in different formulations of Augmentin® (tablets, chewable tablets, extended-release tablets, and suspension). Therefore, except where noted, different dosage forms should not be interchanged.
All dosage forms: Administer dose at the start of a meal. Amoxicillin; clavulanic acid may be administered without regard to meals, however, oral absorption is enhanced when administered at the start of a light meal. Also, administration with food minimizes gastrointestinal irritation. Absorption is decreased when taken on an empty stomach.

Oral Solid Formulations

- Chewable tablets: Chew well before swallowing, do not swallow whole.
- Extended-release tablets: Swallow tablet whole. Do not crush or chew. Scored extended-release tablets are available for patients who have difficulty swallowing.

Oral Liquid Formulations

- Suspension: Shake well prior to each administration. Measure dosage with calibrated spoon, cup, or oral syringe.
- For infants < 3 months of age, the 125mg/5ml oral suspension is recommended by the manufacturer.
- The various suspensions of amoxicillin; clavulanic acid are not interchangeable due to differences in the amount of clavulanic acid potassium contained in each product.

Maximum Dosage Limits
Adults: Augmentin® tablets, chewable tablets, or suspension 1750 mg/day PO amoxicillin component; Augmentin® XR tablets 4000 mg/day PO amoxicillin component.
Geriatric: 1750 mg/day PO for most labeled indications; up to 3000 mg/day PO is recommended off-label for community-acquired pneumonia.
Adolescents: Augmentin® tablets, chewable tablets, or suspension 1750 mg/day PO amoxicillin component; Augmentin® XR tablets 4000 mg/day PO amoxicillin component.
Children: >= 40 kg: Augmentin® tablets, chewable tablets, or suspension 1750 mg/day PO amoxicillin component; Augmentin® XR tablets 4000 mg/day PO amoxicillin component. < 40 kg: Augmentin® chewable tablets or suspension 40 to 45 mg/kg/day PO amoxicillin component depending on formulation for most indications. Augmentin® ES suspension: 90 mg/kg/day PO amoxicillin component.
Infants: >= 3 months: Augmentin® tablets or suspension: 40—45 mg/kg/day PO amoxicillin component depending on formulation for most indications. Augmentin® ES suspension 90 mg/kg/day PO amoxicillin component. 2 months: Augmentin® 125 mg/5 ml suspension 30 mg/kg/day PO amoxicillin component; Augmentin® ES suspension: 90 mg/kg/day PO amoxicillin component has been recommended for the off-label treatment of acute otitis media.[33934] < 2 months: Augmentin® 125 mg/5 ml suspension 30 mg/kg/day PO amoxicillin component.

Maximum Dosage Limits continued

Neonates:

Augmentin® 125 mg/5 ml suspension 30 mg/kg/day PO amoxicillin component.

Patients with Hepatic Impairment Dosing

Dose amoxicillin; clavulanic acid with caution in those patients with pre-existing hepatic disease and monitor liver function during therapy. No specific dosage adjustment recommendations are available. The amoxicillin component is not appreciably metabolized in the liver and does not undergo biliary secretion.

Patients with Renal Impairment Dosing

Dosage adjustments are needed for amoxicillin, but clavulanic acid pharmacokinetics are not changed by the presence of renal impairment unless CrCl < 10 ml/min. No specific dosage adjustments for pediatric patients with renal impairment are available at this time; however, dosages should be adjusted. The manufacturer recommended dosage adjustments for adults are listed below.

CrCl > 30 ml/min:

No dosage adjustment needed.

CrCl 10 to 30 ml/min:

250 to 500 mg PO amoxicillin component every 12 hours, depending on the severity of the infection. Do not use the 875 mg-tablet strength. Augmentin® XR is contraindicated.

CrCl < 10 ml/min:

250 to 500 mg PO amoxicillin component every 24 hours, depending on the severity of the infection. Do not use the 875 mg-tablet strength. Augmentin® XR is contraindicated.

Intermittent hemodialysis

For adults, 250 to 500 mg PO amoxicillin component every 24 hours, depending on the severity of the infection. According to the manufacturer, a supplemental dose should be administered both during and at the end of a

dialysis session. Do not use the 875 mg tablet strength. Augmentin® XR is contraindicated.

Peritoneal dialysis

For those patients receiving continuous ambulatory peritoneal dialysis (CAPD), 250 to 500 mg PO amoxicillin component every 24 hours, depending on the severity of the infection. Do not use the 875 mg tablet strength. Augmentin® XR is contraindicated.

Contraindications/Precautions

Amoxicillin is a penicillin and should not be used in patients with a penicillin hypersensitivity. Amoxicillin; clavulanic acid should be used cautiously in patients with cephalosporin hypersensitivity or carbapenem hypersensitivity. These patients are more susceptible to hypersensitivity reactions during therapy with amoxicillin; the incidence of true cross-sensitivity has been estimated at roughly 3 to 5%. Patients with allergies or atopic conditions including asthma, eczema, hives (urticaria), or hay fever have a greater risk for hypersensitivity reactions to penicillins.

In clinical studies of amoxicillin; clavulanic acid (Augmentin® XR and other dosage forms) no overall differences in safety and effectiveness were observed between geriatric subjects and younger adult subjects, and other clinical experience has not reported differences in responses between the elderly and younger patients. A greater sensitivity of some older individuals cannot be ruled out. Because this drug is known to be substantially excreted by the kidney and because the elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function in these patients.

Amoxicillin; clavulanic acid extended-release tablets are contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min), renal failure, and in hemodialysis (dialysis) patients. In general, other formulations of amoxicillin; clavulanic acid should be used with caution in patients with renal impairment since the drug is eliminated via renal mechanisms. Adjust the dosage in patients with CrCl ≤ 30 ml/min and in patients with renal failure

(see Dosage). Dosage adjustments are also recommended for patients receiving dialysis (see Dosage).

Almost all antibacterial agents have been associated with pseudomembranous colitis (antibiotic-associated colitis) which may range in severity from mild to life-threatening. In the colon, overgrowth of Clostridia may exist when normal flora is altered subsequent to antibacterial administration. The toxin produced by Clostridium difficile is a primary cause of pseudomembranous colitis. It is known that systemic use of antibiotics predisposes patients to development of pseudomembranous colitis. Consideration should be given to the diagnosis of pseudomembranous colitis in patients presenting with diarrhea following antibacterial administration. Systemic antibiotics should be prescribed with caution to patients with inflammatory bowel disease such as ulcerative colitis or other GI disease. If diarrhea develops during therapy, the drug should be discontinued. Following diagnosis of pseudomembranous colitis, therapeutic measures should be instituted. In milder cases, the colitis may respond to discontinuation of the offending agent. In moderate to severe cases, fluids and electrolytes, protein supplementation, and treatment with an antibacterial effective against Clostridium difficile may be warranted. Products inhibiting peristalsis are contraindicated in this clinical situation. Practitioners should be aware that antibiotic-associated colitis has been observed to occur over two months or more following discontinuation of systemic antibiotic therapy; a careful medical history should be taken.

Amoxicillin; clavulanic acid has been used to treat infections in infants < 3 months of age, including neonates. However, dosages must be modified for these age groups compared to infants ≥ 3 months of age because of incompletely developed renal function (see Dosage). Certain dosage forms are not for use in small children; for example, the safety and effectiveness of amoxicillin; clavulanic acid extended-release tablets and regular tablets have not been established in pediatric patients weighing less

than 40 kg.[34356] Children less than 40 kg of body weight should be dosed using oral suspension or chewable tablets. Neonates and infants < 3 months should be dosed using the 125 mg/5 ml oral suspension for dosing only.

Amoxicillin; clavulanic acid is classified in FDA pregnancy risk category B. Animal data reveal no teratogenic effects; however, there are no adequate and well-controlled studies in pregnant women. While amoxicillin should be used with caution in pregnancy, penicillins are usually considered safe during pregnancy when clearly needed. The effects of amoxicillin; clavulanic acid on pregnant women or the fetus during labor and obstetric delivery are unknown; however, one study in women with premature rupture of fetal membranes reported that prophylactic therapy with amoxicillin; clavulanic acid may be associated with an increased risk of necrotizing enterocolitis in the neonate.[43198]

According to the manufacturer, amoxicillin; clavulanic acid should be used cautiously during breast-feeding.[43198] However, unless the infant is allergic to penicillins, breast-feeding is generally safe during maternal penicillin therapy. The American Academy of Pediatrics (AAP) considers amoxicillin a medication that is usually compatible with breast-feeding; however, amoxicillin; clavulanic acid has not been evaluated by the AAP.[27500] Amoxicillin; clavulanic acid is excreted in breast milk in small amounts. Penicillins may cause diarrhea (due to disruption of GI flora), candidiasis, and skin rash in breast-feeding infants. In a study assessing adverse events in breast-fed infants of mothers exposed to antibiotics, 22.3% (15/67) of infants experienced adverse events after exposure to amoxicillin; clavulanic acid. The adverse events included constipation, rash, diarrhea, irritability, and elevated liver enzymes. The rate of adverse events was positively correlated with the dose of amoxicillin; clavulanic acid.[45768]. The infant should be observed for potential effects. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect

related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

Amoxicillin; clavulanic acid chewable tablets contain phenylalanine in the amount of 2.1 mg per 200 mg tablet and 4.2 mg per 400 mg tablet. The 200 mg/5ml, 400 mg/5ml and 600 mg/5 ml oral suspensions of amoxicillin; clavulanic acid each contain 7 mg of phenylalanine per 5 ml. These formulations should be used cautiously in patients with phenylketonuria. Patients with phenylketonuria should be warned that these items contain phenylalanine. However, other amoxicillin; clavulanic acid formulations do not contain phenylalanine.

A false-positive reaction for glucose in the urine has been observed in patients receiving penicillins, such as amoxicillin; clavulanic acid, and using Benedict's solution, Fehling's solution, or Clinitest tablets for urine glucose testing. However, this reaction has not been observed with Tes-tape (glucose Enzymatic Test Strip, USP, Lilly) or Clinistix. Patients with diabetes mellitus who test their urine for glucose should use glucose tests based on enzymatic glucose oxidase reactions while on amoxicillin; clavulanic acid treatment.

Amoxicillin; clavulanic acid should be used with caution in those patients with lymphatic leukemia, because these patients may be more likely to develop a drug rash. Patients with an active viral infection such as CMV, viral respiratory infection, and especially mononucleosis have a high incidence of reported rashes to the penicillins. This drug does not treat viral infections (e.g., common cold). Prescribing amoxicillin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. Patients should be told to complete the full course of treatment, even if they feel better earlier.

Amoxicillin; clavulanic acid is contraindicated for use in any patient with a previous history of drug-

induced cholestasis, jaundice, or other hepatic dysfunction induced by this combination of drugs. Amoxicillin; clavulanic acid should be used with caution in those patients with pre-existing hepatic disease. Monitor liver function in these patients during therapy. The amoxicillin component is not appreciably metabolized in the liver and does not undergo biliary secretion. However, hepatic dysfunction due to amoxicillin; clavulanic acid has been reported on rare occasions; occasionally these reactions have been severe.

The administration of amoxicillin; clavulanic acid to patients currently receiving oral anticoagulant therapy may result in a prolonged prothrombin time. In patients receiving these treatments concurrently; closely monitor international normalized ratio (INR) and make dosage adjustments to anticoagulant therapy as needed. [34356]

Amoxicillin with Clavulanic Acid (Augmentin®) Specific Ocular Use

Adult dose 125-875 mg TID (q8h) x 7-10 day duration
Children 20-40 mg/kg TID (q8h) x 7-10 day duration

PCN allergy/ increased activity against amoxicillin resistant organisms

Example for use: peri-orbital infections such as pre-septal cellulitis, dacryocystitis or dacryoadenitis where in an adult 875 mg BID or 500 mg TID for 10 days would be prescribed or for a child as follows:

1. *Convert pounds to kilograms*
2. *Multiply kilograms by dosage recommendation (20 mg/kg for milder infections verses 40 mg/kg for more serious infections)*
3. *Divide daily mg total by number of doses per day*
4. *Choose from available manufactured doses*
5. *Write Rx*

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Azithromycin

Drug Description

Azithromycin is a semisynthetic antibiotic belonging to the macrolide subgroup of azalides and is similar in structure to erythromycin. Although azithromycin is significantly more expensive, it can be dosed once daily and produces less GI intolerance than does erythromycin. An apparent advantage over erythromycin is that azithromycin reaches higher intracellular concentrations, thus increasing its efficacy and duration of action. These advantages are demonstrated in studies that show that single doses of azithromycin are effective for the treatment of STDs due to chlamydia[23529] and gonorrhea.[24204] While azithromycin has been studied in regimens for H. pylori eradication and some studies show efficacy, the azithromycin-containing regimens have not been as effective as regimens containing clarithromycin in terms of eradication rates; macrolide cross-resistance is also an issue. Azithromycin was initially approved by the FDA in November 1991. An oral suspension was introduced in April 1995 and, in late 1995, was approved for treatment of pediatric otitis media and pharyngitis. In mid-1996, azithromycin was approved for Mycobacterium avium complex (MAC) prophylaxis in patients with advanced HIV disease. An intravenous dosage form is also available for initial treatment of community-acquired pneumonia (CAP) and pelvic inflammatory disease. The oral suspension was subsequently approved for community-acquired pneumonia in children in May 2002. On January 15, 2004, Zithromax® was approved as a 3-day treatment for acute bacterial sinusitis. An extended-release oral suspension (Zmax®) was approved in June 2005. An ophthalmic solution (AzaSite™, azithromycin 1%) was approved for the treatment of bacterial conjunctivitis in April 2007.

Classifications:

- | | |
|------------------------------------|--------------|
| • Anti-infective Agents Macrolides | • Zmax® |
| • Ophthalmic Macrolides | • Zithromax® |
| • Brand Names | • Azasite® |

Mechanism of Action

Mechanism of Action: Azithromycin inhibits protein synthesis in bacterial cells by binding to the 50 S subunit of bacterial ribosomes. Action is generally bacteriostatic but can be bactericidal in high concentrations or against susceptible organisms. Azithromycin is more active against gram-negative organisms but has less activity against streptococci and staphylococci than does erythromycin. In addition to chlamydial infections, it is also useful for treating mild to moderate upper respiratory infections and mild community-acquired pneumonia. It is not clear if azithromycin, like erythromycin, is effective in the treatment of diabetic gastroparesis.

Indications

Per the manufacturer, this drug has been shown to be active against most strains of the following microorganisms either in vitro and/or in clinical infections: Bacteroides bivius, Bordetella pertussis, Borrelia burgdorferi, Campylobacter jejuni, CDC coryneform group G, Chlamydia trachomatis, Chlamydophila pneumoniae, Clostridium perfringens, Haemophilus ducreyi, Haemophilus influenzae (beta-lactamase negative), Haemophilus influenzae (beta-lactamase positive), Legionella pneumophila, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium intracellulare, Mycoplasma hominis, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Peptostreptococcus sp., Prevotella bivia, Staphylococcus aureus (MSSA), Streptococcus agalactiae (group B streptococci), Streptococcus mitis, Streptococcus pneumoniae, Streptococcus pyogenes (group A beta-hemolytic streptococci), Streptococcus sp., Treponema pallidum, Ureaplasma urealyticum, Viridans streptococci

NOTE: The safety and effectiveness in treating clinical infections due to organisms with in vitro data only have not been established in adequate and well-controlled clinical trials.

This drug may also have activity against the following microorganisms: Bacillus anthracis, Gardnerella vaginalis, Helicobacter pylori,

Klebsiella granulomatis, Mycoplasma genitalium, Rickettsia tsutsugamushi, Salmonella typhi, Staphylococcus epidermidis, Streptococcus sp. (Group C), Streptococcus sp. (Group F), Streptococcus sp. (Group G), Toxoplasma gondii, Vibrio cholerae NOTE: Some organisms may not have been adequately studied during clinical trials; therefore, exclusion from this list does not necessarily negate the drug's activity against the organism.

Route-Specific Administration

Azithromycin is administered orally.

Oral Administration - Oral Solid Formulations

Tablets: May be taken with or without food. However, increased tolerability has been observed when the tablets are taken with food.

Oral Liquid Formulations - Oral suspension (Zithromax® 1 gram single-dose packet):

Review the manufacturer reconstitution instructions for the particular product and package size. Do not use for administration of doses other than 1 gram. Zithromax® for oral suspension (1 gram single dose packet) may be taken with or without food. Mix the entire contents of the packet in 60 ml (approximately two ounces) of water. Administer the entire contents immediately, then add an additional 60 ml of water, mix and administer to assure complete administration of the dosage.[43975]

Oral suspension (immediate-release, bottles for reconstitution):

Review the manufacturer reconstitution instructions for the particular product and package size. Zithromax for oral suspension (100 mg/5ml or 200 mg/5 ml strengths) may be taken with or without food. Add water in two portions and shake well after each addition. Storage: After mixing, store suspension at 5 to 30 degrees C (41 to 86 degrees F) and use within 10 days. Administer using a calibrated measuring device.[28855]

Oral suspension (extended release, bottles for reconstitution):

Review the manufacturer reconstitution instructions for the particular product and package size. Zmax®

extended release oral suspension (2 grams azithromycin) should be taken as a single dose at least one hour before or two hours following a meal. If a patient vomits within five minutes of the dose, the manufacturer recommends additional antibiotic treatment due to minimal absorption of the azithromycin dose. If a patient vomits between five to 60 minutes following the dose, consider alternate therapy. In patients with normal gastric emptying, if vomiting occurs $\geq$ 60 minutes after the dose, no additional antibiotic therapy is warranted. In patients with delayed gastric emptying, consider alternative therapy. Constitute with 60 ml of water, replace cap, and shake bottle well.

• *Storage: After mixing, store suspension at 15 to 30 degrees C (59 to 86 degrees F) and use within 12 hours.[34473]*

Maximum Dosage Limits
Adults: 2 g/day PO when given as single dose; 500 mg/day IV infusion.
Geriatric: 2 g/day PO when given as single dose; 500 mg/day IV infusion.
Adolescents: $\geq$ 16 years: 2 g/day PO when given as single dose; 500 mg/day IV infusion. < 16 years: Immediate-release oral suspension or tablets, dosing is individualized to weight, indication, and regimen; extended-release oral suspension, 60 mg/kg single dose (maximum 2 g) PO; up to 10 mg/kg/dose, not to exceed 500 mg, IV has been used off-label for community acquired pneumonia.
Children: Immediate-release oral suspension, dosing is individualized to weight, indication, and regimen; extended-release oral suspension, 60 mg/kg single dose (maximum 2 g) PO; up to 10 mg/kg/dose, not to exceed 500 mg, IV has been used off-label for community acquired pneumonia.

Maximum Dosage Limits continued

Infants:

Immediate-release oral suspension, dosage is individualized to weight and indication for use; extended-release oral suspension, 60 mg/kg single dose PO.

3 to 5 months: Up to 10 mg/kg/dose IV or PO with immediate-release oral suspension has been used off-label for community acquired pneumonia.

< 3 months: Safety and efficacy have not been established.

Patients with Hepatic Impairment Dosing

No dosage adjustment recommendations can be made; azithromycin has not been studied in patients with impaired hepatic function.

Patients with Renal Impairment Dosing

CrCl > 80 ml/min: No dosage adjustment is needed. CrCl 10 to 80 ml/min: No dosage adjustment is recommended. CrCl < 10 ml/min: No dosage adjustment is recommended; however, the manufacturer recommends caution in patients with severe renal impairment since mean AUC is increased roughly 35%.

†Off-label indication

Precautions/Contraindications

Oral therapy with azithromycin is not recommended in patients with serious infections (e.g., pneumonia) who are considered to be inappropriate candidates for oral therapy. This includes patients with moderate or severe illness or risk factors such as patients with cystic fibrosis, with nosocomially acquired infections, with known or suspected bacteremia, who require hospitalization, who are elderly or debilitated, or who have significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Azithromycin does not treat viral infection (e.g., common cold). Prescribing azithromycin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication

is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. Patients should be told to complete the full course of treatment, even if they feel better earlier.

Azithromycin can cause rare, but serious allergic reactions, including angioedema and anaphylaxis. There is a risk of cross sensitivity with other macrolide antibiotics. Some patients have a recurrence of allergic symptoms once symptomatic treatment is withdrawn, even though azithromycin therapy is not reinstated. Patients with a known azithromycin or macrolide hypersensitivity should not receive azithromycin.

Since it is primarily eliminated via the liver, systemically administered azithromycin should be used with caution in patients who have hepatic disease. In addition, abnormal hepatic function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported with use, including cases that have resulted in death. Monitor liver-function tests in patients receiving systemic azithromycin. Discontinue treatment immediately if signs and symptoms of hepatitis and liver dysfunction occur. Also, systemic azithromycin is contraindicated in patients with a history of jaundice and/or hepatic dysfunction associated with the prior use of azithromycin. [28855]

Safe use of systemically- administered azithromycin in patients with severe renal impairment has not been determined; limited data are available. Azithromycin should be used cautiously in patients with preexisting severe renal impairment or renal failure (CrCl < 10 ml/min).

Almost all antibacterial agents have been associated with pseudomembranous colitis (antibiotic-associated colitis) which may range in severity from mild to life-threatening.

In the colon, overgrowth of Clostridia may exist when normal flora is altered subsequent to antibacterial administration. The toxin produced by Clostridium difficile is a primary cause of pseudomembranous colitis. It is known that

systemic use of antibiotics predisposes patients to development of pseudomembranous colitis. Consideration should be given to the diagnosis of pseudomembranous colitis in patients presenting with diarrhea following antibacterial administration. Systemic antibiotics should be prescribed with caution to patients with inflammatory bowel disease such as ulcerative colitis or other GI disease. If diarrhea develops during therapy, the drug should be discontinued. Following diagnosis of pseudomembranous colitis, therapeutic measures should be instituted. In milder cases, the colitis may respond to discontinuation of the offending agent. In moderate to severe cases, fluids and electrolytes, protein supplementation, and treatment with an antibacterial effective against *Clostridium difficile* may be warranted. Products inhibiting peristalsis are contraindicated in this clinical situation. Practitioners should be aware that antibiotic-associated colitis has been observed to occur over two months or more following discontinuation of systemic antibiotic therapy; a careful medical history should be taken.

Data from a cohort study has associated azithromycin with an increased risk of cardiovascular death. The study included persons receiving prescriptions for azithromycin (n=347,795), amoxicillin (n=1,348,672), ciprofloxacin (n=264,626), levofloxacin (n=193,906), and matched persons receiving no antibiotics (n=1,391,180). Analysis of the data found those persons receiving a five-day course of azithromycin had significantly greater risk of cardiovascular death than persons not treated with antibiotics (HR: 2.88; 95% CI: 1.79 to 4.63; P<0.001), persons treated with five days of amoxicillin (HR: 2.49; 95% CI: 1.38 to 4.50; P=0.002), and persons in the first five days of ciprofloxacin therapy (HR: 3.49; 95% CI: 1.32 to 9.26; P=0.01); mortality rate did not differ from levofloxacin.[50182] In addition, cases of torsade de pointes (TdP) have been noted during azithromycin post-marketing surveillance. **Based on these data, the FDA has issued a Drug Safety Communication to alert health care professionals that azithromycin is associated with QT prolongation, imparting a risk of**

developing fatal cardiac arrhythmias such as TdP.[50183] Although this Drug Safety Communication focused on azithromycin, the FDA reminds prescribers that QT prolongation has also been associated with other macrolide and non-macrolide antibiotics, including fluoroquinolones. Health care providers should assess the risks and benefits of prescribing these drugs to at-risk groups, including patients with clinically significant bradycardia or ongoing proarrhythmic conditions, such as uncorrected hypokalemia or hypomagnesemia; patients with known prolongation of the QT interval or a history of TdP, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure; patients receiving other QT prolonging medications. Elderly patients may be more susceptible to drug-associated effects on the QT interval.[34473] [43974] [28855] [53538]

In multiple-dose clinical trials of oral and intravenous azithromycin, no overall difference in safety and effectiveness was observed between geriatric subjects (≥ 65 years) and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Health care providers are advised that elderly patients may be more susceptible to drug-associated effects on the QT interval.[28855]

Azithromycin is classified as FDA pregnancy risk category B. Animal data reveal no teratogenic effects. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Azithromycin has not been studied for use during labor and obstetric delivery. Treatment should be given only if clearly needed.[28855]

According to the manufacturer, azithromycin should be used cautiously in women who are breast-feeding.[28855] A prospective observational study assessing the safety of macrolide antibiotics during lactation found that

12.7% (n = 55) of babies exposed to macrolides via breast milk experienced adverse events including rash, diarrhea, loss of appetite, and somnolence. The adverse event rate was similar to that seen in babies in a control group whose mothers were treated with amoxicillin (8.3%). Only 10 mothers in the study received azithromycin, six received clarithromycin, two received erythromycin, and the remainder were treated with roxythromycin.[45767] A population based cohort study found that babies diagnosed with infantile hypertrophic pyloric stenosis were 2.3 to 3 times more likely to have been exposed to a macrolide antibiotic through breast milk during the first 90 days of life than babies not exposed during that same time period. The study did not specify which antibiotic the mothers of affected babies were prescribed; however, the majority of macrolide prescriptions were for erythromycin (72%), with 7% for azithromycin and 1.7% for clarithromycin.[45779] The American Academy of Pediatric considers erythromycin to be a medication that is usually compatible with breast-feeding; azithromycin and clarithromycin have not been evaluated by the AAP.[27500] Consider the benefits of breast-feeding, the risk of potential drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding baby experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

Oral azithromycin has been used safely and effectively in children and infants six months of age and older. However, the 1 gram oral single dose suspension is not for use in pediatric patients. Safety and efficacy of the azithromycin intravenous formulation have not been established in neonates, infants, children, or adolescents younger than 16 years of age. The safety and effectiveness of azithromycin ophthalmic solution in infants below one year of age have not been established.

