AZITHROMYCIN (Systemic)

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Pseudomonas aeruginosa , Klebsiella , Enterobacter , Citrobacter , Proteus , Providencia , Morganella , and Serratia species are resistant to azithromycin 11.

Azithromycin is two- to fourfold more active than erythromycin against Moraxella (Branhamella) catarrhalis12.

Inhibition of anaerobes, such as Clostridium perfringens , is slightly better with azithromycin than with erythromycin, and azithromycin"s inhibition of Bacteroides fragilis and other Bacteroides species is comparable to that of erythromycin 11, 12.

Azithromycin also has good in vitro activity against Chlamydia trachomatis , Chlamydia pneumoniae , Mycoplasma pneumoniae , Legionella species, Borrelia burgdorferi , Ureaplasma urealyticum , and Gardnerella vaginalis11.

Azithromycin has eightfold more activity than erythromycin against Neisseria gonorrhoeae and tenfold more activity against Haemophilus ducreyi12.

It has also been shown to inhibit Toxoplasma gondii in vitro and in animal models. However, no potentiation against T. gondii could be demonstrated when azithromycin was combined with pyrimethamine 11, 12.

Also, when azithromycin was administered as a single agent in the treatment of cerebral toxoplasmosis in two patients, it failed, although the patients responded to conventional treatment 15.

Accepted

Bronchitis, bacterial exacerbations (treatment) or

Otitis media, acute (treatment)¾Azithromycin is indicated in the treatment of bacterial exacerbations of chronic bronchitis or acute otitis media due to Haemophilus influenzae , Moraxella catarrhalis , or Streptococcus pneumoniae1.

However, azithromycin is not recommended as the first line of therapy for otitis media 18.

Cervicitis, gonococcal (treatment)

Cervicitis, nongonococcal (treatment)

Urethritis, gonococcal (treatment) or

Urethritis, nongonococcal (treatment)¾Azithromycin is indicated in the treatment of cervicitis or urethritis due to Chlamydia trachomatis or Neisseria gonorrhoeae .

Chancroid (treatment)¾Azithromycin is indicated in the treatment of genital ulcer disease in men due to Haemophilus ducreyi1.

Mycobacterium avium complex (MAC) disease, disseminated (prophylaxis) *¾ Azithromycin is indicated in the prevention of disseminated MAC disease in patients with advanced human immunodeficiency virus (HIV) infection 1.

Pelvic inflammatory disease (treatment) *¾Azithromycin is indicated in the treatment of pelvic inflammatory disease due to Chlamydia trachomatis , Mycoplasma hominis , or Neisseria gonorrhoeae1.

Pharyngitis (treatment) or

Tonsillitis (treatment)¾Azithromycin is indicated in the treatment of pharyngitis or tonsillitis due to Streptococcus pyogenes1.

Pneumonia, community-acquired (treatment)¾Azithromycin is indicated in the treatment of community-acquired pneumonia due to Chlamydia pneumoniae * , Haemophilus influenzae , Legionella pneumophila * , Moraxella catarrhalis * , Mycoplasma pneumoniae * , Staphylococcus aureus * , or Streptococcus pneumoniae1.

Skin and soft tissue infections (treatment)¾Azithromycin is indicated in the treatment of uncomplicated skin and soft tissue infections due to Staphylococcus aureus , Streptococcus agalactiae , or Streptococcus pyogenes1.

[Trachoma (treatment)] *¾Azithromycin is indicated in the treatment of trachoma due to Chlamydia trachomatis 19, 20, 21.

Trachoma is the leading cause of preventable blindness. Programs to prevent blindness due to trachoma have been based on community-wide treatment with topical tetracycline. Single-dose azithromycin has been shown to be as effective as a 6-week course of topical tetracycline ointment in the treatment of active trachoma. Therefore, azithromycin is useful in establishing high compliance in the treatment of trachoma 19, 20, 21.

* Not included in Canadian product labeling.

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾Azithromycin: 785.03 17

Mechanism of action/Effect:

Azithromycin binds to the 50S ribosomal subunit of the 70S ribosome of susceptible organisms, thereby inhibiting RNA-dependent protein synthesis 1, 9.

Azithromycin is bactericidal for Streptococcus pyogenes , Streptococcus pneumoniae , and Haemophilus influenzae ; it is bacteriostatic for staphylococci and most aerobic gram-negative species 11.

Absorption:

For oral dosage forms¾Rapidly absorbed 1 ; bioavailability is approximately 37% 5.

Capsule form: Food decreases peak serum concentration (C max) values by approximately 52% and area under the plasma concentration-time curve (AUC) values by approximately 43% 1.