Direct sunlight (UV) exposure should be minimized during therapy with systemic azithromycin. Photosensitivity has been reported as an allergic reaction to azithromycin.

Azithromycin should be discontinued at the first sign of erythema.

Zithromax (azithromycin for injection) contains a total of 4.96 mEq (114 mg) of sodium per vial. At the usual recommended doses, patients would receive 4.96 mEq (114 mg) of sodium. The sodium amounts should be considered in patients with requirements for sodium restriction or blunted natriuresis to salt loading (i.e., cardiac disease, elderly, or hypertension).

Patients should be advised not to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis. Thus, patients who wear contact lenses should avoid wearing them while being treated with azithromycin ophthalmic solution (Azasite) for an ocular infection.

Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving systemic azithromycin therapy.

Adverse Reactions

During clinical trials of azithromycin, adverse reactions were reported as mild to moderate in severity and were reversible upon discontinuation of the drug. **The most common adverse reactions in patients receiving systemic regimens of azithromycin were gastrointestinal-related, which tended to be more frequent in the single-dose oral regimens in adults and higher doses in pediatrics.** Among the most commonly reported gastrointestinal adverse events were diarrhea/ loose stools (4 to 12% of adults; 1.8 to 10% of pediatric patients), nausea (3 to 18% adults; 0.4 to 4% pediatrics), vomiting ($\leq$ 1 to 7% adults; 1.1 to 14% pediatrics), abdominal pain (1.9 to 7% adults; 1.2 to 4% pediatrics), and anorexia (1.9% adults with the IV formulations; $\leq$ 2% pediatrics). Adverse GI effects occurring in $\leq$ 1% of adult and pediatric patients included constipation, dyspepsia, and flatulence; in adults melena, nephritis, and mucositis were also reported in $\leq$ 1%; in pediatrics enteritis and gastritis were reported in $\leq$ 1%, dysuria was noted in $<$ 1%. Elevated BUN (azotemia) and elevated creatinine

occurred in < 1% to ≥ 1% of patients, with elevated creatinine reported in 4—6% of patients receiving IV therapy. Post-marketing adverse gastrointestinal and genitourinary reactions have also included acute renal failure (unspecified), interstitial nephritis, pancreatitis, pyloric stenosis, vomiting/diarrhea rarely resulting in dehydration, and rare reports of tongue discoloration. Laboratory abnormalities have been noted with systemic azithromycin use include decreased bicarbonate (≥ 1%), increased bicarbonate (< 1%), elevated potassium (≥ 1%), decreased potassium (< 1%), decreased sodium (< 1%), elevated blood glucose (≥ 1%), decreased blood glucose (< 1% to ≥ 1%), elevated phosphokinase (1—2%), elevated serum alkaline phosphatase (< 1%), elevated LDH (< 1% to 3%), and elevated phosphate (< 1%).[28855] [34473] [43974] [43975]

In clinical trials, elevated hepatic enzymes (ALT, AST) occurred in 4 to 6% of patients receiving intravenous azithromycin. Elevations of ALT (SGPT), GGT, and AST (SGOT) occurred with an incidence of 1 to 2% in patients receiving oral therapy. Cholestasis with jaundice has been reported in ≤ 1% of patients. Hyperbilirubinemia was reported in < 1 to 3% of patients. Post marketing reports indicate that systemic azithromycin has been associated with abnormal liver function including hepatitis as well as rare cases of hepatic necrosis and hepatic failure, some of which have resulted in death.[28855] [34473] [43974] [43975]

Azithromycin systemic therapy can disturb the normal bacterial flora. Antibiotic interference with the normal flora of the colon during systemic therapy may allow an overgrowth of clostridia. It has been established that a toxin produced by *Clostridium difficile* is a primary cause of 'antibiotic-associated colitis.' The possibility of pseudomembranous colitis should be considered in patients presenting with a severe watery diarrhea. Pseudomembranous colitis has occurred rarely with azithromycin. More commonly, disturbance of the bacterial flora causes an overgrowth of *Candida* species. Oral candidiasis (thrush), vaginal candidiasis

(moniliasis) (< 1%), vaginitis (< 1% to 2.8%), fungal superinfection (< 1%), and fungal dermatitis (< 1%) have been reported for both oral and intravenous dosage forms.[28855] [34473] [43974] [43975]

Hematologic adverse reactions have been reported with systemic azithromycin therapy. In children, anemia and leukopenia have occurred in ≤ 1% of patients. Decreased hemoglobin, hematocrit, lymphocytes (lymphopenia), and neutrophils as well as increased platelet counts, lymphocytes (lymphocytosis), neutrophils, and eosinophils (eosinophilia) have been reported in > 1% of patients. Leukopenia, neutropenia, decreased platelet counts, elevated monocytes, and elevated basophils have been reported in < 1% of adults. Thrombocytopenia and mild neutropenia have been reported during post marketing surveillance.[28855] [34473] [43974] [43975]

Respiratory adverse reactions have been reported in ≤ 1% of pediatric patients receiving azithromycin. These adverse reactions have included asthma, bronchitis, cough, pharyngitis, pleural effusion, and rhinitis. Dyspnea has been noted in 1.9% of patients receiving the intravenous formulation of azithromycin and in ≤ 1% of pediatric patients.[28855] [34473] [43974] [43975] Nasal congestion and sinusitis have been reported in < 1% of patients receiving the ophthalmic preparation of azithromycin.[43976]

Injection site reaction is associated with intravenous azithromycin. Approximately 12% of patients treated for pneumonia experienced a side effect related to the intravenous infusion; most common were pain at the injection site (6.5%) and local inflammation or erythema (3.1%). Application site reactions occurred in 1.9% of patients receiving infusions for pelvic inflammatory disease.[43974]

Fatigue, malaise, and pain (unspecified) have been reported in ≤ 1% of patients receiving systemic azithromycin. Fever was noted in < 1% to 2.1% of patients. Chills and flu-like syndrome were reported in < 1% of pediatric patients in

trials. Paresthesias were noted in post-marketing reports. Asthenia has been reported in < 1% of patients who received the 2 gram oral dose. [28855] [34473] [43974] [43975]

Central nervous system adverse reactions were reported in association with systemic azithromycin. In patients receiving systemic formulations of azithromycin, vertigo ($\leq 1\%$), headache ($\leq 3\%$), dizziness ($\leq 3.9\%$), and somnolence (drowsiness, $\leq 1\%$ adult and pediatric patients) were reported. Adverse events reported in $\leq 1\%$ of pediatric patients include agitation, hyperkinesia, insomnia, and nervousness. In pediatric patients receiving the extended-release suspension, < 1% of patients experienced emotional lability, hostility, hyperkinesia, insomnia, and irritability. Post-marketing CNS effects have also included convulsions (seizures), hyperactivity, nervousness, agitation, and syncope. Post-marketing psychiatric adverse reactions include aggression and anxiety.[28855] [34473] [43974] [43975]

Cardiovascular adverse reactions associated with systemic azithromycin therapy that have been reported in $\leq 1\%$ of patients include chest pain (unspecified) and palpitations. Although uncommon, these are potentially serious adverse reactions. In post-marketing experience, there have been reports of arrhythmias including ventricular tachycardia, hypotension, and rarely QT prolongation and torsade de pointes.[28855] [34473] [43974] [43975]

Conjunctivitis was reported in $\leq 1\%$ of patients receiving systemic azithromycin. Taste perversion (dysgeusia) was reported in $\leq 1\%$ of patients receiving systemic azithromycin and in < 1% of patients using the ophthalmic preparation. Post-marketing reports for azithromycin have included cases of dysosmia (smell perversion) and/or anosmia (loss of smell), and hearing disturbances including hearing loss, deafness and/or tinnitus. [28855] [34473] [43974] [43975] [43976]

Dermatological or hypersensitivity-related adverse reactions have been reported with

azithromycin therapy. Rash (unspecified) has been reported in $\leq 1\%$ of adult patients receiving oral therapy, $\leq 1\%$ to 5% of pediatric patients, 1.9% of patients receiving IV therapy, and in < 1% of patients receiving ophthalmic therapy. Other adverse reactions that have been reported in $\leq 1\%$ of adults and/or pediatric patients include pruritus (1.9% of IV patients), photosensitivity, urticaria, bronchospasm, angioedema, diaphoresis, and vesicular rash. Eczema vaccinatum (atopic dermatitis) was reported in $\leq 1\%$ of pediatric patients, while dermatitis was noted in 2% of pediatric patients. Post-marketing reports of arthralgia and edema have been noted. Rare serious skin reactions including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. Azithromycin therapy should be withdrawn if there are signs and symptoms of an allergic reaction. Some patients have a recurrence of allergic symptoms once symptomatic treatment is withdrawn, even though azithromycin therapy is not reinstated. Correlation between the long tissue half-life and duration of allergic symptoms has not yet been determined. Anaphylaxis (anaphylactoid reactions, anaphylactic shock) have been rarely reported. Other adverse events reported in < 1% of patients using the ophthalmic solution include contact dermatitis, hives, and periocular swelling. [28855] [34473] [43974] [43975] [43976]

Azithromycin (systemic therapy) has been associated with acute generalized exanthematous pustulosis (AGEP). The nonfollicular, pustular, erythematous rash starts suddenly, is associated with fever above 38 degrees C, and is distinct from pustular psoriasis, although biopsy results in each reveal spongiform subcorneal pustules. Drugs are the main cause of AGEP. A period of 2 to 3 weeks after an inciting drug exposure appears necessary for a first episode of AGEP. Unintentional reexposure may cause a second episode within two days. Clinical presentation is diverse with cutaneous lesions beyond erythema and pustules present in half of the cases. For example, bullous lesions, edema, purpura, pruritus, and mucosal erosions are possible. The mean duration of

the pustules is 9.7 days followed by an annular desquamation, as long as the causative drug or factor is discontinued. The physiopathological mechanisms of AGEF have not been determined but the pathological criteria of edema, leukocytoclastic vasculitis, eosinophil exocytosis, and keratinocyte focal necrosis are distinctive. Pustule confluence or very small pustules may lead a clinician to make an incorrect diagnosis of TEN, of drug-induced erythroderma, or of staphylococcal scalded skin syndrome.[27736]

Ocular irritation was the most frequently reported adverse reaction after ophthalmic administration of azithromycin and occurred in approximately 1 to 2% of patients. Other reported adverse reactions occurring in < 1% of patients included blurred vision, corneal erosion, ocular discharge, ocular pain (burning, stinging, and irritation upon instillation), ocular itching, punctate keratitis, visual acuity reduction, and xerophthalmia. [43976]

The exacerbation of myasthenia gravis symptoms as well as the new onset of myasthenic syndrome have been reported with systemic azithromycin therapy. While rare, this side effect has been reported with other macrolide antibacterial agents.[28855] [34473] [43974] [43975] Laboratory abnormalities have been noted

with systemic azithromycin use. These include decreased bicarbonate ($\geq 1\%$), increased bicarbonate ($< 1\%$), hyperkalemia ($\geq 1\%$), hypokalemia ($< 1\%$), hyponatremia ($< 1\%$), hyperglycemia ($\geq 1\%$), hypoglycemia ($< 1\%$ to $\geq 1\%$), elevated phosphokinase (1—2%), elevated serum alkaline phosphatase ($< 1\%$), elevated LDH ($< 1\%$ to 3%), and elevated phosphate ($< 1\%$).[28855] [34473] [43974] [43975]

Azithromycin (Zithromax) Specific Ocular Use

Adult dose 1 g either as a single dose or once weekly for up to three weeks, or

Two 250-mg tablets (a total of 500 mg) on the first day and one 250-mg tablet once daily for the next four days or for children 10 mg/kg as a single dose on the first day, followed by 5 mg/kg/day on days two to five.

Example for use: Conjunctivitis and trachoma due to *Chlamydia trachomatis*

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Erythromycin

Drug Description

Erythromycin is a macrolide antibiotic produced by *Streptomyces erythraeus* and was the first of several macrolide antibiotics now on the market. Although erythromycin is active against many microbes, its clinical applications are relatively few. Erythromycin is commonly used in the treatment of Legionnaire's disease and *Mycoplasma pneumoniae* pneumonia, and as an alternative to beta-lactam antibiotics in patients who are allergic. Erythromycin may have benefits in hypomotility conditions, such as diabetic gastroparesis, due to its actions of increased gastric motility and emptying. Erythromycin was approved by the FDA in 1952 and is available in parenteral, topical, and many oral dosage forms.

Classifications:
• Anti-infective Agents Macrolides • Ophthalmic Macrolides Topical Macrolides • Dermatological Agents Topical Anti-infectives Topical Macrolides • Ophthalmic Agents Ophthalmic Anti-infectives • Ophthalmic Macrolides

Mechanism of Action

Erythromycin binds to the 50 S ribosomal subunit, inhibiting bacterial protein synthesis. It is effective against a wide range of microorganisms and, like other antibiotics that inhibit protein synthesis, is mainly bacteriostatic. Activity against gram-positive organisms generally is greater than against gram-negative organisms due to its superior penetration into gram-positive organisms.

Erythromycin has actions that make it useful outside of the infectious disease field. It mimics the effect of the gastrointestinal polypeptide motilin on gastrointestinal motility. This action is probably due to agonism at the motilin receptors. Motilin receptors are found mainly in the gastric antrum and proximal duodenum. The physiologic action produced is an increased motility during the interdigestive (between-meal) period, without affecting postprandial motility. Erythromycin does not affect either dopamine receptors or increase acetylcholine concentrations in the gut. Tachyphylaxis can result from motilin receptor downregulation.[34223]

Per the manufacturer, this drug has been shown to be active against most strains of the following microorganisms either in vitro and/or in clinical infections:

• <i>Bordetella pertussis</i> • <i>Chlamydia</i> sp. • <i>Chlamydia trachomatis</i> • <i>Corynebacterium diphtheria</i> • <i>Corynebacterium minutissimum</i> • <i>Corynebacterium</i> sp. • <i>Entamoeba histolytica</i> • <i>Haemophilus influenzae</i> (beta-lactamase negative)	• <i>Haemophilus influenzae</i> (beta-lactamase positive) • <i>Helicobacter pylori</i> • <i>Legionella pneumophila</i> • <i>Listeria monocytogenes</i> • <i>Moraxella catarrhalis</i> • <i>Mycobacterium kansasii</i> • <i>Mycobacterium scrofulaceum</i>
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• <i>Mycoplasma pneumonia</i> • <i>Neisseria gonorrhoeae</i> • <i>Propionibacterium acnes</i> • <i>Staphylococcus aureus</i> (MSSA) • <i>Staphylococcus</i> sp. • <i>Streptococcus agalactiae</i> (group B streptococci)	• <i>Streptococcus pneumonia</i> • <i>Streptococcus pyogenes</i> (group A beta-hemolytic streptococci) • <i>Streptococcus</i> sp. • <i>Treponema pallidum</i> • <i>Ureaplasma urealyticum</i> • <i>Viridans streptococci</i>
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NOTE: The safety and effectiveness in treating clinical infections due to organisms with in vitro data only have not been established in adequate and well-controlled clinical trials.

This drug may also have activity against the following microorganisms:

• <i>Actinomyces</i> sp. • <i>Bacillus anthracis</i> • <i>Borrelia burgdorferi</i> • <i>Brucella</i> sp. • <i>Campylobacter jejuni</i> • <i>Clostridium perfringens</i> • <i>Clostridium</i> sp. • <i>Erysipelothrix</i> sp. • <i>Haemophilus ducreyi</i>	• <i>Klebsiella granulomatis</i> • <i>Neisseria meningitidis</i> • <i>Neisseria</i> sp. • <i>Nocardia asteroides</i> • <i>Pasteurella</i> sp. • <i>Peptococcus</i> sp. • <i>Peptostreptococcus</i> sp. • <i>Rickettsia</i> sp. • <i>Vibrio cholera</i>
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NOTE: Some organisms may not have been adequately studied during clinical trials; therefore, exclusion from this list does not necessarily negate the drug's activity against the organism.

Maximum Dosage Limits
Adults: 4 g erythromycin base/day PO.
Elderly: 4 g erythromycin base/day PO.
Adolescents: 4 g erythromycin base/day PO.
Children: 2 g erythromycin base/day PO.

Patients with Hepatic Impairment Dosing

Erythromycin should be used with caution in patients with impaired hepatic function. Although specific dosage guidelines are not available, a reduced dosage may be necessary.

Patients with Renal Impairment Dosing

No dosage adjustment needed.

Route-Specific Administration

Oral Administration

Administer at least one hour before or two hours after meals. If GI irritation occurs, may be administered with food. Administer each dose with a full glass of water; do not administer with fruit juices. Administer pediatric erythromycin ethylsuccinate with infant formula to enhance absorption and reduce GI irritation.

Oral Solid Formulations

- *Chewable tablets: Tablets should be chewed or crushed; do not swallow whole.*
- *Delayed-release tablets or capsules: Swallow whole; do not crush, chew, or open.*
- *Enteric-coated tablets: May be administered without regard to meals.*

Oral Liquid Formulations

*Shake well before administration.[48677] [43258]
Administer using a calibrated measuring device.*

Reconstitution

Review the manufacturer reconstitution instructions for the particular product and package size. Add water in two portions and shake well after each addition. Storage: Store reconstituted suspension in refrigerator. Length of stability depends on the product; consult specific manufacturer's recommendations.[48677] [43258]

Contraindications/Precautions

Antibiotic therapy can result in superinfection or suprainfection with non susceptible organisms. Overgrowth of *Candida* can occur with erythromycin therapy. Patients should be monitored closely during therapy.

Erythromycin does not treat viral infection (e.g.,

common cold). Prescribing erythromycin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. Patients should be told to complete the full course of treatment, even if they feel better earlier.

Patients who have shown macrolide hypersensitivity or sensitivity to any macrolide antibiotic should not be given erythromycin. Erythromycin can cause rare, but serious allergic reactions, including angioedema and anaphylaxis. There is a risk of cross sensitivity with other macrolide antibiotics.

Erythromycin is excreted mainly by the liver. Patients with impaired hepatic or biliary function should receive erythromycin with caution. Hepatic function should be monitored in patients receiving prolonged treatment with erythromycin. The estolate salt of erythromycin should not be used in patients with hepatic disease because of the potential for hepatotoxicity (see Adverse Reactions).

Almost all antibacterial agents, including erythromycin, have been associated with pseudomembranous colitis (antibiotic-associated colitis) which may range in severity from mild to life-threatening. In the colon, overgrowth of *Clostridia* may exist when normal flora is altered subsequent to antibacterial administration. The toxin produced by *Clostridium difficile* is a primary cause of pseudomembranous colitis. It is known that systemic use of antibiotics predisposes patients to development of pseudomembranous colitis. Consideration should be given to the diagnosis of pseudomembranous colitis in patients presenting with diarrhea following antibacterial administration. Erythromycin should be prescribed with caution to patients with inflammatory bowel disease such as ulcerative colitis or other GI disease. If diarrhea develops during therapy, the drug should be discontinued. Following diagnosis of pseudomembranous colitis, therapeutic measures should be instituted. In milder cases, the colitis may respond to

discontinuation of the offending agent. In moderate to severe cases, fluids and electrolytes, protein supplementation, and treatment with an antibacterial effective against *Clostridium difficile* may be warranted. Products inhibiting peristalsis are contraindicated in this clinical situation. Practitioners should be aware that antibiotic-associated colitis has been observed to occur over two months or more following discontinuation of systemic antibiotic therapy; a careful medical history should be taken.

Erythromycin is classified in FDA pregnancy category B.[43258] Data available from human use during pregnancy do not support an association with erythromycin use and congenital malformations. Erythromycin crosses the placenta, but in low concentrations. One salt form, erythromycin estolate, has been observed to produce hepatotoxicity in pregnant patients. Roughly 10% of pregnant women treated with erythromycin estolate have abnormal, elevated hepatic enzymes during treatment. In most cases, the transaminases return to normal levels upon discontinuation of therapy. When pregnant women are treated with erythromycin, a formulation other than the estolate salt is recommended.

According to the manufacturer, erythromycin should be used with caution in breast-feeding mothers because it is excreted into breast milk.[43258] A prospective observational study assessing the safety of macrolide antibiotics during lactation found that 12.7% (n = 55) of babies exposed to macrolides via breast milk experienced adverse events including rash, diarrhea, loss of appetite, and somnolence. The adverse event rate was similar to that seen in babies in a control group whose mothers were treated with amoxicillin (8.3%). Only two mothers in the study received erythromycin, 10 received azithromycin, six received clarithromycin, and the remainder were treated with roxythromycin. [45767] A population based cohort study found that babies diagnosed with infantile hypertrophic pyloric stenosis were 2.3 to 3 times more likely to have been exposed to a macrolide antibiotic through breast milk during the first 90 days of

life than babies not exposed during that same time period. The study did not specify which antibiotic the mothers of affected babies were prescribed; however, the majority of macrolide prescriptions were for erythromycin (72%), with 7% for azithromycin and 1.7% for clarithromycin. [45779] The American Academy of Pediatrics (AAP) considers erythromycin to be a medication that is usually compatible with breast-feeding; azithromycin and clarithromycin have not been evaluated by the AAP. [27500] Consider the benefits of breast-feeding, the risk of potential drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding baby experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

Patients with hearing impairment should use erythromycin with caution. Erythromycin can rarely cause reversible loss of hearing and patients with preexisting hearing impairment may be at greater risk. Geriatric patients, especially those with renal or hepatic function impairment, may be at increased risk for developing hearing loss when doses of erythromycin lactobionate 4 g/day IV or higher are given.

There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. One manufacturer describes a cohort of 157 newborns who were given erythromycin for pertussis prophylaxis, seven neonates (5%) developed symptoms of non-bilious vomiting or irritability with feeding and were subsequently diagnosed as having IHPS requiring surgical pyloromyotomy. A possible dose-response effect was described with an absolute risk of IHPS of 5.1% for infants who took erythromycin for 8-14 days and 10% for infants who took erythromycin for 15-21 days. Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or neonatal *Chlamydia trachomatis* infections), the benefit of erythromycin therapy needs to be weighed against the potential risk of developing IHPS. Parents should be informed

to contact their physician if vomiting or irritability with feeding occurs. Many formulations of erythromycin lactobionate injection contain benzyl alcohol as a preservative. These preparations containing benzyl alcohol should be avoided when possible in neonates because benzyl alcohol has been associated with 'gasping syndrome', a potentially fatal condition. Benzyl alcohol may also cause allergic reactions, therefore, parenteral erythromycin formulations should not be used in patients with benzyl alcohol hypersensitivity.

Systemic erythromycin has been reported to cause QT prolongation resulting in ventricular arrhythmias of the torsade de pointes type. Fatalities have been reported. Erythromycin should be avoided in patients with known QT prolongation or in patients with ongoing proarrhythmic conditions such as uncorrected electrolyte imbalance (hypokalemia, hypomagnesemia), clinically significant bradycardia, and in patients receiving Class 1A or Class III antiarrhythmic agents. Elderly patients may also be more susceptible to the development of torsades de pointes than younger patients. [48676] [48677] Ventricular tachyarrhythmias have also been reported in humans with idiopathic long QT syndrome.[23771] Patients predisposed to torsade de pointes who require IV erythromycin should not receive more than 15 mg/min. Electrolyte abnormalities should be corrected prior to therapy.[23770]

Erythromycin should be used cautiously in patients with a seizure disorder. There have been rare reports of seizures during erythromycin therapy.

Use with caution in patients with myasthenia gravis. Two case reports suggest that erythromycin may aggravate the weakness of patients with myasthenia gravis.[34106] [34107]

Adverse Reactions

Urticaria, rash (unspecified), and interstitial nephritis may suggest an allergic reaction to erythromycin. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal

necrosis have been reported rarely.[48676] [48677] [48678] Pruritus, xerosis, peeling, erythema, skin oiliness, and skin tenderness/skin irritation have been reported occasionally with the topical application of erythromycin.[48946] [48948] Burning was noted in approximately 25% of patients using the topical gel.[48947]

Erythromycin has been associated with acute generalized exanthematous pustulosis (AGEP). The nonfollicular, pustular, erythematous rash starts suddenly, is associated with fever above 38 degrees C, and is distinct from pustular psoriasis, although biopsy results in each reveal spongiform subcorneal pustules. Drugs are the main cause of AGEP. A period of 2—3 weeks after an inciting drug exposure appears necessary for a first episode of AGEP. Unintentional reexposure may cause a second episode within 2 days. Clinical presentation is diverse with cutaneous lesions beyond erythema and pustules present in half of the cases. For example, bullous lesions, edema, purpura, pruritus, and mucosal erosions are possible. The mean duration of the pustules is 9.7 days followed by an annular desquamation, as long as the causative drug or factor is discontinued. The physiopathological mechanisms of AGEP have not been determined but the pathological criteria of edema, leukocytoclastic vasculitis, eosinophil exocytosis, and keratinocyte focal necrosis are distinctive. Pustule confluence or very small pustules may lead a clinician to make an incorrect diagnosis of TEN, of drug-induced erythroderma, or of staphylococcal scalded skin syndrome.[27736]

Nausea, vomiting, abdominal pain, diarrhea, and anorexia are all common GI effects of oral erythromycin. These effects are often dose-related.[48677] [48677] Rare cases of esophagitis have been reported in patients receiving the capsules or tablets. Erythromycin-induced esophagitis is characterized by sudden onset odynophagia, retrosternal pain, and dysphagia. Risk factors for esophageal effects include taking the medication without water and at night. Symptoms usually resolve within days to weeks after stopping the medication. Diarrhea, abdominal cramps, and abdominal

tenderness may suggest antibiotic-associated colitis, also known as pseudomembranous colitis. Erythromycin has been associated with infantile hypertrophic pyloric stenosis (IHPS), especially in newborns < 1 month. Pyloric stenosis rarely affects infants > 3 months or adults. In a report of 200 infants treated with erythromycin for whooping cough, 7 newborns, < 3 weeks of age, developed pyloric stenosis; all recovered. Erythromycin is still considered the safest effective drug for treating newborns exposed to whooping cough.

Hepatotoxicity, hepatic dysfunction, and/or abnormal liver function tests have been reported. [48677] [48677] The incidence of hepatotoxicity is roughly 4.7%. [23519] Jaundice, which is reversible, can result from administration of erythromycin. Symptoms of hepatotoxicity can persist for several weeks after the drug is discontinued, elevated hepatic enzymes can persist for several months. Erythromycin estolate is the formulation most likely to cause cholestatic hepatitis, although hepatotoxicity also has been reported after administration of erythromycin ethylsuccinate. [23627] Patients who developed hepatotoxicity while receiving the estolate salt have been rechallenged successfully with other erythromycin salts; however, repeat administration of the estolate salt should be avoided. Pancreatitis has been reported rarely. [48676] [48677] [48677]

Rare cases of serious cardiovascular adverse events, including QT prolongation, cardiac arrest, torsade de pointes, and other ventricular arrhythmias have been observed with systemic erythromycin use (see Contraindications). [48676] [48677] Patients who may be predisposed to torsade de pointes and require IV erythromycin should have erythromycin infused at a rate of less than 15 mg/min. Risk factors for torsade de pointes, such as electrolyte abnormalities, should also be eliminated prior to erythromycin therapy. [23770]

Seizures have been reported rarely during erythromycin therapy. [48676] [48677] [48677]

Large doses of erythromycin have been associated with ototoxicity. Hearing loss, which is reversible, has occurred in patients receiving large doses and in patients with renal failure. Elderly patients, especially those with renal or hepatic function impairment, may be at increased risk for developing hearing loss. [48676] [48677] [48677]

Intravenous administration of erythromycin is extremely irritating and patients routinely complain of pain along the vein during infusion of IV erythromycin. Slow administration of the infusion may minimize symptoms. [48676] Phlebitis can occur following only several doses of intravenous erythromycin. In a study of 104 patients being treated with IV erythromycin for Legionnaires' disease, 19% developed phlebitis. [30729] Intramuscular injections of erythromycin are also very painful and most clinicians do not administer erythromycin via this route. Patients should be monitored for an injection site reaction any time erythromycin is administered parenterally.

Ocular irritation and redness can occur from the use of erythromycin ophthalmic ointment. [48945] Ocular irritation has also been reported with the use of topical erythromycin. [48946]

Superinfection and flora overgrowth may occur with the use of erythromycin. [48676] [48677] [48677]

Urticaria, rash (unspecified), and interstitial nephritis may suggest an allergic reaction to erythromycin. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely. [48676] [48677] [48678] Pruritus, xerosis, peeling, erythema, skin oiliness, and skin tenderness/skin irritation have been reported occasionally with the topical application of erythromycin. [48946] [48948] Burning was noted in approximately 25% of patients using the topical gel. [48947]

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starts suddenly, is associated with fever above 38 degrees C, and is distinct from pustular psoriasis, although biopsy results in each reveal spongiform subcorneal pustules. Drugs are the main cause of AGEF. A period of two to three weeks after an inciting drug exposure appears necessary for a first episode of AGEF. Unintentional reexposure may cause a second episode within two days. Clinical presentation is diverse with cutaneous lesions beyond erythema and pustules present in half of the cases. For example, bullous lesions, edema, purpura, pruritus, and mucosal erosions are possible. The mean duration of the pustules is 9.7 days followed by an annular desquamation, as long as the causative drug or factor is discontinued. The physiopathological mechanisms of AGEF have not been determined but the pathological criteria of edema, leukocytoclastic vasculitis, eosinophil exocytosis, and keratinocyte focal necrosis are distinctive. Pustule confluence or very small pustules may lead a clinician to make an incorrect diagnosis of TEN, of drug-induced erythroderma, or of staphylococcal scalded skin syndrome.[27736]

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Superinfection and flora overgrowth may occur with the use of erythromycin.[48676] [48677] [48677]

Erythromycin- Specific Ocular Use

Adult dose 250-500 mg QID x 7-10 days

Children 30-50 mg/kg QID x 7-10 days

Example for use: ocular bacterial infections including coverage for trachoma, especially in the treatment of children and lactating or pregnant women.

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Dicloxacillin

Drug Description

Dicloxacillin is an oral semisynthetic isoxazoly antistaphylococcal penicillin. Like other antistaphylococcal penicillins, dicloxacillin is stable against penicillinase, is active against many of the penicillinase-producing strains of *Staphylococcus aureus*, and is used mainly

in the treatment of infections caused by these organisms. It is the most active of the isoxazolyl antistaphylococcal penicillins. Clinical uses of dicloxacillin include skin and soft-tissue infections, bone and joint infections, and urinary and respiratory tract infections. Dicloxacillin was approved by the FDA in 1968.

Classifications:
<i>Anti-Infective Agents</i> <i>Penicillins</i> <i>Penicillinase-resistant penicillins</i>
Brand Names:
<i>Dynapen®</i>

Mechanism of Action

Mechanism of Action: Beta-lactam antibiotics such as dicloxacillin are mainly bactericidal. Dicloxacillin inhibits the third and final stage of bacterial cell wall synthesis by preferentially binding to specific penicillin-binding proteins (PBPs) that are located inside the bacterial cell wall. Like all beta-lactam antibiotics, dicloxacillin's ability to interfere with PBP-mediated cell wall synthesis ultimately leads to cell lysis. Lysis is mediated by bacterial cell wall autolytic enzymes (i.e., autolysins). The relationship between PBPs and autolysins is unclear, but it is possible that the beta-lactam antibiotic interferes with an autolysin inhibitor.

Dicloxacillin, because of its side chain, resists destruction by beta-lactamases. This makes it useful for treating bacteria that resist penicillin due to the presence of penicillinase. Dicloxacillin is ineffective, however, against methicillin-resistant *S. aureus* (MRSA). These organisms appear to resist dicloxacillin and related antistaphylococcal penicillins due to the presence of a relatively insensitive PBP, although this mechanism is not fully understood.

Dicloxacillin is extremely active against most strains of penicillinase-producing *Staphylococcus aureus* and some strains of *Staphylococcus epidermidis*. As mentioned above, methicillin-resistant strains of staphylococci are resistant.

The antistaphylococcal penicillins are active against group A streptococci and *Streptococcus viridans*, but the natural penicillins are more potent against streptococci and are preferred. The antistaphylococcal penicillins have limited activity against gram-negative and anaerobic bacteria and are not recommended for treating these infections. Clinicians are advised to consult susceptibility data to determine dicloxacillin activity.

Indications

Per the manufacturer, this drug has been shown to be active against most strains of the following microorganisms either in vitro and/or in clinical infections: *Staphylococcus* sp.

NOTE: The safety and effectiveness in treating clinical infections due to organisms with in vitro data only have not been established in adequate and well-controlled clinical trials.

Maximum Dosage Limits
Adults: <i>4 g/day PO.</i>
Elderly: <i>4 g/day PO.</i>
Adolescents: <i>4 g/day PO.</i>
Children: <i>Maximum dosage information is not available.</i>

Patients with Hepatic Impairment Dosing

Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.

Patients with Renal Impairment Dosing

No dosage adjustment needed.

Route-Specific Administration

Dicloxacillin is administered orally.

Oral Administration

Food decreases oral bioavailability. Take on an empty stomach (i.e., at least one hour prior to or two hours after a meal).

Contraindications/Precautions

A false-positive reaction for glucose in the urine has been observed in patients receiving penicillins and using Benedict's solution, Fehling's solution, and Clinitest tablets. However, this reaction has not been observed with Tes-tape (glucose Enzymatic Test Strip, USP, Lilly).

Antibiotic therapy can result in superinfection or suprainfection with nonsusceptible organisms. Overgrowth of non susceptible organisms can occur during dicloxacillin therapy.

Dicloxacillin, a penicillin, is contraindicated in patients with penicillin hypersensitivity. Dicloxacillin should be used cautiously in patients with cephalosporin hypersensitivity or carbapenem hypersensitivity because these patients are more susceptible to hypersensitivity reactions. Patients with allergies or allergic conditions including asthma, eczema, hives, or hay fever may have a greater risk for hypersensitivity reactions to penicillins.

Almost all antibacterial agents have been associated with pseudomembranous colitis (antibiotic-associated colitis) which may range in severity from mild to life-threatening. In the colon, overgrowth of Clostridia may exist when normal flora is altered subsequent to antibacterial administration. The toxin produced by Clostridium difficile is a primary cause of pseudomembranous colitis. It is known that systemic use of antibiotics predisposes patients to development of pseudomembranous colitis. Consideration should be given to the diagnosis of pseudomembranous colitis in patients presenting with diarrhea following antibacterial administration. Systemic antibiotics should be prescribed with caution to patients with inflammatory bowel disease such as ulcerative colitis or other GI disease.

If diarrhea develops during therapy, the drug should be discontinued. Following diagnosis of pseudomembranous colitis, therapeutic measures should be instituted. In milder cases, the colitis may respond to discontinuation of the offending agent. In moderate to severe cases, fluids and electrolytes, protein supplementation, and treatment with an antibacterial effective against Clostridium difficile may be warranted. Products inhibiting peristalsis are contraindicated in this clinical situation. Practitioners should be aware that antibiotic-associated colitis has been observed to occur over two months or more following discontinuation of systemic antibiotic therapy; a careful medical history should be taken.

Dicloxacillin is classified FDA pregnancy risk category B. Penicillins do cross the placenta. Use of penicillins in humans has not shown any evidence of harmful effects on the fetus. Animal data have also not demonstrated any evidence of impaired fertility or harmful fetal effects. However, there are no adequate and well-controlled studies in pregnant women show conclusively that harmful effects of penicillins on the fetus can be excluded. Because animal reproduction studies are not always predictive of human response, dicloxacillin should be used in pregnant women only if clearly needed.

Penicillins, including dicloxacillin, are excreted in breast milk in small amounts. The manufacturer recommends caution with use during nursing. [32928] However, unless the infant is allergic to penicillins, breast-feeding is generally safe during maternal dicloxacillin therapy. Breast milk concentrations range from 0.1 to 0.3 mcg/ml.[46785] Penicillins may cause diarrhea (due to disruption of GI flora), candidiasis, and skin rash in the breast-feeding infant. The infant should be observed for potential effects. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally administered drug, healthcare providers are encouraged to report the adverse effect to the FDA.

Hypersensitivity and dermatologic adverse effects can occur with penicillins, such as dicloxacillin. Hypersensitivity reactions are among the most frequently reported adverse reactions to the penicillins. Penicillin allergy has been reported in up to 20% of patients; however, around 90% of reported allergies are incorrectly reported and patients lack penicillin-specific IgE antibodies. The actual prevalence of penicillin allergy is likely no greater than 5%.[44466] [44468] Hypersensitivity reactions can be immediate or delayed. Anaphylactoid reactions including anaphylactic shock has been reported in 0.015 to 0.04% of patients with death occurring in 0.002% of patients. These types of reactions include angioedema, laryngospasm, laryngeal edema, bronchospasm, hypotension, vascular collapse, and death. Other reactions include urticaria, pruritus, fever, serum sickness-like symptoms, malaise, myalgia, arthralgia, and rash (unspecified).[32928] Rash may develop after the first week and may cover the entire body, including the soles, palms, and oral mucosa. The rash usually disappears in three to seven days. [43344] [43346] Other skin reactions which occur infrequently, but can be serious, include Stevens-Johnson syndrome, exfoliative dermatitis, and toxic epidermal necrolysis.

Adverse Reactions

Prolonged antibiotic use is more likely to result in an overgrowth of non-susceptible organisms such as *Candida* sp. and *Clostridium difficile*, which may cause superinfection including pseudomembranous colitis. If pseudomembranous colitis is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Gastrointestinal adverse events may occur in 2 to 5% of patients receiving penicillins, such as dicloxacillin.[44469] Nausea, vomiting, diarrhea, abdominal pain, stomatitis, black or hairy tongue (tongue discoloration), and other symptoms of gastrointestinal irritation have all been reported

during penicillin therapy.[32928]

Neurotoxic reactions such as seizures have been reported when large doses of penicillins were administered to patients, especially patients with renal impairment.[23981] Appropriate dicloxacillin dosage adjustments should be observed in these patients.[32928]

Hematologic adverse events have been reported with the use of other penicillin products and include agranulocytosis, neutropenia, and bone marrow depression. Hepatotoxicity, including elevated hepatic enzymes, has also been reported with the use of other penicillins.[32928]

Renal tubular necrosis (damage) and interstitial nephritis has been associated with other penicillins, including nafcillin and oxacillin. Manifestations include rash, eosinophilia, hematuria, proteinuria, and renal insufficiency. [32928]

Dicloxacillin (Dynapen®) Specific Ocular Use

Adult dose 250-500 mg QID x 7-10 days

Children 12.5- 25 mg/kg QID x 7-10 days

Example for use: Acute Dacryocystitis-internal hordeolum

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Doxycycline

Drug Description

Doxycycline is a tetracycline derived from oxytetracycline. It is classified as a long-acting tetracycline, although this classification scheme is somewhat artificial since tetracycline (classified as short-acting) can be dosed at longer intervals than usually occurs in clinical practice. While once daily dosing is an advantage for doxycycline, adverse reactions were less for minocycline when these two agents were compared in the treatment of urethritis and cervicitis.[23476] Nevertheless, doxycycline is one of the most frequently prescribed tetracyclines. Doxycycline, along with minocycline, can be administered without regard to meals, although some cations can still significantly reduce oral bioavailability. Clinically, doxycycline can be used to treat non-gonococcal urethritis and cervicitis, exacerbations of bronchitis in patients with COPD [23621], and acne vulgaris. Doxycycline is considered the tetracycline of choice in patients with poor renal function due to its limited renal clearance. The Centers for Disease Control have suggested doxycycline be considered as an alternative to ciprofloxacin for the treatment of anthrax. Doxycycline was originally approved by the FDA in 1967. Atridox, a subgingival controlled-release product, was approved September 4, 1998 for the treatment of chronic adult periodontitis. Periostat capsules were approved by the FDA in October 1998 as adjunct to scaling and root planing for the treatment of adult periodontitis; Periostat tablets were approved February 2001 for the same indication. Doryx[®], a delayed-

release enteric-coated oral formulation, was FDA approved in May 2005. A dual-release capsule (Oracea), containing immediate- and delayed-release beads, was approved May 2006 for treating inflammatory lesions (papules and pustules) of rosacea in adults.

Classifications:

Anti-infective Agents
Tetracyclines
Oropharyngeal Agents
Dental and Peridontal Agents

Mechanism of Action

Mechanism of Action: Doxycycline is generally bacteriostatic against a wide variety of organisms, both gram-positive and gram-negative. In gram-negative bacteria, transportation of the drug into the cell occurs either by passive diffusion or through an energy-dependent active transport system. The latter system is also believed to exist in gram-positive bacteria. Doxycycline and minocycline are more lipophilic than the other tetracyclines, which allows them to pass easily through the lipid bilayer of bacteria where reversible binding to the 30 S ribosomal subunits occurs. Binding of doxycycline blocks the binding of aminoacyl transfer RNA (tRNA) to the messenger RNA (mRNA). Bacterial protein synthesis is inhibited, which ultimately accounts for the antibacterial action. High concentrations of antibiotic also can interfere with protein synthesis in mammalian cells, but these cells lack the active transport systems found in bacteria. Resistance develops when the bacterial cell mutates and the cell wall becomes less permeable.

Tetracycline resistance in community-acquired MRSA (CA-MRSA) isolates is primarily associated with the tetK gene. The tetM resistance gene confers resistance to the entire class; however, the tetK gene confers resistance to tetracycline and an inducible resistance to doxycycline, but has no impact on minocycline susceptibility.[29817] [26456] [46693]

The action of tetracyclines in the treatment of acne vulgaris has not been fully established but is believed to be due in part to its antibacterial actions. Several other mechanisms have been proposed but not studied. (See tetracycline monograph for additional information.)

In the treatment of periodontitis, it is thought that doxycycline works by inhibiting collagenase. Collagenase breaks down connective tissue which leads to the separation of the gum from the tooth. Products (e.g., Periostat) used for treatment of periodontitis contain lower amounts of doxycycline. Doxycycline concentrations produced by Periostat are too low to exert a direct antibacterial effect. Clinical studies of patients receiving Periostat for 9—18 months show that Periostat has no effect on total anaerobic and facultative bacteria in plaque samples. Periostat should not be used as an antibiotic in the treatment of periodontitis.

Indications

Per the manufacturer, this drug has been shown to be active against most strains of the following microorganisms either in vitro and/or in clinical infections: *Acinetobacter* sp., *Actinomyces israelii*, *Bacillus anthracis*, *Bacteroides* sp., *Balantidium coli*, *Bartonella bacilliformis*, *Borrelia recurrentis*, *Brucella* sp., *Campylobacter fetus*, *Chlamydia psittaci*, *Chlamydia trachomatis*, *Clostridium* sp., *Entamoeba histolytica*, *Enterobacter aerogenes*, *Enterococcus* sp., *Escherichia coli*, *Francisella tularensis*, *Fusobacterium fusiforme*, *Haemophilus ducreyi*, *Haemophilus influenzae* (beta-lactamase negative), *Haemophilus influenzae* (beta-lactamase positive), *Klebsiella granulomatis*, *Klebsiella* sp., *Leptospira* sp., *Listeria monocytogenes*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Orientia tsutsugamushi*, *Plasmodium falciparum*, *Propionibacterium acnes*, *Rickettsia akari*, *Rickettsia prowazekii*, *Rickettsia rickettsii*, *Shigella* sp., *Staphylococcus aureus* (MSSA), *Streptococcus pneumoniae*, *Streptococcus pyogenes* (group A beta-hemolytic streptococci), *Streptococcus* sp., *Treponema pallidum*, *Treponema pertenue*, *Ureaplasma urealyticum*,

Vibrio cholerae, Viridans streptococci, *Yersinia pestis*

NOTE: The safety and effectiveness in treating clinical infections due to organisms with in vitro data only have not been established in adequate and well-controlled clinical trials.

This drug may also have activity against the following microorganisms: *Bartonella quintana*, *Bordetella pertussis*, *Borrelia burgdorferi*, *Burkholderia mallei*, *Burkholderia pseudomallei*, *Coxiella burnetii*, *Helicobacter pylori*, *Legionella pneumophila*, *Leptotrichia buccalis*, *Mycobacterium fortuitum*, *Mycoplasma hominis*, *Nocardia* sp., *Pasteurella multocida*, *Propionibacterium propionicum*, *Spirillum minus*, *Staphylococcus aureus* (MRSA), *Streptobacillus moniliformis*, *Vibrio parahaemolyticus*, *Wuchereria bancrofti*, *Yersinia enterocolitica*

NOTE: Some organisms may not have been adequately studied during clinical trials; therefore, exclusion from this list does not necessarily negate the drug's activity against the organism

For the treatment of chronic bacterial conjunctivitis[†] caused by susceptible organisms:

Oral dosage
Adults: <i>50 mg PO twice daily for 10—21 days.</i>
Maximum Dosage Limits
Adults: <i>300 mg/day PO/IV; 40 mg PO/day for Oracea or Periostat; 600 mg PO in a single physician's visit for acute gonococcal infections.</i>
Elderly: <i>300 mg/day PO/IV; 40 mg PO/day for Oracea or Periostat; 600 mg PO in a single physician's visit for acute gonococcal infections.</i>

Route-Specific Administration

Oral Administration

- Available for oral administration as capsules, tablets, or suspension. To reduce the risk of esophageal irritation and ulceration, take with adequate amounts of fluid to wash down the drug. Also, for patients with esophageal obstruction or compression, do not administer at bedtime in order to reduce the risk of esophageal irritation or ulceration.
- Divalent and trivalent cations significantly affect absorption. Do not administer sucralfate (contains aluminum), oral iron supplements, or aluminum-, magnesium- or calcium-containing antacids one hour before or four hours after oral doxycycline. Multivitamins containing manganese or zinc salts will also decrease absorption. Proton pump inhibitors may also reduce bioavailability by increasing gastric pH.

Oral Solid Formulations

- Immediate-release tablets or capsules: May be taken with food and/or milk if gastric irritation occurs.
- Delayed-release capsules (e.g., Doryx): May be swallowed whole or may also be administered by carefully opening the capsules and sprinkling the contents on a spoonful of cool applesauce. The applesauce should not be hot and should be swallowed immediately without chewing. If desired, follow with a cool 8 ounce glass of water. If the prepared dose cannot be consumed immediately, it should be discarded; do not stored for later use.
- Dual-release capsules (e.g., Oracea): Take at least one hour prior to or two hours after meals.
- Periostat tablets: Take at least one hour prior to morning and evening meals.

Oral Liquid Formulations

- Shake well prior to each use.
- Use a calibrated oral device (e.g., oral syringe or spoon) to ensure accurate dosage.
- May be taken with food and/or milk if gastric irritation occurs.[29817]

Reconstitution

- Review the reconstitution instructions for the particular product and package size, as the amount of water required for reconstitution varies

Maximum Dosage Limits continued

Adolescents:

≥ 45 kg: 300 mg/day PO/IV; 40 mg PO/day for Oracea or Periostat.

< 45 kg: 4.4 mg/kg/day PO/IV. Do not exceed adult dosage.

Children:

≥ 8 years and ≥ 45 kg: 300 mg/day PO/IV; 40 mg PO/day for Oracea or Periostat.

≥ 8 years and < 45 kg: 4.4 mg/kg/day PO/IV. Do not exceed adult dosage.

< 8 years: Do not use (exception may be considered off-label for anthrax infection or exposure).

Infants:

Do not use.

Neonates:

Do not use.

Patients with Hepatic Impairment Dosing

Doxycycline is cleared both renally and fecally without hepatic metabolism; it appears no dosage adjustments are needed in mild impairment. However, dose adjustment may be necessary when prescribing doxycycline to patients with severe hepatic disease because hepatic excretion into bile may be delayed and elimination half-life extended.

Patients with Renal Impairment Dosing

No dosage adjustment needed.

Intermittent hemodialysis

No dosage adjustment needed.

Administration Information

General Administration Information

For storage information, see the specific product information within the How Supplied section.

from manufacturer to manufacturer.

- *Prior to reconstitution, tap the bottle several times to loosen the powder.*
- *Add water in two portions and shake well after each addition.*
- *Storage: Store reconstituted suspension at room temperature; discard after 14 days.[29817]*

Contraindications/Precautions

Doxycycline and other tetracycline antibiotics are contraindicated in patients with known tetracyclines hypersensitivity.

Use caution when prescribing doxycycline to patients with severe hepatic disease because hepatic excretion into bile may be delayed and elimination half-life extended.

Photosensitivity reactions to doxycycline after sunlight (UV) exposure occur somewhat less frequently than with demeclocycline. Doxycycline should be discontinued at the first sign of erythema. Photosensitivity reactions are believed to be due to accumulation of the drug in the skin and are mostly phototoxic in nature, but photoallergic reactions also can occur with select drugs.[30713] Reactions can develop from within a few minutes to up to several hours after exposure and will last for one to two days after discontinuation of the drug. It is generally agreed that sunscreens provide limited protection for this reaction.

Doxycycline calcium oral suspension contains sodium metabisulfite. Sulfites cause an allergic reaction in some people and this product should be used with caution in patients with a known sulfite hypersensitivity. This sensitivity reaction is more common in asthmatic than in non-asthmatic patients.

Increases in gastric pH may reduce the absorption of doxycycline. For example, the bioavailability of doxycycline may be reduced in patients on proton pump inhibitor therapy (see Drug Interactions) or with achlorhydria.

Doxycycline is classified as FDA pregnancy risk category D. There are no adequate and

well-controlled studies in pregnant women.

The vast majority of reported experience with doxycycline during human pregnancy is short-term, first trimester exposure. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women such as that proposed for treatment of anthrax exposure. An expert review of published data on experiences with doxycycline use during pregnancy by the Teratogen Information System (TERIS) concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk.[27016] One case-control study involved 18,515 mothers of babies with congenital anomalies and 32,804 mothers of babies with no congenital anomalies. Sixty-three (0.19%) of the controls and 56 (0.30%) of the cases were treated with doxycycline. The results showed a weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy. No association was seen when the analysis was confined to maternal treatment during the period of organogenesis (i.e., in the 2nd and 3rd months of gestation) with the exception of a marginal relationship with neural tube defect based on only two exposed cases.[27026] The tetracyclines as a class of drugs have been noted to have a detrimental effect on the skeletal development and bone growth of the fetus; they usually are not used during pregnancy, especially during the second half of pregnancy, unless benefits from treatment outweigh the risks.[32240]

Tetracyclines, including doxycycline, are distributed in small amounts into breast milk. According to the manufacturer, because of the potential for serious adverse reactions in nursing babies, a decision should be made whether to discontinue nursing or to discontinue the drug. [29817] In general, manufacturers recommend that tetracycline antibiotics NOT be used in breast feeding mothers due to a theoretical risk of causing tooth discoloration, enamel hypoplasia, inhibition of linear skeletal growth, oral and vaginal thrush, or photosensitivity reactions in the nursing infant.[29817] However, because

tetracyclines bind to calcium in the maternal breast milk, the risk for oral absorption by the infant is minimal.[47299] Data are available regarding doxycycline milk concentrations in breast-feeding women; however, infant serum concentrations and effects are nursing babies were not reported. In one study, doxycycline (100 mg PO daily) was given to 10 mothers. On the second day of treatment, milk doxycycline averaged 0.82 mg/L (range 0.37 to 1.24 mg/L) 3 hours after the dose, and 0.46 mg/L (range 0.3 to 0.91 mg/L) 24 hours after the dose. Using the average of the peak and trough milk concentrations in this study, the estimated average intake of an exclusively breast-fed infant would be about 6% of the maternal weight-adjusted dosage.[33776] Further available data indicate that after doses of 100 to 200 mg PO, milk concentrations do not exceed an average of 1.8 mg/L.[33777] [33778] [33779] [33780] Studies of long-term tetracycline use in breast-feeding are lacking. Doxycycline does not have a listed American Academy of Pediatrics breast-feeding category, but another tetracycline antibiotic, tetracycline, is rated as usually compatible with breast-feeding.[27500] Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

Tetracyclines, like doxycycline, may have a serious effect on the bones and teeth in young children. Tetracyclines are incorporated into bones and teeth that are undergoing calcification. This may cause permanent yellow or brown discoloration and enamel hypoplasia in developing teeth. Except when other therapy is ineffective, use in neonates, infants, and children to the age of eight years, should be avoided.