Tablet form: Food increases C max values by approximately 23% and 34% for the 250- and 600-mg tablets, respectively, and has no effect on AUC values 1.

Oral suspension form (for adults): Food increases C max values by approximately 56% and has no effect on AUC values 1.

Distribution:

Rapidly and widely distributed throughout the body. Concentrates intracellularly, resulting in tissue concentrations 10 to 100 times higher than those found in plasma or serum 5.

Azithromycin is highly concentrated in phagocytes and fibroblasts. Phagocytes transport the drug to the site of infection and inflammation. Release of azithromycin from phagocytes is gradual, but it is enhanced by exposure to the cell membrane of bacteria 6.

Release of azithromycin from fibroblasts is not enhanced by bacteria, but fibroblasts may act as reservoirs of the antibiotic, releasing azithromycin to phagocytes 6.

Very low concentrations (< 0.01 mcg per mL [mcg/mL]) have been detected in the cerebrospinal fluid of human subjects with noninflamed meninges 1 ; however, higher concentrations were found in brain tissue in animal studies 16.

Vol D¾ For oral dosage forms, approximately 31 L per kg (steady-state) 1.

For parenteral dosage forms, approximately 33 L per kg (following 1000- to 4000-mg doses at a concentration of 1 mg/mL infused over a 2-hour period) 1 .

Protein binding:

Varies with concentration¾Very low to moderate; approximately 7% at 1 mcg/mL, to 50% at 0.02 to 0.05 mcg/mL 1, 5.

Biotransformation:

Hepatic; approximately 35% metabolized by demethylation. Up to 10 metabolites, which are thought to have no significant antimicrobial activity, may be found in the bile 6, 9.

Half-life:

Peripheral leukocytes¾34 to 57 hours (mean) after a single dose of 1200 mg (two 600-mg tablets) [1].

Serum¾11 to 14 hours when measured between 8 and 24 hours after a single, oral dose of 500 mg [5]; however, after several doses, the half-life is approximately the same as the half-life in tissues [5].

Tissue¾2 to 4 days [5, 6, 7].

Time to peak concentration:

Adult subjects¾For oral dosage forms: 2.1 to 3.2 hours [1, 8].

For parenteral dosage forms: 1 to 2 hours [2].

Elderly subjects¾3.8 to 4.4 hours [8].

Peak plasma concentration

For oral dosage forms, after a 500-mg loading dose on day 1, then 250 mg once a day on days 2 through 5 [1, 8¾] Day 1: Approximately 0.41 and 0.38 mcg/mL for healthy young and elderly adults, respectively.
Day 5: Approximately 0.24 and 0.26 mcg/mL for healthy young and elderly adults, respectively.

For parenteral dosage forms¾ Approximately 1.1 mcg/mL after a 3-hour intravenous infusion of 500 mg at a concentration of 1 mg/mL [2].

Approximately 3.6 mcg/mL after a 1-hour intravenous infusion of 500 mg at a concentration of 2 mg/mL [2].

Elimination:

Over 50% of the dose is eliminated through biliary excretion as unchanged drug [6].

For oral dosage forms, approximately 4.5% of the dose is eliminated in the urine as unchanged drug within 72 hours [5].

For parenteral dosage forms, approximately 11 to 14% of the dose is eliminated in the urine as unchanged drug within 24 hours [2].

Precautions to Consider

Cross-sensitivity and/or related problems

Patients who are hypersensitive to erythromycin or other macrolides may also be hypersensitive to azithromycin [1].

Carcinogenicity

Long-term studies have not been done in animals to evaluate the carcinogenic potential of azithromycin 1.

Mutagenicity

Azithromycin was not found to be mutagenic in the mouse lymphoma assay, the human lymphoctye clastogenic assay, or the mouse bone marrow clastogenic assay 1.

Pregnancy/Reproduction

Fertility¾Adequate and well-controlled studies in humans have not been done 1.

Reproduction studies done in rats and mice given azithromycin at doses of up to moderately maternally toxic levels (i.e., 200 mg per kg of body weight [mg/kg] per day) have found no evidence of impaired fertility. On a mg per square meter of body surface area (mg/m 2) basis, these doses are estimated to be four and two times the human daily dose of 500 mg in rats and mice, respectively. 1

Pregnancy¾Adequate and well-controlled studies in humans have not been done 1.

Reproduction studies done in rats and mice given azithromycin at doses of up to moderately maternally toxic levels (i.e., 200 mg/kg per day) have found no evidence of harm to the fetus. On a mg/m 2 basis, these doses are estimated to be four and two times the human daily dose of 500 mg in rats and mice, respectively. 1

FDA Pregnancy Category B 1.

Breast-feeding

It is not known if azithromycin is distributed into breast milk 1.