Almost all antibacterial agents have been associated with pseudomembranous colitis (antibiotic-associated colitis) which may range in severity from mild to life-threatening. In the colon, overgrowth of Clostridia may exist

when normal flora is altered subsequent to antibacterial administration. The toxin produced by Clostridium difficile is a primary cause of pseudomembranous colitis. It is known that systemic use of antibiotics predisposes patients to development of pseudomembranous colitis. Consideration should be given to the diagnosis of pseudomembranous colitis in patients presenting with diarrhea following antibacterial administration. Systemic antibiotics should be prescribed with caution to patients with inflammatory bowel disease such as ulcerative colitis or other GI disease. If diarrhea develops during therapy, the drug should be discontinued. Following diagnosis of pseudomembranous colitis, therapeutic measures should be instituted. In milder cases, the colitis may respond to discontinuation of the offending agent. In moderate to severe cases, fluids and electrolytes, protein supplementation, and treatment with an antibacterial effective against Clostridium difficile may be warranted. Products inhibiting peristalsis are contraindicated in this clinical situation. Practitioners should be aware that antibiotic-associated colitis has been observed to occur over two months or more following discontinuation of systemic antibiotic therapy; a careful medical history should be taken.

In general, tetracyclines should not be used in patients who have renal disease, specifically, renal insufficiency or renal failure. However, if a tetracycline antibiotic is necessary for such a patient, doxycycline or minocycline are preferred due to their minimal degree of renal clearance; doxycycline also rarely increases azotemia. Studies to date have indicated that usual recommended doses of doxycycline do not lead to accumulation in patients with renal impairment (manufacturer product literature).

Doxycycline subgingival formulation (Atridox) has not been clinically evaluated in patients with dental disease/periodontal disease involving extremely severe periodontal defects with very little remaining periodontium. Also, it has not been clinically tested for use in the regeneration of alveolar bone, either in preparation for or in conjunction with the

placement of endosseous (dental) implants or in the treatment of failing implants. Periostat and similar oral formulations for periodontitis produce doxycycline concentrations too low to exert a direct antibacterial effect. Clinical studies of patients show that the products have no effect on total anaerobic and facultative bacteria in plaque samples. These products should not be used as an antibiotic in the treatment of periodontitis/periodontal disease.

Doxycycline subgingival (Atridox) and periodontal oral formulations (Periostat, others) have not been clinically tested in patients with predisposition to oral candidiasis, such as patients with immunosuppression due to diabetes mellitus, chemotherapy, or human immunodeficiency virus (HIV) infection.

Doxycycline does not treat viral infection (e.g., common cold). Prescribing doxycycline in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria (antimicrobial resistance). Patients should be told to complete the full course of treatment, even if they feel better earlier. Antibiotic therapy can result in superinfection or suprainfection with nonsusceptible organisms. Patients should be monitored closely.

Adverse Reactions

Diarrhea (5 to 6%), nausea (8%), vomiting, dyspepsia (6%), glossitis, dysphagia, enterocolitis, abdominal pain (1%), upper abdominal pain (2%), abdominal distention (1%), stomach discomfort (1%), acid indigestion (4%), xerostomia (1%), toothache (7%), periodontal abscess (4%), gum pain (< 1%), and anorexia are all possible gastric side effects of doxycycline.[29817] [32075] [32240] [34113] [40388] [40389] [44000] [44001] **In general, GI complaints occur in roughly 39% of patients receiving oral doxycycline; complaints can be mitigated by administering the drug with food.[23623]** They occur most often following oral administration and may be alleviated by taking with sufficient water and avoiding dosage

at bedtime. Rare cases of esophagitis and esophageal ulceration have been reported in patients receiving capsule and tablet dosage forms of tetracycline antibiotics; however, many of these patients took the medication immediately before going to bed or lying down.[29817] [32075] [32240] [34113] [40388] [44000] [44001] Of all tetracycline antibiotics, doxycycline, especially in capsule form, is most likely to cause esophagitis. Doxycycline-induced esophagitis is characterized by sudden onset odynophagia, retrosternal pain, and dysphagia. Risk factors include taking the medication without water and at night. Symptoms usually resolve within days to weeks after stopping the medication. Abdominal complaints may suggest hepatotoxicity (e.g., elevated hepatic enzymes, hepatitis), although serious liver reactions are relatively uncommon. Elevated aspartate aminotransferase (2%) was reported in some clinical trials.[29817] [32075] [32240] [34113] [40388] [40389] [44000] [44001] In one analysis, the number of patient cases developing acute symptomatic liver disease resulting in hospitalization for each million patients treated with a 10-day course of a tetracycline was 1.56 cases.[23519] The drugs are very rarely associated with hepatic failure (hepatotoxicity). [29817] [32075] [32240] [34113] [40388] [40389] [44000] [44001]

As with other antibiotic preparations, use of doxycycline may result in overgrowth of nonsusceptible organisms and superinfection. Oral or parenteral tetracycline therapy, like doxycycline, can result in oral, rectal, or vaginal candidiasis because of changes in the normal balance of microbial flora. Candidal infections are more likely to occur in debilitated patients, those taking the drug over prolonged periods, and the elderly. The condition usually resolves upon discontinuation of the drug. Pseudomembranous colitis has been reported with the use of doxycycline and may range from mild diarrhea to fatal colitis. Fungal infection (2%) and general infection (2%) have been reported in some clinical trials. The common cold (22%) and influenza or flu-like symptoms have also been reported (2 to 11%).[29817] [32075] [32240] [34113] [40388] [40389] [44000] [44001]

Photosensitivity, if apparent, can appear within minutes of taking the tetracycline, like doxycycline, if the patient is exposed to direct sunlight or UV light.[29817] [32075] [32240] [34113] [40388] [40389] [44000] [44001] Photosensitivity is manifested by an exaggerated sunburn reaction and treatment should be discontinued at the first evidence of skin erythema. Red rashes and onycholysis have been reported on those areas exposed to sunlight. Paresthesias (tingling and burning) in the hands, feet, and nose, may indicate latent photosensitivity. If the drug is discontinued, symptoms usually are alleviated within one to two days. Sunscreens seem to provide only limited protection, and severe response may necessitate treatment with corticosteroids or antihistamines. Photosensitivity is a toxic, rather than an allergic, reaction.

Hypersensitivity reactions to tetracyclines, including doxycycline, have been reported as urticaria, angioedema, anaphylaxis, anaphylactoid reactions such as anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus (lupus-like symptoms). Maculopapular rash, erythematous rashes, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis, and erythema multiforme have also been reported. Exfoliative dermatitis has been reported but is uncommon. Rash (unspecified) has been reported in 4% of patients in some clinical trials. [29817] [32075] [32240] [34113] [40388] [40389] [44000] [44001]

Headache (26% reported with the Oraxyl brand, compared to 26% placebo) and anxiety (2%) have been reported in some clinical trials of doxycycline. Headache may be due to elevated intracranial pressure.[29817] [32075] [32240] [34113] [40388] [40389] [44000] [44001]

Doxycycline has been associated with acute generalized exanthematous pustulosis (AGEP). The nonfollicular, pustular, erythematous rash starts suddenly, is associated with fever above 38 degrees C, and is distinct from pustular psoriasis,

although biopsy results in each reveal spongiform subcorneal pustules. Drugs are the main cause of AGEP. A period of two to three weeks after an inciting drug exposure appears necessary for a first episode of AGEP. Unintentional reexposure may cause a second episode within 2 days. Clinical presentation is diverse with cutaneous lesions beyond erythema and pustules present in half of the cases. For example, bullous lesions, edema, purpura, pruritus, and mucosal erosions are possible. The mean duration of the pustules is 9.7 days followed by an annular desquamation, as long as the causative drug or factor is discontinued. The physiopathological mechanisms of AGEP have not been determined but the pathological criteria of edema, leukocytoclastic vasculitis, eosinophil exocytosis, and keratinocyte focal necrosis are distinctive. Pustule confluence or very small pustules may lead a clinician to make an incorrect diagnosis of TEN, of drug-induced erythroderma, or of staphylococcal scalded skin syndrome.[27736]

Tooth discoloration has been seen in children exposed to a tetracycline during last half of pregnancy, during infancy, or during childhood to the age of 8 years (see Contraindications), but this reaction has also been reported in adults. Drugs in the tetracycline class are known to cause hyperpigmentation, which may affect many organs/tissues, including nails, bone, skin (skin hyperpigmentation), eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclera, and heart valves. This adverse reaction is more common during long-term use of the drugs but skin and oral hyperpigmentation can occur independently of treatment time or amount of drug administered.[29817] [32075] [32240] [34113] [40388] [40389] [44000] [44001] Enamel hypoplasia has also been reported. Although this is not typically thought of as teratogenesis, some references include tetracyclines, like doxycycline, in lists of teratogenic drugs. [24291] While isolated cases of major fetal malformations have been reported in offspring of mothers who received a tetracycline drug during pregnancy, analysis of the data does not support an association between these drugs and these major malformations (e.g., oral clefts, spina

bifida, polydactyly). Limited data exist which support a possible risk of minor malformations (e.g., hypospadias, inguinal hernia). Brown nail discoloration was also reported in an 11-year-old boy treated with doxycycline; normal nail color returned approximately 1 month after stopping doxycycline.[31472]

Hematologic effects such as hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported with doxycycline. Tetracyclines may also depress plasma prothrombin activity. [29817] [32075] [32240] [34113] [40388] [40389] [44000] [44001] Neutropenia and eosinophilia are more likely to occur during long-term therapy with doxycycline. Patients should be evaluated regularly in these instances.

Adverse renal effects of tetracyclines are usually a problem only for patients with seriously impaired renal function. Tetracyclines may increase azotemia (BUN) in such patients due to the antianabolic actions of the drugs, with doxycycline the effect on BUN may be dose related.[29817] [32075] [32240] [34113] [40388] [40389] [44000] [44001] Historically, a Fanconi syndrome has been associated with use of outdated or degraded tetracycline products, so shelf-life dates for doxycycline products should be strictly adhered to. The cases of the Fanconi-like syndrome resulted in modifications in formulations of tetracycline class products on the market today, so this complication is unlikely to recur.

Phlebitis is a frequent side effect following IV administration of doxycycline, especially if the therapy is long-term or the same vein is used. Rapid administration should be avoided. Extravasation can result in a serious reaction, and whenever possible the oral route of administration should be used. Patients receiving parenteral doxycycline should be observed for any injection site reaction.[40389]

Benign increased intracranial pressure (pseudotumor cerebri) in adults and bulging fontanels in infants can occur with doxycycline. Symptoms are usually reversible following

discontinuation of the drug but may produce permanent sequelae. Clinical manifestations include headache and blurred vision.[29817] [32075] [32240] [34113] [40388] [40389] [44000] [44001]

Respiratory adverse events noted in some clinical trials with doxycycline include naso-pharyngitis (5% vs. 3% placebo), pharyngolaryngeal pain (1% vs. 1% placebo), sinusitis (3% vs. 8% placebo), nasal congestion (2% vs. 1% placebo), sore throat / throat irritation (5% vs. 6% placebo), sinus congestion (5% vs. 5% placebo), sinus headache (1 to 4% vs. 4% placebo), cough (4% vs. 5% placebo), and bronchitis (3% vs. 2% placebo).[29817] [32075] [32240] [34113] [40388] [40389] [44000] [44001]

Musculoskeletal adverse events were reported in some doxycycline clinical trials and include back pain (1 to 3%), back ache (2%), menstrual cramp (4%), general pain (2 to 4%), injury (5%), and muscle and joint pain (musculoskeletal pain) (1 to 6%).[29817] [32075] [32240] [34113] [40388] [40389] [44000] [44001]

Hypertension (3%) and increased blood pressure (2%) have been reported in some clinical trials with doxycycline.[29817] [32075] [32240] [34113] [40388] [40389] [44000] [44001]

Increased blood glucose (hyperglycemia) (1%) and increased blood lactate dehydrogenase (2%) were reported in some doxycycline clinical trials. [29817] [32075] [32240] [34113] [40388] [40389] [44000] [44001]

Doxycycline (Alodox®)-Specific Ocular Use

Adult dose 50-100 mg QD- BID for 1-6 weeks

Children 1-2 mg/kg q12h-24h for a duration that is less than five days and if over 12 years of age)

Doxycycline (Alodox®)-Specific Ocular Use continued

Contraindicated in pregnant or lactating patients and causes increased photosensitivity. May provide some coverage for suspected MRSA.

Example for use: Blepharitis, MGD, adult inclusion conjunctivitis, internal or external hordeolum where treatment for an adult patient is 100 mg BID x 7-21 days.

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Cephalexin

Drug Description

Cephalexin is an oral, first-generation cephalosporin antibiotic with excellent activity against most gram-positive bacteria. Cephalexin is used primarily in the treatment of otitis media and infections of the respiratory tract (e.g., pharyngitis, tonsillitis, lobar pneumonia) caused by susceptible staphylococci, *Streptococcus pneumoniae*, and group A beta-hemolytic streptococci. Cephalexin (Keflex®) was approved by the FDA in 1971. Cephalexin hydrochloride (Keftab®) was later approved on October 29, 1987.

Classifications:	
<i>Anti-infective Agents</i> <i>Cephalosporins</i> <i>First-Generation Cephalosporins</i>	
Brand Names:	
<i>Bio-Cef®</i> <i>Keftab®</i>	<i>Keflex®</i> <i>Panixine DisperDose®</i>

Mechanism of Action

Cephalexin, a beta-lactam antibiotic like the penicillins, is mainly bactericidal. It inhibits the third and final stage of bacterial cell wall synthesis by preferentially binding to specific penicillin-binding proteins (PBPs) that are located inside the bacterial cell wall. Penicillin-binding proteins are responsible for several steps in the synthesis of the cell wall and are found in quantities of several hundred to several thousand molecules per bacterial cell. Penicillin-binding proteins vary among different bacterial species. Thus, the intrinsic activity of cephalexin as well as the other cephalosporins and penicillins against a particular organism depends on its ability to gain access to and bind with the necessary PBP. Like all beta-lactam antibiotics, cephalexin's ability to interfere with PBP-mediated cell wall synthesis ultimately leads to cell lysis. Lysis is mediated by bacterial cell wall autolytic enzymes (i.e., autolysins). The

relationship between PBPs and autolysins is unclear, but it is possible that the beta-lactam antibiotic interferes with an autolysin inhibitor.

As a rule, first-generation cephalosporins are more active against gram-positive organisms than are second- and third-generation cephalosporins, but they have relatively little activity against gram-negative species. Gram-positive coverage includes nonpenicillinase- and penicillinase-producing staphylococci (e.g., *S. aureus*) and streptococci (except enterococci). Its gram-negative spectrum is limited to *E. coli*, *Klebsiella*, and *Proteus mirabilis*. Cephalexin is not recommended for soft-tissue infections caused by gram-negative bacteria due to the relatively high MICs of these organisms and the relatively low serum levels achieved with cephalexin.

Indications

Per the manufacturer, this drug has been shown to be active against most strains of the following microorganisms either in vitro and/or in clinical infections:

- *Escherichia coli*
- *Haemophilus influenzae* (beta-lactamase negative)
- *Klebsiella pneumoniae*
- *Moraxella catarrhalis*
- *Proteus mirabilis*
- *Staphylococcus aureus* (MSSA)
- *Staphylococcus epidermidis*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
(group A beta-hemolytic streptococci)

NOTE: The safety and effectiveness in treating clinical infections due to organisms with in vitro data only have not been established in adequate and well-controlled clinical trials.

This drug may also have activity against the following microorganisms:

- *Streptococcus agalactiae* (group B streptococci)

NOTE: Some organisms may not have been adequately studied during clinical trials; therefore,

exclusion from this list does not necessarily negate the drug's activity against the organism.

Maximum Dosage Limits
Adults: 4 g/day PO.
Elderly: 4 g/day PO.
Adolescents: 4 g/day PO.
Children: 100 mg/kg/day PO for most indications, not to exceed 4 g/day; 2 g single dose PO for endocarditis prophylaxis.

Patients with Hepatic Impairment Dosing

No dosage adjustments are necessary.

Patients with Renal Impairment Dosing

The following are recommended adjustments for adults with renal impairment.

CrCl $\geq$ 40 ml/min: No dosage adjustment needed.
CrCl 11 to 40 ml/min: Following a loading dose of 250 to 500 mg PO, a dose of 250 to 500 mg PO every eight to 12 hours has been recommended.
CrCl $\leq$ 10 ml/min: Following a loading dose of 250 to 500 mg PO, a dose of 250 mg PO every 12 to 24 hours has been recommended.

*Off-label indication

Route-Specific Administration

Oral Administration

- *Cephalexin is administered orally. All dosage forms may be administered without regard to meals.*
- *Cephalexin and cephalexin hydrochloride are commercially available as monohydrates; the dosage is expressed as cephalexin base.*

Oral Solid Formulations

- *Capsules: Swallow whole with a drink of water.*
- *Soluble tablets (Panixine DisperDose): Administer only after complete mixing in water. Mix 1 tablet in a small amount of water [roughly 10 ml (2 teaspoonfuls)]. Have patient drink the entire mixture. Rinse the container with an additional small amount of water and have patient drink the contents to assure the whole dose is taken. Patients should NOT chew or swallow the tablets. The tablets will NOT rapidly dissolve in the patient's mouth.*

Oral Liquid Formulations

- *Oral suspension: Shake well prior to each use. To ensure accurate dosage, measure dose with a calibrated oral syringe, spoon, or measuring cup.*

Reconstitution of oral suspension

- *Follow the manufacturer's directions for mixing; the water volume is usually added in two aliquots, shaking well after each addition.*
- *After mixing, store oral suspension in a refrigerator. May be kept for 14 days without significant loss of potency. Shake well before using. Keep tightly closed.*

Contraindications/Precautions

Cephalexin does not treat viral infection (e.g., common cold). Prescribing in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria (antimicrobial resistance). Patients should be told to complete the full course of treatment, even if they feel better earlier.

Cephalexin is contraindicated for use in patients with cephalosporin hypersensitivity.

Cephalosporins cause hypersensitivity reactions in $\leq 5\%$ of patients receiving them. A variety of hypersensitivity reactions ranging from mild rash to fatal anaphylaxis may occur. Serum sickness reactions are a form of hypersensitivity to cephalosporins and may occur after a second course of cephalosporin therapy. Certain individuals may be more susceptible to allergic reactions to cephalosporins. The structural similarity between cephalexin and penicillin means that cross-reactivity can occur. The incidence of cross-reactivity to cephalosporins is approximately 3 to 7% in patients with a documented history of allergy to penicillin. Cephalexin should be administered with caution to individuals with a history of hypersensitivity to penicillin. Patients who have experienced severe, immediate-type penicillin hypersensitivity (e.g., acute bronchospasm, anaphylaxis, severe dermatologic reactions) should not receive cephalexin. The health care professional should have immediate availability of agents used in the treatment of severe anaphylaxis in the event of a serious allergic reaction to cephalexin.

Cephalexin should be used with caution in patients with renal impairment or renal failure since the drug is eliminated via renal mechanisms. The degree of renal impairment and the severity of the infection will determine if renal dose adjustments or dosage interval adjustments are required. Dosages may need to be reduced in these patients (see Dosage, renal impairment). Cephalexin may rarely worsen renal function; pre-existing renal impairment may increase the risk of drug-induced renal toxicity. In clinical studies of cephalexin, no overall differences in safety or effectiveness were observed between the geriatric and younger adults. However, because geriatric patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Prolonged use of cephalexin may result in overgrowth of nonsusceptible organisms. Observe the patient for signs of a superinfection, particularly with *Candida* or *Clostridium difficile*. Antibacterial agents have been associated with

pseudomembranous colitis (antibiotic-associated colitis) which may range in severity from mild to life-threatening. In the colon, overgrowth of *Clostridia* may exist when normal flora is altered subsequent to antibacterial administration. The toxin produced by *Clostridium difficile* is a primary cause of pseudomembranous colitis. It is known that systemic use of antibiotics predisposes patients to development of pseudomembranous colitis. Consideration should be given to the diagnosis of pseudomembranous colitis in patients presenting with diarrhea following antibacterial administration. Systemic antibiotics should be prescribed with caution to patients with inflammatory bowel disease such as ulcerative colitis or other GI disease. If diarrhea develops during therapy, the drug should be discontinued. Following diagnosis of pseudomembranous colitis, therapeutic measures should be instituted. In milder cases, the colitis may respond to discontinuation of the offending agent. In moderate to severe cases, fluids and electrolytes, protein supplementation, and treatment with an antibacterial effective against *Clostridium difficile* may be warranted. Products inhibiting peristalsis are contraindicated in this clinical situation. Practitioners should be aware that antibiotic-associated colitis has been observed to occur over two months or more following discontinuation of systemic antibiotic therapy; a careful medical history should be taken.

According to the manufacturer, cephalexin should be used with caution during breast-feeding.[29922] Most cephalosporins, including cephalexin, are excreted in breast milk in small quantities. After a 500 mg dose, the excretion of cephalexin in human milk increased up to 4 hours after the dose and reached a maximum concentration of 4 mcg/ml. The concentration then decreased gradually and was undetectable 8 hours after administration.[29922] In one mother being treated for a breast infection with cephalexin (500 mg PO q6h) and probenecid (500 mg PO q6h), breast milk concentrations of cephalexin and probenecid were 0.745 and 0.964 mcg/ml, respectively.[32196] These concentrations correspond to infant doses of 112 mcg/kg/day for cephalexin and 145 mcg/kg/day

day probenecid assuming a milk consumption of 150 ml/kg/day. This dose of cephalexin is significantly lower (i.e. < 1%) than doses prescribed for infants and children. In this case report, the nursing infant had severe diarrhea and discomfort and was crying; it is unclear whether these same effects would have been seen with cephalexin monotherapy. As with other oral antibiotics, alterations in the infant gut flora resulting in diarrhea may be expected; however, significant systemic effects do not appear to be common. Although the American Academy of Pediatrics (AAP) has not evaluated the use of cephalexin during breast-feeding, the AAP considers several other cephalosporins, such as cefazolin, cefprozil, and cefadroxil, to be usually compatible with breast-feeding.[27500] Consider the benefits of breast-feeding, the risk of potential drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding baby experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

Cephalexin is classified in FDA pregnancy risk category B. Animal data suggest that cephalexin does not impair fertility or cause harm to the fetus. Cephalexin does cross the placenta and distributes to fetal tissues. However, there are no adequate and well-controlled studies in pregnant women. Because limited data are available, cephalexin should be used during pregnancy only if clearly needed.[29922]

All cephalosporins, including cephalexin, may rarely cause hypoprothrombinemia and have the potential to cause bleeding. The mechanism is usually via the inhibition of normal gut flora and decreases in normal vitamin K synthesis, leading to coagulopathy. Cephalosporins which contain the NMTT side chain (i.e., cefoperazone, cefamandole, cefotetan) have been associated with an increased risk of hypoprothrombinemia. Cephalosporins should be used cautiously when there is a need for prolonged antibiotic therapy or other risk factors (e.g., malnutrition). Patients with a preexisting coagulopathy (e.g., vitamin K deficiency) may be at higher risk for developing

bleeding complications.

Cephalosporins have also been reported to cause false-positive results in urine glucose tests that contain cupric sulfate solution (e.g., Benedict's reagent, Clinitest); patients with diabetes mellitus who use urinary testing methods may receive caution regarding this interference. In addition, positive direct Coombs' tests have been reported in patients receiving cephalosporins, including cephalexin. If hematological testing is done in patients receiving cephalosporins, a false-positive Coombs' test may be caused by the antibiotic.

The cephalexin tablet for oral suspension should be used with caution in patients with phenylketonuria. Each 125 mg tablet for oral suspension contains 2.8 mg phenylalanine and each 250 mg tablet for oral suspension contains 5.6 mg phenylalanine.[43293]

Adverse Reactions

Gastrointestinal adverse reactions (nausea, vomiting, diarrhea) generally occur in < 5% of patients receiving cephalexin.[44471] Other gastrointestinal effects include abdominal pain, gastritis, and dyspepsia. Pseudomembranous colitis can occur during use or after the discontinuation of cephalexin, but this effect is rare. Pseudomembranous colitis may range from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Antibiotics alter the normal flora of the colon and may permit overgrowth of Clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of "antibiotic-associated" colitis. After establishing the diagnosis of pseudomembranous colitis, initiate treatment. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consider management with fluids and electrolytes, protein supplementation, and an antibacterial drug clinically effective against Clostridium difficile colitis. As with other cephalosporins and penicillins, transient hepatitis and cholestatic jaundice have been reported rarely. Colitis has also been reported with the

cephalosporin class.[29922] [43293] [43869]

Allergic reactions in the form of rash (unspecified), angioedema, maculopapular rash, urticaria and rarely erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis have been observed with cephalexin. Approximately 1—3% of treatment courses result in some kind of dermatologic allergic reaction. These reactions usually resolve upon discontinuation of the drug. Anaphylactoid reactions have also been reported and are likely occur in 0.0001—0.1% of patients.[29922] [43293] [43869] [44646] [44647]

Cephalexin has been associated with acute generalized exanthematous pustulosis (AGEP). The nonfollicular, pustular, erythematous rash starts suddenly, is associated with fever above 38 degrees C, and is distinct from pustular psoriasis, although biopsy results in each reveal spongiform subcorneal pustules. Drugs are the main cause of AGEP. A period of 2—3 weeks after an inciting drug exposure appears necessary for a first episode of AGEP. Unintentional reexposure may cause a second episode within 2 days. Clinical presentation is diverse with cutaneous lesions beyond erythema and pustules present in half of the cases. For example, bullous lesions, edema, purpura, pruritus, and mucosal erosions are possible. The mean duration of the pustules is 9.7 days followed by an annular desquamation, as long as the causative drug or factor is discontinued. The physiopathological mechanisms of AGEP have not been determined but the pathological criteria of edema, leukocytoclastic vasculitis, eosinophil exocytosis, and keratinocyte focal necrosis are distinctive. Pustule confluence or very small pustules may lead a clinician to make an incorrect diagnosis of TEN, of drug-induced erythroderma, or of staphylococcal scalded skin syndrome.[27736]

Nephrotoxicity occurs very rarely during therapy with cephalexin, but patients with renal dysfunction, patients receiving other nephrotoxic drugs, and patients over 50 years of age may be more susceptible. Interstitial nephritis (< 1%), a hypersensitivity reaction, has been reported

with many of the cephalosporins, including rarely with cephalexin. Renal dysfunction and toxic nephropathy have been reported with the cephalosporin class.[29922] [43293] [43869] [44649]

Seizures (< 1%) are rare, but a serious complication of cephalosporin therapy.[29922] [43293] [43869] [44649] More commonly associated with penicillins, the epileptogenic properties of both penicillins and cephalosporins are thought to be related to their beta-lactam ring. High doses and administration to patients with renal impairment (when the dosage was not reduced) are associated with an increased risk of seizures. Discontinue the drug if seizures occur; if clinically indicated, anticonvulsant therapy can be used.[23981]

Adverse reactions reported with cephalexin include genital and anal pruritus (pruritus ani). Superinfection due to alterations in local flora has resulted in local candidiasis such as thrush, genital moniliasis, as well as symptoms of vaginitis and vaginal discharge. Other reported adverse reactions include dizziness, fatigue, headache, agitation, confusion, hallucinations, arthralgia, arthritis, and joint disorder. There are rare reports of neutropenia, thrombocytopenia, and hemolytic anemia, which have all been reported in < 1% of patients on cephalosporin therapy. Elevated hepatic enzymes (slight increases in AST and ALT) has been reported in 1 to 7% of patients during cephalosporin use. Eosinophilia has been reported with cefazolin and occurs in 2.7 to 8.2% of patients receiving cephalosporins. Laboratory abnormalities and adverse reactions reported with cephalosporin-class antibiotics include fever, aplastic anemia, hemorrhage (bleeding), prolonged prothrombin time (hypoprothrombinemia) (< 1%), increased BUN, increased creatinine, elevated alkaline phosphatase, elevated bilirubin, elevated LDH, pancytopenia, leukopenia, and agranulocytosis. [29922] [43293] [43869] [44646] [44647] [44649]

Cephalexin (Keflex®) Specific Ocular Use

Adult dose 250- 500 mg QID x 7 - 14 days

Children 25-50 mg/kg QID x 7-14 days

Sulfa cross-sensitivity in 15% of cases

Example for use: preseptal cellulitis - internal hordeolum where an early/ acute hordeolum in an adult may be treated with 500 mg BID x 7 days or for early pre-septal cellulitis in an adult may be treated with 500 mg QID x 7 days.

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Minocycline

Drug Description

Minocycline is a tetracycline antibiotic with activity against many gram-negative and gram-positive organisms. It is inactive against viruses and fungi. In general, minocycline is the most lipid soluble and is considered the most active of the tetracycline group. Like doxycycline, minocycline is considered a long-acting tetracycline. Because of its lipid solubility, minocycline attains concentrations in the tears and saliva sufficient to eradicate the meningococcal carrier state. Minocycline is equivalent to doxycycline in the treatment of nongonococcal urethritis and mucopurulent cervicitis, but causes fewer adverse effects than doxycycline.[23476] Minocycline also has activity against some bacteria that are resistant to other tetracyclines. It has recently been shown to be effective in the treatment of rheumatoid arthritis, but is not a commonly employed modality.[24009] Minocycline was approved by the FDA in 1971. Arestin microspheres were approved by the FDA February 16, 2001 as adjunct in the treatment of periodontitis. An extended-release tablet (Solodyn®) was approved May 8, 2006 for treating nonnodular moderate to severe acne vulgaris. Although the manufacture of the intravenous formulation was discontinued in 2005, it was resumed in May 2009.

Classifications:	
Anti-infective Agents Tetracyclines	Dermatological Agents Topical Anti-infectives
Brand Names:	
Arestin® Minocin® Cleeravue-M®	Myrac® Dynacin® Solodyn®

Mechanism of Action

Minocycline is generally bacteriostatic against most organisms, although high concentrations of tetracyclines may be bactericidal. Bacteriostatic action appears to be a result of reversible binding to ribosomal units of susceptible organisms and inhibition of protein synthesis. Tetracyclines gain access to the ribosome after passive diffusion through porin channels in the bacterial membrane; however, minocycline, because of its lipid solubility, may also pass directly through the lipid bilayer. An active transport process also exists in bacterial cells. Tetracyclines bind to the 30 S ribosomal subunit. This prevents binding of tRNA to the mRNA-ribosome complex, interfering with protein synthesis. Only multiplying organisms are affected. In general, gram-positive bacteria are more susceptible than are gram-negative bacteria. Tetracycline resistance in community-acquired MRSA (CA-MRSA) isolates is primarily associated with the tetK gene. The tetM resistance gene confers resistance to the entire class; however, the tetK gene confers resistance to tetracycline and an inducible resistance to doxycycline, but has no impact on minocycline susceptibility.[26456] [35529] [41812] [46693]

Indications

Per the manufacturer, this drug has been shown to be active against most strains of the following microorganisms either in vitro and/or in clinical infections: *Acinetobacter* sp., *Actinomyces israelii*, *Actinomyces* sp., *Bacillus anthracis*, *Bartonella bacilliformis*, *Bordetella pertussis*, *Borrelia burgdorferi*, *Borrelia recurrentis*, *Brucella* sp., *Burkholderia mallei*, *Burkholderia pseudomallei*, *Campylobacter fetus*, *Chlamydia psittaci*, *Chlamydia trachomatis*, *Clostridium perfringens*, *Clostridium* sp., *Clostridium tetani*, *Coxiella burnetii*, *Eikenella corrodens*, *Entamoeba* sp., *Enterobacter aerogenes*, *Escherichia coli*, *Francisella tularensis*, *Fusobacterium fusiforme*, *Fusobacterium nucleatum*, *Haemophilus ducreyi*, *Haemophilus influenzae* (beta-lactamase negative), *Haemophilus influenzae* (beta-lactamase positive), *Klebsiella granulomatis*, *Klebsiella* sp., *Legionella pneumophila*, *Leptospira* sp., *Leptotrichia buccalis*, *Listeria*

monocytogenes, Mycobacterium marinum, Mycoplasma hominis, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia sp., Pasteurella multocida, Porphyromonas gingivalis, Prevotella intermedia, Propionibacterium acnes, Propionibacterium propionicum, Rickettsia akari, Rickettsia prowazekii, Rickettsia rickettsii, Rickettsia tsutsugamushi, Shigella sp., Spirillum minus, Staphylococcus aureus (MRSA), Staphylococcus aureus (MSSA), Streptobacillus moniliformis, Streptococcus pneumoniae, Treponema pallidum, Treponema pertenue, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Yersinia enterocolitica, Yersinia pestis

NOTE: The safety and effectiveness in treating clinical infections due to organisms with in vitro data only have not been established in adequate and well-controlled clinical trials.

Intravenous and Oral dosage:
Adults: <i>Minocycline is not included in the CDC's sexually transmitted diseases guidelines for lymphogranuloma venereum.[43632] Manufacturer recommends 200 mg IV/PO initially, then 100 mg IV/PO every 12 hours. Alternatively, if more frequent oral doses are preferred, 100 to 200 mg PO initially followed by 50 mg PO every six hours.[44476]</i>
Children 8 years and Adolescents: <i>Minocycline is not included in the CDC's sexually transmitted diseases guidelines for lymphogranuloma venereum.[43632] The manufacturer recommends 4 mg/kg IV/PO initially, followed by 2 mg/kg IV/PO every 12 hours (do not exceed adult dose).[44476]</i>
Maximum Dosage Limits
Adults: 350 mg base PO on day 1, then 200 mg/day PO; 400 mg base/day IV.
Elderly: 350 mg base PO on day 1, then 200 mg/day PO; 400 mg base/day IV.

Maximum Dosage Limits continued
Adolescents: <i>Maximum dosage information is not available. Do not exceed adult dosage.</i>
Children: <i>>= 8 years: Maximum dosage information is not available. Do not exceed adult dosage. < 8 years: Safety and efficacy have not been established.</i>

For the treatment of other chlamydial infections (e.g., psittacosis) including chlamydial conjunctivitis (e.g., trachoma and inclusion conjunctivitis) and lymphogranuloma venereum:

Patients with Hepatic Impairment Dosing

Although data are lacking, dose adjustment may be required in patients with hepatic disease because hepatic metabolism of minocycline may theoretically be delayed in these patients. If signs and symptoms of hepatitis develop during minocycline therapy, the patient should be evaluated for potential minocycline-induced hepatitis (see Adverse Reactions) and alternative therapy considered.

Patients with Renal Impairment Dosing

Minocycline should be avoided in patients who have end-stage renal disease. Doses should be reduced or the time intervals between doses should be extended in patients with renal impairment due to the potential for dose-related elevations in BUN. Patients with renal impairment should not exceed minocycline doses of 200 mg/day IV or PO.

Route-Specific Administration

Oral Administration

- *May be administered without regard to meals or milk. Administering with food may reduce the risk of esophageal irritation and ulceration. Do not administer at bedtime or to patients with esophageal obstruction or compression because of increased risk of esophageal irritation or ulceration.*

- *Divalent and trivalent cations significantly affect absorption. Do not administer sucralfate (contains aluminum), oral iron supplements, or aluminum-, magnesium- or calcium-containing antacids with or within 4 hours of oral minocycline. Multivitamins containing manganese or zinc salts will also decrease absorption.*

Oral Solid Formulations

- *Extended-release capsules: Swallow whole. Do not crush, chew, or split.[51234]*

Contraindications / Precautions

Minocycline microspheres (e.g., Arestin) has not been clinically tested for use in the regeneration of alveolar bone, either in preparation for or in conjunction with the placement of endosseous (dental) implants or in the treatment of failing implants.

Minocycline and other tetracycline antibiotics are contraindicated in patients with known tetracyclines hypersensitivity. Post-marketing reports have included cases of severe hypersensitivity reactions and autoimmune syndromes including a lupus-like syndrome.

Minocycline microspheres for periodontal disease should be used cautiously in patients with a history of predisposition to oral candidiasis. The safe and effective use of this formulation has not been established for the treatment of periodontitis in patients with coexistent oral candidiasis. Also, minocycline microspheres have not been clinically tested in patients with immunosuppression (i.e., those with immune suppression from diabetes, chemotherapy, radiation therapy, or HIV infection).

Minocycline crosses the placenta and is classified as pregnancy category D. No adequate and well-controlled trials have been conducted to assess the risk of fetal harm, but post-marketing reports have included cases of congenital anomalies, including limb reduction. Tetracyclines also may affect the dentin and enamel of developing teeth during the second and third trimesters and may cause permanent yellow or brown discoloration and enamel hypoplasia. Tooth development occurs during the last half of pregnancy, infancy,

and childhood. Tooth discoloration is more common during the long-term use of the drug but has been observed after repeated short-term courses. If minocycline is used during pregnancy or if the patient becomes pregnant while taking the medication, the patient should be apprised of the potential hazard to the fetus.[41812] Minocycline microspheres for periodontitis have not been clinically tested in pregnant women. [44475]

Tetracyclines are distributed in small amounts into breast milk. In general, manufacturers recommend that tetracycline antibiotics, including minocycline, not be used in breast-feeding mothers due to a theoretical risk of causing teeth discoloration, enamel hypoplasia, inhibition of linear skeletal growth, oral and vaginal thrush, or photosensitivity reactions in the nursing infant. [41812] However, because tetracyclines bind to calcium in the maternal breast milk, the risk for oral absorption by the infant is minimal.[47299] Minocycline does not have a listed American Academy of Pediatrics (AAP) breast-feeding category, but another tetracycline antibiotic, tetracycline, is rated as usually compatible with breast-feeding.[27500] Doxycycline may be a potential alternative to consider during breast-feeding. However, site of infection, patient factors, local susceptibility patterns, and specific microbial susceptibility should be assessed before choosing an alternative agent. Although doxycycline has also not been evaluated by the AAP, data indicate that after doses of 100 to 200 mg PO, milk concentrations do not exceed an average of 1.8 mg/L.[33777] [33778] [33779] [33780] Based on breast milk concentrations after doxycycline doses of 100 mg/day, the estimated average intake of an exclusively breast-fed infant would be about 6% of the maternal weight-adjusted dosage.[33776] Studies of long-term tetracycline use in breast-feeding are lacking. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

In general, minocycline tablets, capsules, and intravenous formulations should not be used in neonates, infants, and children under the age of eight years. The extended-release tablets should not be used in neonates, infants, and children less than 12 years old. The minocycline subgingival powder should not be used in neonates, infants, children, and adolescents. Tetracyclines may cause a permanent yellow-gray-brown discoloration of teeth and a reversible decrease in fibula growth rate caused by complexation with calcium in growing bone tissue. Tooth discoloration is more common during the long-term use of the drug but has been observed after repeated short-term courses. Minocycline is recommended for use in children under 8 years of age only if other drugs are contraindicated or are not likely to be effective.

Minocycline should not be used in patients who have end-stage renal disease or renal failure. Doxycycline is the preferred tetracycline in this situation. Minocycline, however, has less renal clearance than other tetracyclines and is acceptable to use in patients with mild to moderate renal impairment. Doses should be reduced or the time intervals between doses should be extended in patients with renal impairment due to the potential for dose-related elevations in serum BUN (see Dosage). Monitoring of serum creatinine and BUN is recommended.

Although data are lacking, dose adjustment may be required in patients with hepatic disease because hepatic metabolism of minocycline may theoretically be delayed in these patients. If signs and symptoms of hepatitis develop during minocycline therapy, the patient should be evaluated for potential minocycline-induced hepatitis (see Adverse Reactions) and alternative therapy considered.

Sufficient numbers of geriatric patients (age 65 and over) were not included in clinical studies of minocycline. It has not been determined whether elderly patients respond differently from younger ones. In general, dose selection for an elderly patient should be cautious, usually starting at the

low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Photosensitivity is a risk of tetracycline therapy.[30713] Direct sunlight (UV) exposure should be avoided or minimized.

Photosensitivity reactions are believed to be caused by accumulation of the drug in the skin and are mostly phototoxic in nature, but photoallergic reactions also can occur. Reactions can develop within a few minutes or up to several hours after exposure and can occur one to two days after discontinuation of the drug. Minocycline is less likely to produce this reaction than other tetracyclines. It is generally agreed that sunscreens do little to prevent this reaction.

Minocycline oral suspension may contain sodium sulfite. Sulfites cause an allergic reaction in some people and this product should be used with caution in patients with a known sulfite hypersensitivity. This sensitivity reaction is more common in asthmatic than in non-asthmatic patients.

Almost all antibacterial agents have been associated with pseudomembranous colitis (antibiotic-associated colitis) which may range in severity from mild to life-threatening.

In the colon, overgrowth of Clostridia may exist when normal flora is altered subsequent to antibacterial administration. The toxin produced by Clostridium difficile is a primary cause of pseudomembranous colitis. It is known that systemic use of antibiotics predisposes patients to development of pseudomembranous colitis. Consideration should be given to the diagnosis of pseudomembranous colitis in patients presenting with diarrhea following minocycline administration. Systemic antibiotics should be prescribed with caution to patients with inflammatory bowel disease such as ulcerative colitis or other GI disease. If diarrhea develops during therapy, the drug should be discontinued. Following diagnosis of pseudomembranous colitis, therapeutic measures should be instituted. In milder cases, the colitis may respond to

discontinuation of the offending agent. In moderate to severe cases, fluids and electrolytes, protein supplementation, and treatment with an antibacterial effective against *Clostridium difficile* may be warranted. Products inhibiting peristalsis are contraindicated in this clinical situation. Practitioners should be aware that antibiotic-associated colitis has been observed to occur over two months or more following discontinuation of systemic antibiotic therapy; a careful medical history should be taken.

Autoimmune disease, including drug-induced lupus-like syndrome, autoimmune hepatitis and vasculitis, have been associated with prolonged use of minocycline. Additionally, cases of serum sickness have been observed shortly after minocycline treatment. Appropriate laboratory tests (e.g., liver function tests, ANA, CBC) should be performed in patients developing symptoms of fever, rash, arthralgia, and malaise. Consider discontinuing treatment in symptomatic patients. [51234]

Minocycline has been associated with the development of serious rash, including some fatalities. Consider immediate discontinuation of therapy in patients developing a rash or exfoliative dermatitis in conjunction with eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis, or pericarditis.[51234]

As with other antibiotics, antimicrobial resistance and overgrowth of non-susceptible organisms may occur during treatment with minocycline. If a superinfection develops, initiate appropriate therapy and consider discontinuing minocycline. [51234]

Increased intracranial pressure resulting in papilledema has been reported following treatment with minocycline in the adult and adolescent populations. Symptoms, including headache and blurred vision, often resolve following treatment discontinuation; however in some cases, the possibility of permanent vision loss exists. Question patients regarding visual disturbances prior to initiating minocycline

therapy and monitor for visual impairment during treatment. Avoid concomitant use with other medications known to increase intracranial pressure, such as isotretinoin (see Interactions). In infants, cases of bulging fontanels have been associated with tetracyclines.[51234]

Adverse Reactions

Gastrointestinal adverse events are the most commonly reported side effects associated with minocycline. Anorexia, nausea, and vomiting can occur in 30 to 40% of patients.[44477] Diarrhea, enterocolitis, glossitis, pancreatitis, and pseudomembranous colitis are also possible adverse GI effects. Stomatitis can also occur with minocycline use and was reported in 6.4% of patients using the periodontal powder in studies. Dyspepsia has been reported with minocycline use and occurred in 4% of patients using the periodontal powder in studies. Dry mouth (xerostomia) was reported in 1% of patients using the extended-release tablets. Abdominal complaints occur most often following oral administration and can be minimized by taking each dose with a large volume of water and avoiding dosage at bedtime.[35529] [36112] [41812] [44475] [44476] [44477] One study revealed that adverse GI effects were less common with minocycline than with doxycycline.[23476] Rare cases of esophagitis and esophageal ulceration have been reported in patients receiving capsule and tablet dosage forms of tetracycline antibiotics. Minocycline-induced esophagitis is characterized by sudden onset odynophagia, retrosternal pain, and dysphagia. Risk factors include taking the medication without water and at night. Symptoms usually resolve within days to weeks after stopping the medication.[35529] [36112] [41812] [44475] [44476] [44477]

Hepatotoxicity (e.g., elevated hepatic enzymes, hyperbilirubinemia, hepatic cholestasis, hepatic failure with some fatalities, hepatitis with autoimmune features, and jaundice) has been reported.[35529] [36112] [41812] [44475] [44476] [44477] Abdominal complaints may suggest hepatotoxicity; the incidence of this effect is roughly 4.7%.[23519] Liver toxicity is possible

with excessive accumulation of the minocycline, which can occur in patients with renal impairment receiving even usual oral or parenteral doses. [35529] [36112] [41812] [44475] [44476] [44477]

As with any antibiotic, superinfection, including fungal overgrowth can occur with minocycline therapy. This can result in oral, rectal, or vaginal candidiasis. The condition usually resolves upon discontinuation of the drug. Vulvovaginitis (vaginitis) has also been reported. Dental infection (3.8%), unspecified infection (7.6%), and flu syndrome (influenza) (5%) have been noted with the use of the periodontal powder. [35529] [36112] [41812] [44475] [44476]

Hematologic effects such as agranulocytosis, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and eosinophilia have been reported rarely with minocycline. [35529] [36112] [41812] [44475] [44476]

Arthralgia (1%), arthritis, bone discoloration, myalgia (1%), joint stiffness, and joint swelling have been reported with minocycline use. [35529] [36112] [41812] [44475] [44476]

Fever and discoloration of body secretions have been reported with minocycline use. Malaise was reported in 4% of patients using the extended-release tablets. Unspecified pain was reported in 4.3% of patients receiving the periodontal powder. [35529] [36112] [41812] [44475] [44476]

Photosensitivity can occur if patients taking tetracycline antibiotics are exposed to direct sunlight or UV light. Warning signs, including tingling and burning of the hands, feet, and nose, may indicate latent photosensitivity. If the drug is discontinued, symptoms are usually alleviated within one to two days. Sunscreens seem to provide only limited protection, and a severe response may necessitate treatment with corticosteroids or antihistamines. Some patients being treated for acne or rheumatoid arthritis with minocycline have shown a muddy brown skin hyperpigmentation, which is accentuated by exposure to sunlight. Patients with

immunobullous disease (e.g., pemphigus) also tend to show significant skin hyperpigmentation when taking minocycline. Hyperpigmentation of the skin, mucous membranes, and other tissues and organs (nails, bone, eyes, thyroid, visceral tissues, oral cavity, sclerae, and heart valves) can occur. Skin and oral pigmentation are independent of drug exposure, but other tissue pigmentation is related to prolonged use. Other dermatological adverse effects have included alopecia, erythema nodosum, nail discoloration, pruritus (5%), rash (unspecified), and vasculitis. Erythematous and maculopapular rash have been reported. Also, tetracyclines have been associated with exfoliative dermatitis, toxic epidermal necrolysis, and erythema multiforme, and Stevens-Johnson syndrome (aching joints and muscles; redness, blistering, peeling of the skin). Fixed drug eruptions have also occurred with lesions on the glans penis causing balanitis. In addition, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), which is also known as Hypersensitivity Syndrome (HHS), has been reported. [40959] [35529] [41812] [36112] [44475] [44476]

Oral minocycline has been associated with the development of autoimmune syndromes including a lupus-like syndrome. Common lupus-like symptoms included positive antinuclear antibody; myalgia, arthralgia, arthritis, and swelling of the joints; morning stiffness, pleuritic chest pain, fever, rash, vasculitis, and hepatitis have also been reported. [35529] [36112] [41812] [44475] [44476] Time of presentation of symptoms ranged from as early as 10 days after initiation of minocycline to after 6 years of continued use. In a case-controlled study, the use of minocycline for acne was associated with an 8.5-fold increased risk of developing a lupus-like syndrome as compared with patients who had not taken minocycline or who had been past users of tetracycline. Women and patients who have used minocycline for extended periods may be at increased risk. The syndrome is uncommon and is reversible upon stopping minocycline. [25548] A serum sickness-like reaction consisting of fever, urticaria (2%) or rash, and arthralgia,

arthritis, joint stiffness, or joint swelling has also been reported sporadically and shortly after oral minocycline use. Eosinophilia may be present. Other hypersensitivity reactions have included anaphylaxis/anaphylactoid reactions (including anaphylactic shock and fatalities), anaphylactoid purpura, erythema multiforme, myocarditis, pericarditis, polyarthralgia, Stevens-Johnson syndrome, systemic lupus erythematosus exacerbation, pulmonary infiltrates with eosinophilia, and urticaria.[35529] [36112] [41812] [44475] [44476]

Tooth discoloration has been seen in children who received a tetracycline antibiotic (see Contraindications), but this reaction has also been reported in adults. Enamel hypoplasia can result.[35529] [36112] [41812] [44475] [44476] Although this is not typically thought of as teratogenesis, some references include tetracyclines in lists of teratogenic drugs. [24291] While isolated cases of major fetal malformations have been reported in offspring of mothers who received a tetracycline drug during pregnancy, analysis of the data does not support an association between these drugs and these major malformations (e.g., oral clefts, spina bifida, polydactyly). Limited data exist which support a possible risk of minor malformations (e.g., hypospadias, inguinal hernia). Tongue discoloration, lip discoloration, gum discoloration, and bone discoloration have also been reported. All are cosmetically troubling for patients.[35529] [36112] [41812] [44475] [44476] Bone discoloration is also more common with minocycline than with other tetracyclines. Because minocycline is lipid soluble, it penetrates easily into body fluids and various body tissues including saliva, gingival crevicular fluid, bone and soft tissue. Minocycline-associated discoloration may take months to years to resolve. Ascorbic acid administered while taking minocycline may inhibit minocycline-associated pigmentation.[32777]

Adverse renal effects are usually a problem only for patients with seriously impaired renal function. Interstitial nephritis has been reported with minocycline. The antianabolic action of the

tetracyclines may cause an increase in BUN. High serum levels of the tetracyclines may lead to azotemia, hyperphosphatemia, or metabolic acidosis. Under such conditions, monitoring of creatinine and BUN is recommended and dosage restrictions are suggested. Acute renal failure (unspecified) has been reported. If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulation of the drug and possible liver toxicity.[35529] [36112] [41812] [44475] [44476] Historically, Fanconi syndrome has been associated with use of outdated tetracyclines, although new formulations will probably minimize the risk of this adverse reaction.