Pediatrics

Appropriate studies on the relationship of age to the effects of parenteral azithromycin or of the capsule or tablet dosage form of oral azithromycin have not been performed in children up to 16 years of age. Safety and efficacy have not been established. However, the oral suspension dosage form of azithromycin is approved for use in infants and children 6 months of age and older. 1, 2

Geriatrics

Pharmacokinetic data in healthy elderly subjects (65 to 85 years old) were similar to those for younger volunteers (18 to 40 years old). A higher peak concentration (by 30 to 50%) was found in elderly women; however, no significant accumulation occurred. Dosage adjustment does not appear to be necessary in older patients with normal renal and hepatic function. 1, 8

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
>> Antacids, aluminum- and magnesium-containing 1, 4, 10

(concurrent use with antacids decreases the peak serum concentration [C max] of azithromycin by approximately 24%, but has no effect on the area under the plasma concentration-time curve [AUC] 1 ; oral azithromycin should be administered at least 1 hour before or 2 hours after aluminum- and magnesium-containing antacids)

Carbamazepine 1 or

Cyclosporine 1 or

Digoxin 1 or

Hexobarbital 1 or

Phenytoin 1 or

Terfenadine 1

(concurrent use with macrolide antibiotics has been associated with increased serum concentrations of carbamazepine, cyclosporine, digoxin, hexobarbital, phenytoin, and terfenadine 1 ; patients concurrently receiving azithromycin and any of these medications should be monitored carefully 1)

Dihydroergotamine 1 or

Ergotamine 1

(concurrent use with macrolide antibiotics has been associated with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia 1 ; patients concurrently receiving azithromycin and either of these medications should be monitored carefully 1)

Theophylline 1

(concurrent use with macrolide antibiotics has been associated with increased serum concentrations of theophylline 1 ; pending further investigation, plasma concentrations of theophylline should be monitored in patients concurrently receiving azithromycin and theophylline 1)

Triazolam 1

(concurrent use with macrolide antibiotics has been associated with a decrease in the clearance of triazolam, which may increase its effects 1 ; patients concurrently receiving azithromycin and triazolam should be monitored carefully 1)

Warfarin 1

(concurrent use with macrolide antibiotics has been associated with increased anticoagulant effects 1 ; prothrombin time should be monitored carefully in patients concurrently receiving azithromycin and warfarin 1)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]) 1 and

Aspartate aminotransferase (AST [SGOT]) 1 and

Creatine kinase 1 and

Gamma-glutamyltransferase 1 and

Lactate dehydrogenase 2

(serum values may be increased 1, 2, 4)

Bilirubin 2 and

Potassium, serum 1

(concentrations may be increased 1, 2)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problem exists

>> Hypersensitivity to azithromycin, erythromycins, or other macrolides 1

Risk-benefit should be considered when the following medical problem exists

>> Hepatic function impairment 1, 4

(because biliary excretion is the major route of elimination, caution should be used in patients with hepatic function impairment 1, 4)

Side/Adverse Effects

Note: Rarely, serious allergic reactions, such as anaphylaxis and angioedema, have been reported in patients taking azithromycin. Despite discontinuation of azithromycin and successful symptomatic treatment of the allergic reactions, allergic symptoms soon recurred in some patients when the symptomatic therapy was discontinued. These patients require prolonged periods of observation and symptomatic treatment. 14

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence more frequent¾for injection form only

Thrombophlebitis 2 pain, redness, and swelling at site of injection)
Incidence rare

Acute interstitial nephritis 14 fever); joint pain); skin rash); allergic reactions 1 difficulty in breathing); swelling of face, mouth, neck, hands, and feet); skin rash); pseudomembranous colitis 1 abdominal or stomach cramps or pain, severe); abdominal tenderness); diarrhea, watery and severe, which may also be bloody); fever)
Those indicating need for medical attention only if they continue or are bothersome

Incidence less frequent

Gastrointestinal disturbances 1, 4 (abdominal pain; diarrhea, mild; nausea; vomiting)
Incidence rare

Dizziness 1, 4; headache 1, 4

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Azithromycin (Systemic) .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Hypersensitivity to azithromycin, erythromycins, or other macrolides
Other medications, especially aluminum- and magnesium-containing antacids
Other medical problems, especially hepatic function impairment
Proper use of this medication

Azithromycin capsules and pediatric oral suspension should be given at least 1 hour before or 2 hours after meals

Azithromycin tablets and adult single dose oral suspension may be taken with or without food

Compliance with full course of therapy

>> Importance of not taking more medication than prescribed; importance of not discontinuing medication without checking with physician