CNS side effects, including dizziness (9%), drowsiness (2%), fatigue (9%), hyperesthesia, lightheadedness, paresthesias, seizures, and vertigo (1%) have been reported with minocycline and tend to disappear rapidly once the drug is discontinued. Headache has also been reported including with the extended release tablets (23%) and the periodontal powder (9%). Mood alterations (3%) have been noted with the extended release tablets. Minocycline has also been reported to cause benign increased intracranial pressure (pseudotumor cerebri) in adults and bulging fontanels in infants.[35529] [36112] [41812] [44475] [44476]

Phlebitis can occur following IV injection of minocycline, especially if therapy is prolonged. Other types of injection site reaction include erythema and pain.[35529]

Respiratory adverse reactions to minocycline have included asthma exacerbation, cough, dyspnea, bronchospasm, and pneumonitis. [35529] [36112] [41812] [44475] [44476]

Tinnitus (2%) and hearing loss have been reported in patients receiving minocycline.[35529] [36112] [41812] [44475] [44476]

A secondary malignancy, thyroid cancer, has been linked to minocycline in post-marketing reports. In addition, prolonged therapy with tetracyclines, such as minocycline, have been

reported to produce brown-black microscopic discoloration of the thyroid gland; cases of abnormal thyroid function have been reported. Monitor for signs of thyroid cancer and abnormal thyroid function in patients receiving extended treatment with minocycline.[35529] [36112] [41812] [44475] [44476]

Oral adverse events reported with the minocycline periodontal powder include periodontitis (16.3%), tooth disorder (12.3%), dental caries (9.9%), dental pain (9.9%), gingivitis (9.2%), oral ulceration (5%), pharyngitis (4.3%), and mucous membrane disorder (3.3%). [44475]

Minocycline Specific Ocular Use

Adult dose 50-100 mg BID x 1-6 weeks

Children 50 mg q12h for a duration that is less than 5 days and if over 12 years of age)

Contraindicated in pregnant or lactating patients and causes increased photosensitivity

Example for use: Blepharitis, MGD, internal or external hordeolum where treatment for an adult patient is 100 mg BID x 7-21 days .

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Overview of AntiVirals

Antiviral drugs are a class of medication used specifically for treating viral infections.[1] Like antibiotics for bacteria, specific antivirals are used for specific viruses. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead they inhibit their development.

Antiviral drugs are one class of antimicrobials, a larger group which also includes antibiotic (also termed antibacterial), antifungal and antiparasitic drugs. They are relatively harmless to the host, and therefore can be used to treat infections. They should be distinguished from viricides, which are not medication but deactivate or destroy virus particles, either inside or outside the body. Antivirals also can be found in essential oils of some herbs, such as eucalyptus oil and its constituents.[2]

Most of the antiviral drugs now available are designed to help deal with HIV, herpes viruses (best known for causing cold sores and genital herpes, but actually the cause of a wide range of other diseases, such as chicken pox), the hepatitis B and C viruses, which can cause liver cancer, and influenza A and B viruses. Researchers are working to extend the range of antivirals to other families of pathogens.

Designing safe and effective antiviral drugs is difficult, because viruses use the host's cells to replicate. This makes it difficult to find targets for the drug that would interfere with the virus without also harming the host organism's cells. Moreover, the major difficulty in developing vaccines and antiviral drugs is due to viral variation.

The emergence of antivirals is the product of a greatly expanded knowledge of the genetic and molecular function of organisms, allowing biomedical researchers to understand the structure and function of viruses, major advances in the techniques for finding new drugs, and the intense pressure placed on the medical profession to deal with the human immunodeficiency virus (HIV), the cause of the deadly acquired immunodeficiency syndrome (AIDS) pandemic.

The Oral Ocular Formulary includes the following AntiVirals or their generic or therapeutic equivalents:

1. *Acyclovir*

2. *Famciclovir*

3. *Valacyclovir*

The following sections will provide relevant clinical information about each of the agents listed above, including mechanism of action, indication, contraindications, adverse reactions, drug interactions, general dosing guides, special instructions, and most importantly, dosages and examples of use specifically for optometrists for the treatment of ocular conditions. This particular information for optometrists is included at the end of each drug section.

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Acyclovir

Drug Description

Acyclovir is a synthetic deoxyguanosine analog and it is the prototype antiviral agent that is activated by viral thymidine kinase. The antiviral activity of acyclovir is primarily against herpes viruses (e.g., herpes simplex virus [HSV] and varicella-zoster virus [VZV]); although, it has limited efficacy against cytomegalovirus (CMV) and Epstein-Barr virus (EBV). The selective activity of acyclovir is due to its affinity for the thymidine kinase enzyme encoded by HSV and VZV. Acyclovir is approximately 10-times more potent against HSV-1 and -2 than against VZV. It has even less activity against CMV and EBV. The effectiveness of acyclovir against EBV is limited to actively infected cells; latent or persistent EBV infection is not affected. Acyclovir is not effective against the human immunodeficiency virus. Clinically, acyclovir is used in the treatment of herpes simplex, herpes genitalis, and herpes zoster infections. The FDA approved acyclovir in March 1982. It is available as oral, buccal, parenteral, and topical formulations.[54268]

Classifications:
<i>Anti-infective Agents Antivirals</i> <i>Topical Antivirals</i> <i>Dermatological Agents Topical Antiinfectives</i> <i>Topical Antivirals</i>
Brand Names:
<i>Zovirax®</i>

Mechanism of Action

Acyclovir inhibits viral DNA synthesis. Acyclovir must be phosphorylated intracellularly to be active. Acyclovir is converted to the monophosphate by viral thymidine kinase, then to diphosphate by cellular guanylate kinase, and finally to the triphosphate by various cellular enzymes. Acyclovir triphosphate competitively inhibits viral DNA polymerase, and to a lesser extent human DNA polymerase. Acyclovir triphosphate also competes with the natural

substrate, deoxyguanosine triphosphate, for incorporation into viral DNA. Formation of a complex at the end of the DNA strand may lead to irreversible inactivation of viral DNA polymerase. Herpes virus DNA polymerases differ in sensitivity to acyclovir. Acyclovir is effective only against actively replicating viruses; it does not eliminate the latent herpes virus genome. The range of in vitro minimum inhibitory concentrations of acyclovir are as follows: HSV-1, 0.02 to 0.9 mcg/ml; HSV-2, 0.3 to 2.2 mcg/ml; VZV, 0.8 to 4 mcg/ml; CMV 2 to 57 mcg/ml; and EBV, 1.6 mcg/ml. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral thymidine kinase. Uninfected cells show only minimal phosphorylation of acyclovir, and there is only a small amount of acyclovir taken up into these cells. The concentration of acyclovir triphosphate is 40 to 100 times higher in HSV-infected cells than non-infected cells.

Viral resistance to acyclovir may occur due to loss of thymidine kinase activity, alterations in thymidine kinase substrate specificity, or decreased DNA-polymerase sensitivity. Alterations in these enzymes occur due to point mutations or base insertions or deletions in the specific genes. The most common mechanism of resistance is loss of thymidine kinase activity. These viral variants are also cross resistant to other antiviral agents activated by thymidine kinase (e.g., ganciclovir or penciclovir). Thymidine kinase negative variants of herpes virus may cause severe disease in infants and immunocompromised patients. Acyclovir-resistant herpes simplex virus has been seen in immunocompromised patients, patients with concurrent HIV infection, and immunocompetent patients with genital herpes. Repeated systemic treatment may lead to the development of viral resistance in immunosuppressed patients.

Indications

Per the manufacturer, this drug has been shown to be active against most strains of the following microorganisms either in vitro and/or in clinical infections:

- *herpes simplex virus type 1*

- *herpes simplex virus type 2*
- *varicella-zoster virus*

NOTE: The safety and effectiveness in treating clinical infections due to organisms with in vitro data only have not been established in adequate and well-controlled clinical trials.

This drug may also have activity against the following microorganisms:

- *B virus (cercopithecine herpesvirus)*
- *cytomegalovirus (CMV)*

NOTE: Some organisms may not have been adequately studied during clinical trials; therefore, exclusion from this list does not necessarily negate the drug's activity against the organism.

For the treatment of acute herpes zoster ocular infection[†] (herpes zoster ophthalmicus[†]) in immunocompetent patients:

Oral dosage:
Adults: 600 mg PO every four hours five times per day for 10 days. Initiate therapy within 72 hours but no later than seven days of rash onset.
Maximum Dosage Limits
Adults: 60 mg/kg/day IV; 4000 mg/day PO; 50 mg/dose buccal.
Geriatric: 60 mg/kg/day IV; 4000 mg/day PO; 50 mg/dose buccal
Adolescents: 60 mg/kg/day IV; 4000 mg/day PO; safety and efficacy of buccal tablet not established.
Children: 60 mg/kg/day IV; 80 mg/kg/day PO or 4000 mg/day PO, whichever is less; safety and efficacy of buccal tablet not established.

Maximum Dosage Limits continued
Infants: See indications.
Neonates: See indications.

Patients with Hepatic Impairment Dosing

No dosage adjustment needed.

Patients with Renal Impairment Dosing

CrCl > 50 ml/min or for neonates with CrCl > 50 ml/min/1.73 m² or serum creatinine < 0.7 mg/dl [33853]: No dosage adjustment needed.
CrCl 25 to 50 ml/min or for neonates with CrCl 25 to 50 ml/min/ 1.73 m² or serum creatinine 0.8 to 1.1 mg/dl [33853]: Extend IV dosing interval to every 12 hours. No adjustment required for oral dosage regimens.
CrCl 10 to 24 ml/min or for neonates with CrCl 10 to 24 ml/min/1.73 m² or serum creatinine 1.2 to 1.5 mg/ml [33853]: Extend IV dosing interval to every 24 hours. For patients receiving 800 mg PO five times per day, the dosage interval should be extended to every 8 hours. No dosage adjustment is necessary for patients receiving 400 mg PO every 12 hours or 200 mg PO five times per day. a loading dose of 250 to 500 mg PO, a dose of 250 mg PO every 12 to 24 hours has been recommended.
CrCl < 10 ml/min or for neonates with CrCl < 10 ml/min/1.73 m², serum creatinine > 1.5 mg/dl, or urine output < 1 ml/kg/hr [33853]: Reduce recommended IV dose by 50% and extend dosing interval to every 24 hours. For patients receiving 200 mg PO five times per day or 400 mg PO every 12 hours, reduce dose to 200 mg PO every 12 hours. For patients receiving 800 mg PO five times per day, reduce dose to 800 mg PO every 12 hours.

Intermittent hemodialysis

See oral dosage for CrCl < 10 ml/min. If using IV dosing, extend the intravenous dosing interval to every 24 hours and adjust the dosing schedule so a dose is administered after each

dialysis session. Alternatively, some clinicians recommend a dose of 2.5 mg/kg IV every 24 hours, with a supplemental dose of 2.5 mg/kg IV given after each standard dialysis session.

Continuous hemodialysis (CAVHD, CVVHD)

Definitive dosage recommendations have not been established. Acyclovir is significantly removed by CAVHD or CVVHD. A dose 1.3 times that used for anuric nondialyzed patients has been recommended, assuming a combined dialysis and ultrafiltrate flow rate of 1.5 L/hr.[24879]

Route-Specific Administration

Oral Administration

- *All oral dosage forms: May be administered without regard to meals.*

Oral Solid Formulations

Buccal tablet:

- *With a dry finger, remove the tablet out of the blister.*
- *On the same side of the mouth as the herpes labialis symptoms, immediately apply the rounded side of the tablet to the upper gum above the incisor tooth (canine fossa). Hold the tablet in place with slight pressure for 30 seconds.*
- *Once adhered, the tablet will gradually dissolve. Do not crush, chew, suck, or swallow the tablet.*
- *If adhesion does not occur or the tablet falls off within the first six hours, immediately reposition the same tablet. If the tablet cannot be repositioned, a new tablet should be applied.*
- *If the tablet is swallowed within the first six hours, instruct the patient to drink a glass of water and apply a new tablet.*
- *If the tablet falls or is swallowed after the first six hours, reapplication is not needed.[54268]*

Oral Liquid Formulations

- *Shake the suspension well prior to administration. Measure the suspension with a calibrated oral dosing device to give accurate dosage.*

Contraindications/Precautions

Acyclovir is contraindicated in patients who have developed acyclovir hypersensitivity or

valacyclovir hypersensitivity. Because of similar chemical structures and possible cross-sensitivity, acyclovir should not be used in patients with famciclovir hypersensitivity, ganciclovir hypersensitivity, penciclovir hypersensitivity, or valganciclovir hypersensitivity. Alternative agents such as foscarnet or cidofovir may be suitable since they are not structurally related to these antivirals. The buccal tablet contains milk protein concentrate, and is therefore contraindicated in patients with milk protein hypersensitivity.[54268]

Since acyclovir is excreted primarily by glomerular filtration and tubular secretion, use caution when administering systemic acyclovir to patients with renal dysfunction. Patients with renal impairment or renal failure should receive lower doses of acyclovir at longer intervals (see Dosage). Patients with renal dysfunction are at increased risk of acyclovir-induced neurotoxicity due to high levels of acyclovir. In order to prevent crystalluria, patients should be well-hydrated to maintain a high urine volume and avoid dehydration during therapy with acyclovir. Patients receiving potentially nephrotoxic drugs together with acyclovir may have an increased risk of renal dysfunction. Additionally, intravenous acyclovir must be administered over 1 hour to avoid the precipitation of acyclovir crystals in the renal tubules which could result in damage and acute renal failure.[41766] [28977]

Systemic acyclovir should be used with caution in patients with a preexisting seizure disorder or other neurological disease due to a possible increased risk of adverse effects.[41766] [28977]

For systemic acyclovir, the duration of pain after healing was longer in geriatric patients ≥ 65 years compared to younger patients. Renal adverse events, nausea, vomiting, and dizziness are more frequently in elderly subjects. Elderly patients are more likely to have reduced renal function and require dose reduction. Elderly patients are also more likely to have CNS adverse events (e.g., somnolence, hallucinations, confusion, or coma) possibly related to changes in renal function.[28977] [41766]

Oral, buccal, intravenous, and topical acyclovir products are classified as FDA pregnancy risk category B. No complete or well-controlled pregnancy studies have been performed in humans. Acyclovir was not found to be teratogenic in standard animal studies. A prospective epidemiologic registry of acyclovir use during pregnancy was established in 1984 and completed in April 1999. There were 756 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for specific defects or to permit definitive conclusions regarding the safety of acyclovir in pregnant women. Systemic use should be avoided during pregnancy unless the potential benefits outweigh the possible risks to the fetus.[28977] [41766] [43519] [54268]

Following oral administration of acyclovir, breast milk concentrations one to four times that of those found in maternal plasma have been observed.[24464] These concentrations would potentially expose the nursing infant to a dose of acyclovir as high as 0.3 mg/kg/day. Intravenous acyclovir doses of 60 mg/kg/day are used for the treatment of neonatal herpes, and the American Academy of Pediatrics considers maternal use of systemic acyclovir to be compatible with breast-feeding [27500]. Exposure of the infant after maternal use of topical administration of acyclovir is minimal, provided the treatment area does not involve the breast. Women who have active herpetic lesions on or near the breast should avoid nursing until the lesions have completely resolved. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

The safe and effective use of acyclovir ointment in neonates, infants, children, and adolescents has not been established. Safety and efficacy

of acyclovir cream have not been established in neonates, infants, and children less than 12 years of age. Use of the buccal tablet should be avoided in pediatric populations because of its complex administration procedure and the potential risk of choking. Oral formulations are not recommended by the manufacturer for use in children < 2 years of age, infants, and neonates. The intravenous formulations are approved for all pediatric populations, including neonates.[28977] [41766] [43519] [43520] [54268]

Acyclovir cream and ointment products are for external topical use only. Avoid ophthalmic administration or use inside the mouth or nose. [43519] [43520]

Acyclovir for injection is intended for intravenous use only. It is not for intramuscular administration or subcutaneous administration.[41766]

Adverse Reactions

Systemic acyclovir is associated with nephrotoxicity, which occurs as a result of crystallization of the drug within the nephron. Acyclovir has low solubility in urine. Low urine volume associated with volume contraction may contribute to crystalluria. Crystalluria can lead to azotemia, renal tubular obstruction, renal failure (unspecified), and death. Crystalluria is more likely to occur during administration of large, parenteral doses or in patients who are dehydrated. Rapid or bolus infusions of acyclovir have been associated with renal toxicity; therefore, intravenous infusions must be administered over a period of at least one hour. During clinical trials, transient elevations of serum creatinine and blood urea nitrogen (BUN) were observed in 5 to 10% of acyclovir recipients, with the higher incidence occurring after rapid (< 10 minute) infusions. Health care providers are instructed to maintain adequate hydration and a high urine flow to minimize the potential for crystalluria. It is recommended that renal and fluid status be monitored during therapy. In the event of renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored. During post-marketing use of acyclovir, renal pain, which may be associated with renal

failure, has been reported. Due to the voluntary nature of post-marketing reports, neither a frequency nor a definitive causal relationship can be established.[28977] [34408]

Neurotoxicity has been reported during systemic acyclovir administration, especially when administered in high doses and/or in patients with renal, hepatic, or electrolyte abnormalities. Neurologic adverse reactions usually occur within one to two days of achieving the maximum acyclovir concentration and may not be directly correlated with the present acyclovir serum concentrations. Neurotoxic adverse events occurring in approximately 1% of intravenous acyclovir recipients include coma, confusion, encephalopathy, hallucinations, lethargy, obtundation, agitation, seizures, or tremor. During oral acyclovir clinical trials, malaise and headache were reported in 11.5% and 2.2%, respectively, of drug recipients. Headache (3%), dizziness (1%), and lethargy (1%), were observed in the buccal tablet clinical trial. Additional neurologic adverse events noted during post-marketing use of systemic acyclovir, both intravenous and oral formulations, include aggressive behavior, agitation, ataxia, coma, confusion, decreased consciousness, delirium, dizziness, drowsiness, dysarthria, encephalopathy, fatigue, hallucinations, headache, obtundation, paresthesias, psychosis, seizures, and tremors. Due to the voluntary nature of post-marketing reports, neither a frequency nor a definitive causal relationship can be established.[28977] [34408] [54268]

Injection site reaction, manifested as inflammation or phlebitis, occurs in approximately 9% of parenteral acyclovir recipients. Avoid using the same IV site if a reaction develops. More concentrated acyclovir solutions (i.e., > 7 mg/ml) are associated with an increased risk of infusion-related reactions; final acyclovir infusion concentrations > 10 mg/ml are not recommended. Severe local inflammatory reactions, including tissue necrosis, have occurred following infusion of acyclovir into extravascular tissues.[34408]

Gastrointestinal and digestive adverse reactions have developed in patients receiving systemic acyclovir therapy. During clinical trials, episodes of nausea and vomiting were experienced by 2.4 to 7% and 2.7 to 7%, respectively, of acyclovir recipients. Diarrhea was reported by 2.4 to 3.2% of patients treated with oral acyclovir. Anorexia and elevated hepatic enzymes (1 to 2%) were noted with the intravenous formulation. Digestive/GI adverse events experienced by patients receiving systemic acyclovir during the post-marketing period include abdominal pain or gastrointestinal distress, diarrhea, elevated hepatic enzymes, hepatitis, hyperbilirubinemia, and jaundice. Due to the voluntary nature of post-marketing reports, neither a frequency nor a definitive causal relationship can be established. [28977] [34408]

Dermatologic adverse events have occurred in patients receiving systemic and topical acyclovir formulations. Pruritus was reported in 2% of patients during clinical trials of the intravenous formulation and with post-marketing reports of the oral formulations; local pruritus was reported with the cream (1%) and ointment (4%). Rash (unspecified) was reported in 2% of patients during clinical trials of the intravenous formulation, 1% of patients in the buccal tablet clinical trial, and with the oral and topical ointment formulations in post-marketing reports. During clinical trials, 2% of intravenous acyclovir recipients developed hives and 1% of buccal tablet recipients developed erythema. With systemic formulations (both oral and intravenous) there have been post-marketing reports of alopecia, photosensitivity rash, urticaria, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. In topical acyclovir clinical trials, skin irritation (manifested as stinging, burning, pain) was experienced by 1—2% of patients following application of the topical cream and 30% of patients receiving acyclovir ointment. Other dermatologic adverse reactions experienced by topical product recipients during clinical trials included contact sensitization (2%, cream), peeling skin or desquamation (1%, cream), dry and cracked lips (1%, cream), and xerosis (1%,

cream). Post-marketing dermatologic adverse events associated with topical formulations include application site inflammation (cream and ointment), contact dermatitis (cream), eczema (cream), edema (ointment), pruritus (ointment). Due to the voluntary nature of post-marketing reports, neither a frequency nor a definitive causal relationship can be established.[28977] [34408] [43519] [43520] [54268]

Thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) have occurred in immunocompromised patients receiving systemic acyclovir therapy; some of these events have resulted in patient death.[28977] [34408]

Post-marketing adverse events associated with systemic acyclovir (both oral and IV) include anaphylactoid reactions, angioedema, peripheral edema, hypotension (IV only), fever, myalgia, generalized pain, and visual impairment. Cases of anaphylactoid reactions and angioedema have also been noted following use of the topical cream. Due to the voluntary nature of post-marketing reports, neither a frequency nor a definitive causal relationship can be established. [28977] [34408] [43519]

Hematologic adverse events have occurred in patients receiving treatment with systemic acyclovir. During intravenous acyclovir clinical trials, the following adverse events were observed in < 1% of drug recipients: anemia, neutropenia, thrombocytopenia, thrombocytosis, leukocytosis, and neutrophilia. Cases of hematuria were also noted in patients treated with IV acyclovir during clinical trials. During the post-marketing period, hematologic adverse events associated with the use of systemic acyclovir (both oral and IV) included anemia, disseminated intravascular coagulation (DIC) (IV formulation only), hematuria, hemolysis (IV formulation only), leukocytoclastic vasculitis, leukopenia, lymphadenopathy, and thrombocytopenia. Due to the voluntary nature of post-marketing reports, neither a frequency nor a definitive causal relationship can be established. [28977] [34408]

Adverse events reported by 1% of acyclovir buccal tablet recipients during the clinical trial include aphthous stomatitis, gingival pain, and application site pain and irritation.[54268]

Acyclovir (Zovirax®) Specific Ocular Use

Adult dose 600-800 mg 5 x day for 7-10 days

Children - no data is available to support use in this age group, therefore it is not recommended for use in patients < 12 years of age

Example for use: Herpes Zoster keratoconjunctivitis)

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Famciclovir

Drug Description

Famciclovir is an oral antiviral agent. It is the diacetyl 6-deoxy analog of the active antiviral agent penciclovir. Penciclovir itself is marketed as a topical and intravenous antiviral agent (see separate monograph). Penciclovir has a similar spectrum of activity to acyclovir but has a longer duration of action due to a longer intracellular half-life. Thus, famciclovir can be dosed less frequently than oral acyclovir. Twice daily dosing of oral famciclovir has been shown effective in suppressing HSV-2 infection in HIV-positive patients. Despite the bioavailability and duration of action advantages for famciclovir/penciclovir, acyclovir possesses a higher affinity for the target enzyme than penciclovir. Famciclovir was originally FDA-approved on June 30, 1994. Famciclovir is FDA-approved for treatment of acute herpes zoster (shingles), treatment or suppression of recurrent genital herpes in immunocompetent patients, acute treatment of recurrent herpes labialis (cold sores) in immunocompetent patients, and treatment of recurrent mucocutaneous herpes simplex infection in HIV-infected patients.

Classifications:
<i>Anti-infective Agents Antivirals</i>
Brand Names:
<i>Famvir®</i>

Mechanism of Action

Penciclovir is the active antiviral compound produced by biotransformation of famciclovir. Penciclovir is a selective substrate for HSV-1, HSV-2, and varicella-zoster virus thymidine kinase (TK). Cellular kinases

convert the monophosphate form of the drug to the triphosphate. In vitro studies show that penciclovir triphosphate selectively inhibits viral DNA polymerase by competing with deoxyguanosine triphosphate. Phosphorylation of penciclovir to a monophosphate form depends on viral TK, which only occurs in virus-infected cells. Inhibition of DNA synthesis of virus-infected cells inhibits viral replication. DNA synthesis in cells not infected with the virus is unaltered.

Penciclovir is active against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella zoster virus (VZV). The degree of antiviral activity is dependent on several factors, including the time interval between infection and treatment. Resistance of HSV and VZV to penciclovir can result from mutations in the viral TK and DNA polymerase genes. Mutations in the viral TK may lead to the complete loss of viral TK activity, reduced levels of TK activity, or alterations in the ability of viral TK to phosphorylate thymidine. The most common type of resistance is the loss of viral TK activity (TK negative isolates).

Indications

Per the manufacturer, this drug has been shown to be active against most strains of the following microorganisms either in vitro and/or in clinical infections:

- *herpes simplex virus type 1*
- *herpes simplex virus type 2*
- *varicella-zoster virus*

NOTE: The safety and effectiveness in treating clinical infections due to organisms with in vitro data only have not been established in adequate and well-controlled clinical trials.

This drug may also have activity against the following microorganisms:

- *Epstein-Barr virus*

NOTE: Some organisms may not have been adequately studied during clinical trials; therefore, exclusion from this list does not necessarily negate the drug's activity against the organism.

Maximum Dosage Limits
Adults: <i>2000 mg/day PO for single-day therapy or 1500 mg/day PO for multiple-day therapy.</i>
Elderly: <i>2000 mg/day PO for single-day therapy or 1500 mg/day PO for multiple-day therapy.</i>
Adolescents: <i>Safety and efficacy have not been established.</i>
Children: <i>Safety and efficacy have not been established.</i>

Patients with Hepatic Impairment Dosing

No dosage adjustment is recommended for patients with well-compensated hepatic impairment. The pharmacokinetics of penciclovir (the active moiety of famciclovir) have not been evaluated in patients with severe uncompensated hepatic impairment.

Intermittent hemodialysis

For recurrent genital herpes or herpes labialis in immunocompetent patients, give 250 mg PO as a single dose following dialysis session. For herpes genitalis prophylaxis in immunocompetent patients, give 125 mg PO after each dialysis session. For herpes zoster and recurrent herpes simplex virus infection in HIV-infected patients, give 250 mg PO after each dialysis session.

Route-Specific Administration

Oral Administration

Famciclovir may be administered without regard to meals.

Contraindications/Precautions

Patients who have developed famciclovir hypersensitivity or penciclovir hypersensitivity should not receive famciclovir. Because of similar chemical structures and possible cross-sensitivity, famciclovir should not be used in patients with acyclovir hypersensitivity, ganciclovir

hypersensitivity, valacyclovir hypersensitivity, or valganciclovir hypersensitivity. Alternative agents such as foscarnet or cidofovir may be suitable since they are not structurally related to these antivirals.

Renal clearance of penciclovir (the active metabolite of famciclovir) is decreased in patients with renal impairment. Lower doses of famciclovir are suggested for patients with creatinine clearance values less than 60 ml/min, including patients with renal failure receiving dialysis. Acute renal failure has been reported in patients receiving inappropriately high doses of famciclovir for their level of renal function. Geriatric patients over age 65 years may also have reduced rates of clearance which, in part, may be due to changes in renal function.

Safe use of famciclovir in neonates, infants, children, and adolescents under the age of 18 years has not been established.

The efficacy of famciclovir in other herpes infection such as ophthalmic zoster, disseminated zoster (varicella), or immunocompromised patients with herpes zoster has not been determined.

Although famciclovir is classified as pregnancy category B, only animal reproduction studies have been conducted producing no evidence of teratogenicity. No safety studies have been undertaken in humans. Famciclovir should only be used during pregnancy when the benefits to the mother outweigh risks to the fetus. To monitor maternal-fetal outcomes of pregnant women exposed to famciclovir, health care providers are encouraged to register patients in the Famvir Pregnancy Registry by calling (888) 669-6682. [30877]

According to the manufacturer, famciclovir should only be used in nursing mothers if the potential benefits to the mother outweigh the potential risks to the infant. It is not known if penciclovir, a metabolite of famciclovir, is excreted into human milk and there is no published experience with famciclovir during breast-feeding; thus,

other agents may be preferred. Acyclovir and valacyclovir may be potential alternatives to consider during breast-feeding. However, patient factors, local susceptibility patterns, and specific microbial susceptibility should be assessed before choosing an alternative agent. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.[30877] [27500] [29970]

Adverse Reactions

During clinical trials, episodes of headache and migraine were experienced by 8.5 to 39.3% and 0.2 to 3.1% of famciclovir recipients, respectively. Other neurologic adverse events included fatigue (0.6 to 4.8%) and paresthesias (0.9 to 2.6%). Cases of confusion, delirium, disorientation, dizziness, drowsiness, and hallucinations have been noted during the post-marketing period. Due to the voluntary nature of post-marketing reports, neither a frequency nor a definitive causal relationship can be established.[30877]

During clinical trials for genital herpes suppression, 0.2% of famciclovir recipients and 0.3% of patients receiving placebo experienced increased serum creatinine $> 1.5 \times$ upper limits of normal. Patients with underlying renal dysfunction have developed acute renal failure (unspecified) after receiving inappropriately high doses of famciclovir. Dosage reduction is recommended for patients with preexisting renal impairment (See Indications/Dosage).[30877]

Gastrointestinal/digestive adverse events have been associated with famciclovir treatment. During clinical trials, nausea (2.2 to 12.5%), vomiting (0.7 to 5%), abdominal pain (0.2 to 7.9%), diarrhea (1.6 to 9%), and flatulence (0.2 to 4.8%) were reported. Additionally, cases of hyperamylasemia ($> 1.5 \times$ upper limit of normal, ULN) and elevated lipase concentrations ($> 1.5 \times$ ULN) were reported in 1.5% and 4.9% of famciclovir recipients, respectively.[30877]

During clinical trials, rash (unspecified) and pruritus were observed in 0.4 to 3.3% and 2.2 to 3.7% of famciclovir recipients, respectively. Other dermatologic adverse events reported during the post-marketing period include urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, leukocytoclastic vasculitis, and angioedema. Due to the voluntary nature of post-marketing reports, neither a frequency nor a definitive causal relationship can be established. [30877]

Hematologic adverse events observed in patients receiving treatment with famciclovir for genital herpes suppression include anemia (0.1%, $< 0.8 \times$ lower limits of normal, LLN), leukopenia (1.3%, $< 0.75 \times$ LLN), and neutropenia (3.2%, $< 0.8 \times$ LLN). Cases of thrombocytopenia have been noted during the post-marketing period. Due to the voluntary nature of post-marketing reports, neither a frequency nor a definitive causal relationship can be established.[30877]

Cases of hyperbilirubinemia ($> 1.5 \times$ upper limit of normal, ULN) and elevated hepatic enzymes ($> 2 \times$ ULN) were observed in 1.9% and 2.3 to 3.2%, respectively, of patients receiving famciclovir during clinical trials for genital herpes suppression. Additionally, famciclovir has been associated with the development of cholestatic jaundice during the post-marketing period. Due to the voluntary nature of post-marketing reports, neither a frequency nor a definitive causal relationship can be established.[30877]

During clinical trials, dysmenorrhea was reported by 0.4 to 7.6% of famciclovir recipients and 0.6 to 6.3% of patients receiving placebo.[30877]

Famciclovir has been associated with the development of palpitations during the post-marketing period.[30877]

Famciclovir (Famvir) Specified Ocular Use

Adult dose 500 mg TID for 7 days

Famciclovir (Famvir) Specified Ocular Use continued

Children - no data is available to support use in this age group, therefore it is not recommended for use in patients < 12 years of age

Example for use: Herpes Zoster keratoconjunctivitis

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Valacyclovir

Drug Description

Valacyclovir is the L-valyl ester of acyclovir; the result of an effort to develop a prodrug to improve acyclovir oral bioavailability. Improved bioavailability means less frequent dosing for valacyclovir than acyclovir, which is especially beneficial during maintenance therapy. While valacyclovir is only available as an oral caplet, extemporaneous compounding instructions are available to prepare an oral suspension. The FDA originally approved valacyclovir for the treatment of herpes zoster (shingles) in immunocompetent patients in June 1995. Valacyclovir has since received additional FDA approvals for the following things:

- *treatment of recurrent herpes genitalis*
- *treatment of initial episodes of herpes genitalis*
- *maintenance (i.e., suppressive) therapy of herpes genitalis in otherwise healthy patients*
- *treatment of herpes labialis*
- *treatment for the suppression of recurrent genital herpes in HIV-infected individuals*
- *treatment for the reduction of genital herpes transmission*
- *treatment of chickenpox.*

Classifications:

Anti-infective Agents Antivirals

Brand Names:

Valtrex®

References

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30877. Famvir (famciclovir) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corp.; 2013 Apr.

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34362. Centers for Disease Control and Prevention (CDC). Treating opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America (HIVMA/IDSA). *MMWR Mar* 2009;58 (early release):1-198.

Mechanism of Action

Valacyclovir is rapidly converted to acyclovir, which inhibits DNA synthesis. Acyclovir is a synthetic purine nucleoside analogue with inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV). Acyclovir inhibits viral DNA synthesis and must be phosphorylated intracellularly to be active. Acyclovir is converted to the monophosphate by viral thymidine kinase (TK), then to diphosphate by cellular guanylate kinase, and finally to the triphosphate by various cellular enzymes. Acyclovir triphosphate stops replication of herpes viral DNA by the following 3 mechanisms: competitive inhibition of viral DNA polymerase, incorporation into and termination of the growing viral DNA chain, and inactivation of the viral DNA polymerase.[28977][29970]

Herpes virus DNA polymerases differ in sensitivity to acyclovir. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral thymidine kinase. Acyclovir is effective only against actively replicating viruses; therefore, it does not eliminate the latent herpes virus genome. Uninfected cells show only minimal phosphorylation of acyclovir, and there is only a small amount of acyclovir taken up into these cells. The concentration of acyclovir triphosphate is 40- to 100- times higher in HSV-infected cells than non-infected cells.[51534] Acyclovir-resistant herpes simplex virus has been seen in immunocompromised patients, patients with concurrent HIV infection, and immunocompetent patients with genital herpes. Repeated systemic treatment may lead to the development of viral resistance in immunosuppressed patients.[51536] [51532] [51543]

Viral resistance to acyclovir may occur due to loss of thymidine kinase activity, alterations in thymidine kinase substrate specificity, or decreased DNA-polymerase sensitivity. The alterations in these enzymes occur due to point mutations or base insertions or deletions in the specific genes. The most common mechanism of resistance is loss of thymidine kinase activity. These viral variants are also

cross resistant to other antiviral agents activated by thymidine kinase (e.g., ganciclovir or penciclovir). Thymidine kinase negative variants of herpes virus may cause severe disease in immunocompromised patients. Acyclovir-resistant herpes simplex virus has been seen in immunocompromised patients, patients with concurrent HIV infection, and immunocompetent patients with genital herpes. Repeated systemic treatment may lead to the development of viral resistance in immunosuppressed patients.[29970] [54905]

Indications

Per the manufacturer, this drug has been shown to be active against most strains of the following microorganisms either in vitro and/or in clinical infections:

- *herpes simplex virus type 1*
- *herpes simplex virus type 2*
- *varicella-zoster virus*

NOTE: The safety and effectiveness in treating clinical infections due to organisms with in vitro data only have not been established in adequate and well-controlled clinical trials.

This drug may also have activity against the following microorganisms:

- *B virus (cercopithecine herpesvirus),*
- *cytomegalovirus (CMV)*
- *Epstein-Barr virus*

NOTE: Some organisms may not have been adequately studied during clinical trials; therefore, exclusion from this list does not necessarily negate the drug's activity against the organism.

For the treatment of acute retinal necrosis (ARN)[†] due to varicella-zoster virus in HIV-infected patients:

Oral dosage:

Adults:

After 10 to 14 days of IV acyclovir, the CDC recommends valacyclovir 1 g PO three times daily for 6 weeks.[34362]

Maximum Dosage Limits

Adults:

4 g/day PO for one-day treatment regimens or 3 g/day for regimens lasting > 1 day.

Elderly:

4 g/day PO for one-day treatment regimens or 3 g/day for regimens lasting > 1 day.

Adolescents:

4 g/day PO for one-day treatment regimens or 3 g/day for regimens lasting > 1 day.

Children:

≥ 12 years: 4 g/day PO for one-day treatment regimens or 3 g/day for regimens lasting > 1 day.

≥ 2 years and < 12 years: 60 mg/kg/day PO, not to exceed 3 g/day PO.

< 2 years: Safety and efficacy have not been established.

CrCl < 10 ml/min:

For regimens of 1 g PO every eight to 24 hours or 500 mg PO every 12 hours, reduce dose to 500 mg PO once daily. For regimens of 500 mg PO once daily, change dose to 500 mg PO every 48 hours. For one-day treatment of herpes labialis, give 500 mg PO x 1 dose.

Route-Specific Administration

Oral Administration

May be administered without regard to meals.
[29970]

Contraindications/Precautions

Valacyclovir is contraindicated in patients with acyclovir hypersensitivity or valacyclovir hypersensitivity. Because of similar chemical structures and possible cross-sensitivity, valacyclovir should be used with caution in patients with famciclovir hypersensitivity, ganciclovir hypersensitivity, penciclovir hypersensitivity, or valganciclovir hypersensitivity. Alternative agents such as foscarnet or cidofovir may be suitable since they are not structurally related to these antivirals.

Valacyclovir should be used with caution in patients with renal dysfunction. Patients with renal impairment or renal failure may require dosage adjustment. Acute renal failure and CNS toxicity have been reported in patients with underlying renal dysfunction who have received inappropriately high doses of valacyclovir for their level of renal function. Patients receiving potentially nephrotoxic drugs together with valacyclovir may have an increased risk of renal dysfunction.[29970]

In a clinical study of herpes zoster, the duration of pain after healing (post-herpetic neuralgia) was longer in geriatric patients (≥ 65 years) compared with younger adults. Elderly patients are more likely to have impaired renal function and may require lower doses of valacyclovir. Elderly patients are also more likely to have renal or CNS adverse events. With respect to CNS adverse events observed during clinical practice, agitation, hallucinations, confusion, delirium, and

Patients with Hepatic Impairment Dosing

No dosage adjustment is necessary.[29970]

Patients with Renal Impairment Dosing

FDA-approved dosage adjustments in adults:
[29970]

CrCl ≥ 50 ml/min:

No dosage adjustment needed.

CrCl 30 to 49 ml/min:

For regimens of 1 g PO every 8 hours, change to 1 g PO every 12 hours. For one-day treatment of herpes labialis, give 1 g PO every 12 hours x 2 doses. Other regimens do not require a dosage adjustment.

CrCl 10 to 29 ml/min:

For regimens of 1 g PO every 8 to 12 hours, reduce dose to 1 g PO every 24 hours. For regimens of 1 g PO once daily or 500 mg PO every 12 hours, reduce dose to 500 mg PO once daily. For regimens of 500 mg PO once daily, change dose to 500 mg PO every 48 hours. For one-day treatment of herpes labialis, give 500 mg PO every 12 hours x 2 doses.

encephalopathy were reported more frequently in elderly patients.

Precipitation of acyclovir in renal tubules may occur when the solubility is exceeded in the intratubular fluid. Patients should be well-hydrated to maintain a high urine volume and avoid dehydration during treatment with valacyclovir.

The safe use of valacyclovir in neonates, infants, and children less than two years old has not been established. Oral administration of the related drug acyclovir has been studied in infants and children.

Valacyclovir has been classified as FDA pregnancy category B. No complete or well-controlled pregnancy studies have been performed in humans. Acyclovir, the active component of valacyclovir, was not found to be teratogenic in standard animal studies. A prospective epidemiologic registry of acyclovir use during pregnancy was established in 1984 and completed in April 1999. There were 756 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for specific defects or to permit definitive conclusions regarding the safety of acyclovir in pregnant women. Valacyclovir should be avoided during pregnancy unless the potential benefits outweigh the possible risks to the fetus.[29970]

According to the manufacturer, valacyclovir should be administered to a nursing mother with caution and only when indicated. Although the American Academy of Pediatrics (AAP) has not specifically evaluated valacyclovir, systemic maternal acyclovir is considered to be usually compatible with breast-feeding.[27500] In a small study of 5 lactating women, valacyclovir was administered orally as a single 500 mg dose. Peak acyclovir concentrations in breast milk ranged from 0.5 to 2.3 times (median 1.4) the corresponding maternal acyclovir serum

concentrations, and the acyclovir AUC in breast milk ranged from 1.4 to 2.6 times (median 2.2) maternal serum AUC. The administration of valacyclovir 500 mg twice daily to a breast-feeding woman would provide the nursing infant with an oral acyclovir dosage of approximately 0.6 mg/kg/day, resulting in less than 1% of the exposure obtained after administering a neonatal intravenous dose for the treatment of neonatal herpes (i.e., 60 mg/kg/day). In the study, unchanged valacyclovir was not detected in maternal serum, breast milk, or infant urine. [29970] Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally ingested drug, health care providers are encouraged to report the adverse effect to the FDA.

Adverse Reactions

The adverse effect profile of valacyclovir is similar to that of acyclovir. The most commonly reported adverse events are headache (11 to 38%), nausea (4 to 15%), and abdominal pain (3 to 11%). Other less common adverse events include arthralgia (5 to 6%), depression (5 to 7%), dizziness (2 to 4%), dysmenorrhea (5 to 8%), fatigue (8%), pharyngitis (16%, reported as nasopharyngitis), upper respiratory tract infection (9%, e.g., sinusitis), and vomiting (3 to 6%). [29970]

During clinical trials with valacyclovir (8 g/day for 8 to 84 weeks), cases of thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) have occurred in patients with advanced HIV disease, bone marrow transplantations, and renal transplantations. Some of these cases were associated with fatal outcomes. In other studies of healthy and HIV-infected patients, there have been no reports of TTP or HUS during use of valacyclovir for the treatment or suppression of genital herpes when using lower doses (≤ 3 g/day) and shorter treatment durations. Post-market reports of these serious reactions have also been received. The manufacturer recommends discontinuing valacyclovir treatment

if clinical symptoms and laboratory finding suggest development of TTP or HUS.[29970]

During clinical trials with valacyclovir in pediatric patients aged 1 month to < 12 years, 5% of patients experienced diarrhea. Diarrhea has also been reported by adult patients during post-marketing use of valacyclovir.[29970]

During three valacyclovir clinical trials, pediatric patients aged 1 month to < 12 years experienced systemic adverse reactions not previously reported in the adult population including pyrexia or fever (4%), dehydration (2%), and rhinorrhea (2%).[29970]

Hematologic abnormalities have occurred following treatment with valacyclovir during clinical trials. Laboratory changes observed in recipients of valacyclovir include anemia (0.2 to 0.8%), elevated hepatic enzymes (1 to 16%), neutropenia (0.6 to 18%), and thrombocytopenia (0.1 to 3%).[29970]

Cases of renal failure (unspecified) have been reported during treatment with valacyclovir. According to the manufacturer, the following patient populations are at increased risk of developing valacyclovir-associated renal failure: elderly patients, patients with underlying renal disease who receive dosages not adjusted based on their renal function, patients concurrently receiving other nephrotoxic medications, and patients without adequate hydration. If anuria or renal failure develops during treatment with valacyclovir, the patient may benefit from hemodialysis until restoration of renal function can be achieved.[29970]

Central nervous system adverse events including agitation, hallucinations, confusion, delirium, encephalopathy, and seizures have been reported during treatment with valacyclovir. These adverse reactions are more likely to occur in elderly patients; however, they have been reported in both adult and pediatric populations. Health care providers are advised to discontinue valacyclovir treatment in any patient that develops signs or symptoms of central nervous

system adverse reactions.[29970]

During a clinical trial evaluating the use of valacyclovir for suppression of recurrent genital herpes in HIV-infected patients, 8% of valacyclovir recipients developed a rash (unspecified); only 1% of the study patients who received a placebo developed a rash. Rashes have also been reported by patients during post-marketing use of valacyclovir.[29970]

During clinical experience with the use of valacyclovir, other severe adverse reactions have been reported to the manufacturer. Allergic reactions have included anaphylactoid reactions, anaphylaxis, angioedema, dyspnea, erythema multiforme, facial edema, pruritus, and urticaria. Neuropsychiatric reactions have included aggressive behavior, ataxia, impaired cognition, tremor, coma, mania, and psychosis. Hepatic and gastrointestinal reactions have included liver enzyme abnormalities, hepatitis, and diarrhea. Renal reactions have included elevated serum creatinine, renal failure (unspecified), renal pain (possibly associated with renal failure). Other reactions have included leukocytoclastic vasculitis, aplastic anemia, alopecia, dysarthria, photosensitivity, visual impairment, hypertension, and sinus tachycardia. Due to the uncontrolled and voluntary nature of post-marketing reports, neither the frequency nor a definitive causal relationship to valacyclovir can be established. [29970]

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During clinical trials with valacyclovir (8 g/day for eight to 84 weeks), cases of thrombotic thrombocytopenic purpura (TTP) and hemolytic-

uremic syndrome (HUS) have occurred in patients with advanced HIV disease, bone marrow transplantations, and renal transplantations. Some of these cases were associated with fatal outcomes. In other studies of healthy and HIV-infected patients, there have been no reports of TTP or HUS during use of valacyclovir for the treatment or suppression of genital herpes when using lower doses (≤ 3 g/day) and shorter treatment durations. Post-market reports of these serious reactions have also been received. The manufacturer recommends discontinuing valacyclovir treatment if clinical symptoms and laboratory findings suggest development of TTP or HUS.[29970]

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Hematologic abnormalities have occurred following treatment with valacyclovir during clinical trials. Laboratory changes observed in recipients of valacyclovir include anemia (0.2 to 0.8%), elevated hepatic enzymes (1 to 16%), neutropenia (0.6 to 18%), and thrombocytopenia (0.1 to 3%).[29970]

Cases of renal failure (unspecified) have been reported during treatment with valacyclovir. According to the manufacturer, the following patient populations are at increased risk of developing valacyclovir-associated renal failure: elderly patients, patients with underlying renal disease who receive dosages not adjusted based on their renal function, patients concurrently receiving other nephrotoxic medications, and patients without adequate hydration. If anuria or renal failure develops during treatment with valacyclovir, the patient may benefit from

hemodialysis until restoration of renal function can be achieved.[29970]

Central nervous system adverse events including agitation, hallucinations, confusion, delirium, encephalopathy, and seizures have been reported during treatment with valacyclovir. These adverse reactions are more likely to occur in elderly patients; however, they have been reported in both adult and pediatric populations. Health care providers are advised to discontinue valacyclovir treatment in any patient that develops signs or symptoms of central nervous system adverse reactions.[29970]

During a clinical trial evaluating the use of valacyclovir for suppression of recurrent genital herpes in HIV-infected patients, 8% of valacyclovir recipients developed a rash (unspecified); only 1% of the study patients who received a placebo developed a rash. Rashes have also been reported by patients during post-marketing use of valacyclovir.[29970]

During clinical experience with the use of valacyclovir, other severe adverse reactions have been reported to the manufacturer. Allergic reactions have included anaphylactoid reactions, anaphylaxis, angioedema, dyspnea, erythema multiforme, facial edema, pruritus, and urticaria. Neuropsychiatric reactions have included aggressive behavior, ataxia, impaired cognition, tremor, coma, mania, and psychosis. Hepatic and gastrointestinal reactions have included liver enzyme abnormalities, hepatitis, and diarrhea. Renal reactions have included elevated serum creatinine, renal failure (unspecified), renal pain (possibly associated with renal failure). Other reactions have included leukocytoclastic vasculitis, aplastic anemia, alopecia, dysarthria, photosensitivity, visual impairment, hypertension, and sinus tachycardia. Due to the uncontrolled and voluntary nature of post-marketing reports, neither the frequency nor a definitive causal relationship to valacyclovir can be established. [29970]

Valacyclovir (Valtrex) Specific Ocular Use

Adult dose 1000 mg TID x 7 days

Children - no data is available to support use in this age group, therefore it is not recommended for use in patients < 12 years of age

Example for use: Herpes Zoster
keratoconjunctivitis

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Overview of Oral Anti-Glaucoma Agents

Glaucoma treatment generally starts with medicated eyedrops or topical ocular medications. If these treatments alone are not effective, oral anti-glaucoma agents may become necessary. The Oral Ocular Formulary includes the following Oral Anti-Glaucoma Agents or their generic or therapeutic equivalents:

1. Acetazolamide

2. Methazolamide

The following sections will provide relevant clinical information about each of the agents listed above, including mechanism of action, indication, contraindications, adverse reactions, drug interactions, general dosing guides, special instructions, and most importantly, dosages and examples of use specifically for optometrists for the treatment of ocular conditions. This particular information for optometrists is included at the end of each drug section.

Acetazolamide

Drug Description

Acetazolamide is an oral and parenteral carbonic anhydrase inhibitor. Other members of this class include methazolamide and dichlorphenamide. Acetazolamide is used for the prophylaxis and treatment of altitude sickness, and as an adjunct treatment for glaucoma and epilepsy (i.e., absence seizures). Acetazolamide has been used as a diuretic for edema due to congestive heart failure, but it has been replaced by thiazide and loop diuretics because it rapidly loses its diuretic effect and is less potent than other classes of diuretics. Acetazolamide has also been used as an adjunctive agent to reverse metabolic alkalosis in mechanically ventilated patients, after fluid and electrolyte imbalances have been corrected. [26821][26822] Acetazolamide was approved by the FDA in 1953.

Classifications:

Electrolytic and Renal Agents Diuretics
Carbonic Anhydrase Inhibitors
Neurological Agents Anticonvulsants
Ophthalmic Agents Antiglaucoma Agents
Carbonic Anhydrase Inhibitors

Brand Names:

Diamox®

Mechanism of Action

Carbonic anhydrase is an enzyme responsible for forming hydrogen and bicarbonate ions from carbon dioxide and water. By inhibiting this enzyme, acetazolamide reduces the availability of these ions for active transport. Hydrogen ion concentrations in the renal tubule lumen are reduced by acetazolamide, leading to an alkaline urine and an increased excretion of bicarbonate, sodium, potassium, and water. A reduction in plasma bicarbonate results in metabolic acidosis, which rapidly reverses the diuretic effect. Reduced intraocular pressure (IOP) is the result of a 50 to 60% reduction in aqueous humor production by acetazolamide and is likely due to decreased bicarbonate ion concentrations in ocular fluid.

The anticonvulsant activity of acetazolamide may depend on a direct inhibition of carbonic anhydrase in the CNS, which increases carbon dioxide tension and inhibits neuronal transmission. The successful treatment of altitude sickness involves production of respiratory and metabolic acidosis, which increases ventilation and binding of oxygen to hemoglobin. This occurs because the drug decreases carbon dioxide tension in the pulmonary alveoli, thus increasing arterial oxygen tension.

Indications

For the treatment of glaucoma:

Adjunctive treatment of open-angle glaucoma:

Oral dosage (regular-release tablets):
Adults: <i>250 mg PO given one to four times per day. Maintenance dosage should be titrated to response. The maximum dosage is 1 g/day.</i>
Elderly: <i>Consider dosage reduction. An elderly patient is more likely to develop hyperchloremic metabolic acidosis in addition to an age-related renal impairment.</i>
Children[†]: <i>8 to 30 mg/kg/day PO or 300 to 900 mg/m²/day, given in divided doses every 8 hours.</i>
Oral dosage (extended-release capsules):
Adults: <i>500 mg PO twice daily. The maximum dosage is 1 g/day.</i>
Elderly: <i>Consider dosage reduction. An elderly patient is more likely to develop hyperchloremic metabolic acidosis in addition to an age-related renal impairment.</i>
Intravenous dosage:
Adults: <i>500 mg IV for acute lowering of IOP or in patients unable to take the oral dosage. If needed, may repeat the dose in two to four hours.</i>
Elderly: <i>Consider dosage reduction. An elderly patient is more likely to develop hyperchloremic metabolic acidosis in addition to an age-related renal impairment.</i>
Children[†]: <i>5 to 10 mg/kg IV every six hours for acute glaucoma. The maximum dosage is 1 g/day.</i>

Secondary glaucoma and pre-operatively for acute angle-closure glaucoma:

Oral dosage (regular-release tablets): NOTE: Sequels are a sustained-release dosage form and are not appropriate for acute treatment of angle-closure glaucoma.
Adults: <i>250 mg PO every four hours. Alternately, treatment of some acute types of glaucoma has been initiated with a dose of 500 mg, followed by 125 to 250 mg PO every 4 hours.</i>
Elderly: <i>Consider dosage reduction. An elderly patient is more likely to develop hyperchloremic metabolic acidosis in addition to an age-related renal impairment.</i>
Intravenous dosage:
Adults: <i>500 mg IV for acute lowering of IOP or in patients unable to take the oral dosage. If needed, may repeat the dose in two to four hours.</i>
Elderly: <i>Consider dosage reduction. An elderly patient is more likely to develop hyperchloremic metabolic acidosis in addition to an age-related renal impairment.</i>
Children[†]: <i>5 to 10 mg/kg IV every 6 hours for acute glaucoma. Maximum dosage is 1 g/day.</i>
Maximum Dosage Limits
Adults: <i>1000 mg/day PO/IV.</i>
Elderly: <i>1000 mg/day PO/IV.</i>
Adolescents: <i>Safety and efficacy have not been established; do not exceed the adult maximum dose of 1000 mg/day PO/IV.</i>
Children: <i>Safety and efficacy have not been established.</i>

Patients with Hepatic Impairment Dosing

Acetazolamide is contraindicated in cases of marked liver disease or dysfunction. Acetazolamide is contraindicated in patients with cirrhosis because of the risk of development of hepatic encephalopathy and electrolyte imbalance.

Patients with Renal Impairment Dosing

CrCl 50 to 80 ml/min: <i>Dosing interval $\geq$ 6 hours for IV or regular-release tablets. No dosage guidelines are available for sustained-release capsules.</i>
CrCl 10 to 50 ml/min: <i>Dosing interval $\geq$ 12 hours for IV or regular-release tablets. No dosage guidelines are available for sustained-release capsules.</i>
CrCl < 10 ml/min: <i>Avoid use. Acetazolamide is contraindicated in marked kidney disease or dysfunction.</i>

Intermittent hemodialysis

Contraindicated in patients with severe renal disease; may potentiate acidosis and may cause CNS adverse effects in dialysis patients.

Oral Administration

Oral Solid Formulations:

Administer regular-release tablets or sustained-release capsules by mouth; may administer with or without food. Administer with food if stomach upset occurs.

Contraindications/Precautions

Increasing the dose of acetazolamide does not increase the diuresis and may increase the incidence of CNS adverse events. Increasing the dose often results in a decrease in diuresis. Under certain circumstances, however, very large doses have been given in conjunction with other diuretics in order to secure diuresis in complete refractory failure.[31254]

Acetazolamide can be used for treatment or prevention of high altitude sickness. Gradual

ascent is desirable to try to avoid acute mountain sickness. If rapid ascent is undertaken and acetazolamide is used, it should be noted that such use does not obviate the need for prompt descent if severe forms of high altitude sickness occur, i.e., high altitude pulmonary edema (HAPE) or high altitude cerebral edema.[31254]

Acetazolamide interferes with the HPLC method of assay for theophylline. Interference with the theophylline assay by acetazolamide depends on the solvent used in the extraction; acetazolamide may not interfere with other assay methods. [31254]

Acetazolamide is contraindicated in patients with a history of acetazolamide hypersensitivity and should be avoided in patients with a history of carbonic anhydrase inhibitor hypersensitivity. Acetazolamide is a chemical sulfonamide possessing a structure and pharmacologic activity distinct from the bacteriostatic sulfonamides. Rarely, sulfonamides of any type can produce allergic reactions, some of which may be severe. A case of anaphylactic shock (30 minutes following acetazolamide for cataract surgery) has been reported in a patient with documented sulfonamide hypersensitivity. While the risk of cross-sensitivity between acetazolamide and antibacterial sulfonamides appears low, acetazolamide should be discontinued in any person who exhibits reactions suggestive of sulfonamide hypersensitivity. Rare fatalities have occurred due to severe hypersensitivity reactions to sulfonamides (see Adverse Reactions). Sensitizations may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of hypersensitivity or other serious reactions occur, discontinue use of acetazolamide.[31254]

Acetazolamide should be avoided in patients with marked hepatic disease; these patients are more susceptible to electrolyte and acid/base imbalance. In addition, patients with cirrhosis are at an increased risk for hepatic encephalopathy.

Acetazolamide is contraindicated in patients with electrolyte imbalance (e.g., hyponatremia,

hypokalemia, hyperchloremia), acid/base imbalance (metabolic acidosis, acidemia), or adrenal insufficiency. Acetazolamide is contraindicated in patients with severe renal disease (renal failure, anuria). Dosage reduction is warranted in patients with renal impairment (see Dosage). Acetazolamide may potentiate acidosis and cause neurologic side effects in dialysis patients. Geriatric patients may be more likely to develop hyperchloremic non-anion gap metabolic acidosis; reduced dosage may be needed due to an age-related decline in renal function. Plasma chloride levels and excretion of sodium and potassium are altered during treatment, and these conditions can be exacerbated by the renal and metabolic effects of the drug.[31254]

Long-term administration of acetazolamide is contraindicated in patients with closed-angle glaucoma as acetazolamide may allow closure of the angle to occur while lowered intraocular pressure masks the worsening glaucoma.

Patients with pulmonary disease, including those with pulmonary infection, obstruction, emphysema, or respiratory acidosis should be monitored closely during treatment with acetazolamide because of the potential for respiratory acidosis.

Acetazolamide, as with other sulfonamide derivatives, can induce bone marrow suppression, agranulocytosis, aplastic anemia, and other blood dyscrasias so precaution is advised for early detection of such reactions. If they occur, the drug should be discontinued and appropriate therapy instituted.

Like other sulfonamide derivatives, photosensitivity may occur with carbonic anhydrase inhibitors including acetazolamide. Some patients may be more sensitive to sunlight (UV) exposure while receiving acetazolamide. Patients should avoid prolonged exposure to sunlight or sunlamps, and to follow appropriate sun precautions.

Acetazolamide is classified as FDA pregnancy risk category C. Acetazolamide has been shown

to be teratogenic (defects in the limbs) in animals. There are not adequate and well-controlled studies in pregnant women. Acetazolamide should only be used if the benefit justifies the potential risk to the fetus.[28267]

According to the manufacturer, because of the potential for adverse reactions in nursing infants from acetazolamide, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.[28267] However, content experts and the American Academy of Pediatrics consider acetazolamide to be usually compatible with breast-feeding.[27500] Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

Some adverse reactions to acetazolamide, such as drowsiness, fatigue, and myopia may impair the ability for driving or operating machinery.

Adverse Reactions

Acetazolamide commonly produces central nervous system (CNS) side effects and these effects often indicate the activity of the drug in the CNS. Adverse CNS effects, such as drowsiness, fatigue, headache, malaise, seizures, irritability, libido decrease, vertigo, confusion, and paresthesias can develop. Paresthesias occur frequently and are manifested as numbness, tingling, or burning in the hands, fingers, feet, toes, mouth, tongue, lips, or anus.

Acetazolamide has rarely caused hyperglycemia and glycosuria in patients with diabetes mellitus. Hyperglycemia may be due to the acetazolamide-induced decreases in serum potassium. Both increases and decreases in blood glucose have been described in some patients treated with acetazolamide.

In patients with hepatic disease, especially cirrhosis, acetazolamide can induce hepatic encephalopathy as a result of electrolyte and

acid base disturbances and elevations in serum ammonia concentrations. Abnormal liver function (elevated hepatic enzymes), cholestatic jaundice, hepatic insufficiency, and fulminant hepatic necrosis have also been reported.

Hyperuricemia can develop during treatment with acetazolamide. Gout can be exacerbated in susceptible patients. Alterations in serum uric acid levels are reversible following discontinuation of the drug.

The manufacturer lists photosensitivity as an occasional adverse reaction to acetazolamide. The exact incidence is not known.

Acetazolamide is a sulfonamide. Although rarely reported with acetazolamide, administration of sulfonamides by any route can precipitate a possibly severe reaction in sulfonamide-sensitive patients, including anaphylactoid reactions. One case of cross-sensitivity with acetazolamide in a patient with documented sulfonamide hypersensitivity has been reported. The patient developed anaphylactic shock with acute respiratory failure 30 minutes following administration of acetazolamide for cataract surgery. In this case, skin testing identified a sulfonamide hypersensitivity. Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including acetazolamide. Serious 'sulfonamide-type' reactions reported with acetazolamide have included agranulocytosis, aplastic anemia, hemolysis (producing hemolytic anemia), leukopenia, pancytopenia, Stevens-Johnson syndrome, thrombocytopenia, toxic epidermal necrolysis, and other blood dyscrasias. [31254]

Acetazolamide has also been associated with acute generalized exanthematous pustulosis (AGEP). The nonfollicular, pustular, erythematous rash starts suddenly, is associated with fever above 38 degrees C, and is distinct from pustular psoriasis, although biopsy results in each reveal spongiform subcorneal pustules. Drugs are the main cause of AGEP. A period of two to three weeks after an inciting drug exposure appears necessary for a first episode of AGEP.

Unintentional reexposure may cause a second episode within two days. Clinical presentation is diverse with cutaneous lesions beyond erythema and pustules present in half of the cases. For example, bullous lesions, edema, purpura, pruritus, and mucosal erosions are possible. The mean duration of the pustules is 9.7 days followed by an annular desquamation, as long as the causative drug or factor is discontinued. The physiopathological mechanisms of AGEP have not been determined but the pathological criteria of edema, leukocytoclastic vasculitis, eosinophil exocytosis, and keratinocyte focal necrosis are distinctive. Pustule confluence or very small pustules may lead a clinician to make an incorrect diagnosis of TEN, of drug-induced erythroderma, or of staphylococcal scalded skin syndrome.[27736]

The inhibition of carbonic anhydrase affects excretion of electrolytes. Hyperchloremia and/or metabolic acidosis can result from an increase in plasma chloride concentrations. Acetazolamide increases the excretion of bicarbonate, potassium, and sodium, decreasing the extracellular fluid concentration of bicarbonate and causing metabolic acidosis and possibly hypokalemia. Increased excretion of potassium is most likely to occur during the use of high dosages or during concurrent use of other potassium-depleting agents. Carbonic anhydrase inhibitors are sulfonamide derivatives and have caused crystalluria and sulfonamide-like nephrotoxicity characterized by renal tubular obstruction, hematuria, dysuria, and oliguria. An increase in calcium excretion can cause nephrolithiasis. Patients with preexisting hypercalcemia develop renal calculi most frequently.

Adverse GI effects that have been reported with acetazolamide include nausea and vomiting, diarrhea, dysgeusia (altered taste), xerostomia, excessive thirst, and anorexia. Symptoms such as nausea/vomiting, xerostomia, and increased thirst may indicate hypokalemia.

Flushing, injection site reaction (pain) and flaccid paralysis are other adverse events noted by the

manufacturer. Specific incidences and associated causality with acetazolamide were not reported. [31254] Growth inhibition in children receiving long-term acetazolamide therapy has also been reported and is believed to occur secondary to chronic acidosis.

Acetazolamide (Diamox®) Specific Ocular Use

Adult dose 250 mg QID or 500 mg sequels BID up to 72 hours.

Children- no adequate studies have been conducted to determine patient safety for this age group. Adverse incidence reports ranging from growth retardation to SJS to anaphylaxis have been reported for this drug, therefore it is not recommend for use in patients < 12 years of age.

Sulfa allergy/contraindicated in patients with hepatic or renal disease or COPD.

Use caution when treating patients who are diabetic and prone to ketoacidosis or have sickle cell disease.

Example for use: Acute Angle Closure Glaucoma in an adult where a 500 mg dose is given STAT followed by 250 mg BID - QID if IOP not responsive.

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Methazolamide

Drug Description

Methazolamide is an oral carbonic anhydrase inhibitor. It is used in the treatment of glaucoma to rapidly reduce intraocular pressure. Methazolamide works by decreasing the production of aqueous humor. The drug is used off-label for the treatment of benign familial tremor and has also been used in prevention of altitude sickness. A topical ophthalmic formulation of methazolamide complexed in cyclodextrin is being investigated for ocular hypertension. [26578] Oral methazolamide (Neptazane®) was approved by the FDA in 1959.

Classifications:
Electrolytic and Renal Agents Diuretics Carbonic Anhydrase Inhibitors Neurological Agents Anticonvulsants Ophthalmic Agents Antiglaucoma Agents Carbonic Anhydrase Inhibitors
Brand Names:
• GlaucoTabs® • Neptazane®

Mechanism of Action

Carbonic anhydrase is an enzyme responsible for forming hydrogen and bicarbonate ions from carbon dioxide and water. By inhibiting this enzyme, methazolamide reduces the availability of these ions for active transport. Hydrogen ion concentrations in the renal tubule lumen are reduced by methazolamide, leading to alkaline urine and an increased excretion of bicarbonate, sodium, potassium, and water. A reduction in plasma bicarbonate results in metabolic acidosis, which rapidly reverses the diuretic effect. Reduced intraocular pressure (IOP) is the result of a 50 to 60% reduction in aqueous humor production and is likely due to decreased bicarbonate ion concentrations in ocular fluid. For altitude sickness prophylaxis, methazolamide produces respiratory and metabolic acidosis, which increases ventilation and binding of oxygen to hemoglobin. This occurs because the drug decreases carbon dioxide tension in the pulmonary alveoli, thus increasing arterial oxygen tension.

Indications

For the adjunctive treatment of open-angle glaucoma, for the treatment of secondary glaucoma, and for use pre-operatively for acute angle-closure glaucoma:

Oral dosage (regular-release tablets):
Adults, including the Elderly: 50 to 100 mg PO two to three times per day. Methazolamide may be used temporarily in patients with elevated IOPs (e.g., postsurgery or post-laser), or continuously in patients with glaucoma resistant to other treatment.[26579]
Adolescents and Children: Safety and efficacy have not been established.
Maximum Dosage Limits:
Adults: 300 mg/day PO.
Elderly: 300 mg/day PO.
Adolescents: Safety and efficacy have not been established.
Children: Safety and efficacy have not been established.

Patients with Hepatic Impairment Dosing

Use not recommended in patients with severe hepatic impairment (e.g., cirrhosis); the use of methazolamide may precipitate hepatic encephalopathy or coma.

Patients with Renal Impairment Dosing Intermittent hemodialysis

Contraindicated in patients with severe renal disease; may potentiate acidosis and may cause CNS adverse effects in dialysis patients.

CrCl > 50 ml/min: No dosage adjustment needed.

CrCl 10 to 50 ml/min:

Extend dosage interval; no quantitative recommendations available.

CrCl < 10 ml/min:

Avoid use.

Route-Specific Administration

Oral Administration

- *May take with food.*
- *Consume extra fluids to help prevent kidney stones.*

Contraindication/Precautions

Methazolamide is a chemical sulfonamide possessing a structure and pharmacologic activity distinct from the bacteriostatic sulfonamides. Rarely, sulfonamides of any type can produce allergic reactions, some of which may be severe. Although no reports exist of cross-sensitivity between methazolamide and other sulfa-type drugs, including antibacterial sulfonamides and thiazide diuretics, one case has been reported with acetazolamide. While the risk of cross-sensitivity appears low, methazolamide should be discontinued in any person who exhibits reactions suggestive of sulfonamide hypersensitivity. Methazolamide should be avoided in patients with a history of carbonic anhydrase inhibitor hypersensitivity.

Methazolamide use is contraindicated in patients with uncorrected electrolyte imbalance (e.g., hyponatremia, hypokalemia, hyperchloremia), acid/base imbalance (metabolic acidosis, acidemia), or adrenal insufficiency (e.g., Addison's disease). Baseline serum electrolytes should be monitored prior to drug initiation and repeated at regular intervals. Methazolamide is contraindicated in patients with severe renal disease (renal failure, anuria). Dosage reduction is warranted in patients with renal impairment. Methazolamide may potentiate acidosis and cause neurologic side effects in dialysis patients. The drug may also cause or worsen kidney stones (nephrolithiasis).

Methazolamide may cause hyperglycemia and should be used cautiously in patients with diabetes mellitus.

Methazolamide is contraindicated in patients with significant hepatic disease. The excretion of potassium is increased initially upon administration methazolamide. In patients with severe hepatic disease such as cirrhosis the use of methazolamide may precipitate hepatic encephalopathy or coma.

Geriatric patients may be more likely to develop hyperchloremic non-anion gap metabolic acidosis from the use of carbonic anhydrase inhibitors; reduced dosage may be needed due to an age-related decline in renal function. As methazolamide may cause drowsiness or confusion, especially in the elderly, performing hazardous tasks like driving or operating machinery should be delayed until the effects of the medication are known.

Long-term use of methazolamide is contraindicated in closed-angle glaucoma; however, the medication may temporarily be used preoperatively. Organic closure of the angle may occur in patients with closed-angle glaucoma despite methazolamide lowered intraocular pressure. Worsening glaucoma would be masked by a lowered IOP.

In patients with pulmonary disease or obstruction, like chronic obstructive pulmonary disease (COPD) (e.g., chronic bronchitis or emphysema) or any condition where alveolar ventilation may be impaired, methazolamide should be used with caution because it may precipitate or aggravate acidosis and/or acute respiratory failure.

Methazolamide has been reported to induce bone marrow suppression, agranulocytosis, neutropenia, aplastic anemia, purpura and thrombocytopenia so patients with a pre-existing hematological disease should have periodic hematologic evaluations.

Methazolamide is classified in FDA pregnancy risk category C. Skeletal anomalies have occurred in rats at doses 40 times the human

dose on a weight basis; no embryonic abnormalities were observed in rabbits at 20 times the human dose of methazolamide. Controlled studies are lacking in pregnant women; therefore, methazolamide should be used during pregnancy only when the benefit clearly outweighs the risk.

Methazolamide should be used cautiously in lactating women. It is not known whether methazolamide is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when methazolamide is given to a woman who is breast-feeding her infant.

The safety and effectiveness of methazolamide in pediatric patients including children and infants have not been established.

Like other sulfonamide derivatives, photosensitivity may occur with carbonic anhydrase inhibitors including methazolamide. Some patients may be more sensitive to sunlight (UV) exposure while receiving methazolamide. Advise patients to avoid prolonged exposure to sunlight or sunlamps.

Although methazolamide's action results in increased output of urine and excretion of sodium, potassium and chloride, methazolamide should not be used as a diuretic to treat edema or other related conditions. The diuretic effect is weak and transient.

Adverse Reactions

Frequent adverse GI effects of methazolamide include nausea/vomiting, diarrhea, anorexia, and weight loss. Melena, xerostomia, and excessive thirst have also been reported. Dysgeusia (often a metallic taste) is also a frequent adverse effect that may occur with all carbonic anhydrase inhibitors. Loss of smell and loss of taste have been reported.

Adverse CNS effects, such as drowsiness, seizures, irritability, libido decrease, vertigo, confusion, and paresthesias can develop. Paresthesias are manifested as numbness,

tingling, or burning in the hands, fingers, feet, toes, mouth, tongue, lips, or anus. Paresthesias may be less common with methazolamide than with acetazolamide; however, complaints of paresthesias may signal the need for dosage reduction.

The inhibition of carbonic anhydrase by methazolamide affects the excretion of electrolytes. Rarely, hyperchloremia and/or metabolic acidosis can result from an increase in plasma chloride concentrations. The increased excretion of bicarbonate, potassium, and sodium decreases the extracellular fluid concentration of bicarbonate and causes metabolic acidosis and possibly hypokalemia. Xerostomia, increased thirst, arrhythmias, muscle cramps, and nausea may all be signs of hypokalemia. Malaise, fatigue, asthenia, weakness, and complaints of paresthesia or myalgia may also be signs of need for dosage reduction (i.e., acidosis). Hypokalemia may be more of a risk if potassium intake is inadequate or if multiple potassium-wasting drugs are being used, or in those patients with hepatic cirrhosis. In patients with hepatic disease, especially cirrhosis, hepatic encephalopathy can occur as a result of hypokalemia and elevations in serum ammonia concentrations. Other metabolic disturbances, like hyperglycemia, glycosuria, and hyperuricemia may occur in susceptible patients.

Tinnitus and hearing loss have been reported early in therapy with methazolamide. Transient myopia (nearsightedness) has also occurred and is usually reversible upon a reduction in dose or discontinuation of therapy. Myopia may not return if methazolamide is restarted after discontinuation.

Like other sulfonamide derivatives, photosensitivity may occur with carbonic anhydrase inhibitors including methazolamide. Patients should avoid prolonged exposure to sunlight or sunlamps.

Increased urinary frequency is a less frequent side effect of methazolamide compared to the other carbonic anhydrase inhibitors.

Methazolamide has weak diuretic properties. Methazolamide has rarely caused crystalluria and sulfonamide-like nephrotoxicity characterized by renal tubular obstruction, hematuria, dysuria, and oliguria. An increase in calcium excretion or preexisting hypercalcemia can cause nephrolithiasis, although renal calculi formation is less with methazolamide than with acetazolamide.

'Sulfonamide-type' allergic reactions including urticaria, pruritus, and rash (unspecified) are relatively rare, including cross-sensitivity and anaphylactoid reactions or anaphylactic shock. Fever should be reported to the prescriber. Serious 'sulfonamide-type' skin and hematologic reactions reported with carbonic anhydrase inhibitors like methazolamide have included erythema multiforme, hemolysis (producing hemolytic anemia), leukopenia, pancytopenia, thrombocytopenia, thrombotic thrombocytopenic purpura (TTP), and other blood dyscrasias. For leukopenia and thrombocytopenia, prompt discontinuation of therapy resulted in complete recovery of white blood cell and platelet counts within five days.[26586] Rarely, fatalities have occurred due to 'sulfonamide-type' reactions including toxic epidermal necrolysis, Stevens-Johnson syndrome, fulminant hepatic necrosis, agranulocytosis, and aplastic anemia.

As sexual impotence (erectile dysfunction) and decreased libido have been reported as adverse effects of carbonic anhydrase inhibitor therapy[26587] such effects may occur in patient receiving methazolamide.

Methazolamide (Neptazane®) Specific Ocular Use

Adult dose: 25 -50 mg BID to TID up to 72 hours

Children: No adequate studies have been conducted to determine patient safety for this age group. Adverse incidence reports ranging from growth retardation to SJS to anaphylaxis have been reported for this drug, therefore it is

Methazolamide (Neptazane®) Specific Ocular Use continued

not recommend for use in patients < 12 years of age.

Sulfa allergy/ contraindicated in patients with hepatic or renal disease/ COPD. Better in treating patients who are prone to kidney stones or diabetic patients prone to ketoacidosis than Diamox®.

If unable to use Diamox® for an adult patient with Acute Angle Closure Glaucoma, recommend Neptazane® 50 mg STAT followed by 25-50 mg q 12h.

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Final Remarks

The intent of this course has been to overview the Florida Optometry Oral Drug Bill and provide the necessary regulatory and clinical information that certified optometrists need in order to qualify to prescribe the oral medications listed on Florida's Oral Ocular Pharmaceutical Agents Formulary.

The required post-examination for this activity is solely based on the content provided within the content of the course. This examination has been developed to ensure that a certified optometrist in Florida has the requisite knowledge and competence to prescribe oral ocular pharmaceutical agents for ocular conditions safely and effectively.

Optometrists who review the course material and successfully pass the post-examination with a minimum of 75% will be able to print a certificate of successful completion. The Florida Medical Association reports successful completions of this course to CE Broker every 24-48 hours. CE Broker in turn reports this information to the Florida Board of Optometry on a regular basis.

Successful completion of this course and examination may count toward 20 hours of required continuing education once during the 2-year licensure term in which they were taken.

Accessing the Post-Examination

Once you have reviewed the content of this course and are ready to access the examination questions, you will need to return to your online CME account (Purchased Courses Page) and click on the Test Evaluation Certificate button. Complete the post-test and the evaluation. Once these items are completed, you may print a CME certificate. The FMA will report the successful completion of the course and examination to CE Broker within 48-72 hours.



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