>> Proper dosing
Missed dose: Taking as soon as possible; not taking if almost time for next dose; not doubling doses
>> Proper storage
Precautions while using this medication

Checking with physician if no improvement within a few days or if condition becomes worse

Side/adverse effects

Signs of potential side effects, especially thrombophlebitis, acute interstitial nephritis, allergic reactions, and pseudomembranous colitis

General Dosing Information

No adjustment in dose is required in patients with mild renal function impairment (creatinine clearance ³ 40 mL per minute [0.67 mL per second]). No data are available on the use of azithromycin in patients with more severe renal function impairment. 4, 9

Diet/Nutrition

Azithromycin capsules and oral suspension in dropper bottles (for children) should be given at least 1 hour before or 2 hours after meals.
Azithromycin tablets and oral suspension in 1-gram packets (for adults) may be taken with or without food.

Oral Dosage Forms

AZITHROMYCIN CAPSULES USP

Usual adult and adolescent dose

Bronchitis, bacterial exacerbations or
Pharyngitis, streptococcal or
Pneumonia, due to Streptococcus pneumoniae or Haemophilus influenzae , or
Skin and soft tissue infections, uncomplicated, due to Staphylococcus aureus , Streptococcus agalactiae , or Streptococcus pyogenes or
Tonsillitis, streptococcal¾Adults and adolescents 16 years of age and older: Oral, 500 mg as a single dose on the first day, then 250 mg once a day on days two through five 1.

Adolescents up to 16 years of age: Safety and efficacy have not been established 1.

Cervicitis, nongonococcal or

Urethritis, nongonococcal¾Adults and adolescents 16 years of age and older: Oral, 1000 mg as a single dose 1.

Adolescents up to 16 years of age: Safety and efficacy have not been established 1.

Usual pediatric dose

Children up to 16 years of age¾Safety and efficacy have not been established 1.

Strength(s) usually available

U.S.¾250 mg (Rx)[Zithromax (lactose)] 1

Canada¾250 mg (Rx)[Zithromax (lactose)] 3

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F) in a well-closed container.

Auxiliary labeling:

· Do not take with food.
· Continue medicine for full time of treatment.

AZITHROMYCIN FOR ORAL SUSPENSION USP

Usual adult and adolescent dose

Cervicitis, nongonococcal or
Chancroid, in men or
Urethritis, nongonococcal¾Oral, 1 gram as a single dose 1.

Cervicitis, gonococcal or
Urethritis, gonococcal¾Oral, 2 grams as a single dose 1.

Usual pediatric dose

Otitis media, acute or
Pneumonia, due to Chlamydia pneumoniae * , Haemophilus influenzae , Mycoplasma pneumoniae * , or Streptococcus pneumoniae¾Infants and children 6 months to 12 years of age: Oral, 10 mg per kg of body weight, up to 500 mg, on the first day, then 5 mg per kg of body weight, up to 250 mg, on days two through five 1.

Infants up to 6 months of age: Safety and efficacy have not been established 1.

Pharyngitis, streptococcal or
Tonsillitis, streptococcal¾Children 2 to 12 years of age: Oral, 12 mg per kg of body weight, up to 500 mg, once a day for five days 1.

Infants and children up to 2 years of age: Safety and efficacy have not been established 1.

[Trachoma (treatment)] *¾Children 2 to 10 years of age: Oral, 20 mg per kg of body weight as a single dose 19, 20, 21.

Infants and children up to 2 years of age: Safety and efficacy have not been established 1.

Note: Depending on the severity of the trachoma and the initial clinical response, doses of azithromycin oral suspension may be repeated once every 28 days for a total of 6 doses 19, 20, 21.

Usual pediatric prescribing limits

500 mg per day for pharyngitis, tonsillitis, and the first day of dosing for otitis media and pneumonia.
250 mg per day for days two through five for otitis media and pneumonia 1.

Strength(s) usually available
U.S.¾100 mg per 5 mL (when reconstituted according to manufacturer"s instructions) (available in 300-mg bottles) (Rx)[Zithromax (sucrose)] 1

200 mg per 5 mL (when reconstituted according to manufacturer"s instructions) (available in 600-, 900-, and 1200-mg bottles) (Rx)[Zithromax (sucrose)] 1

1 gram (single dose packet) (Rx)[Zithromax (sucrose)] 1

Canada¾100 mg per 5 mL (when reconstituted according to manufacturer"s instructions) (available in 300-mg bottles) (Rx)[Zithromax (sucrose)] 3

200 mg per 5 mL (when reconstituted according to manufacturer"s instructions) (available in 600- and 900-mg bottles) (Rx)[Zithromax (sucrose)] 3

1 gram (single dose packet) (Rx)[Zithromax (sucrose)] 3

Packaging and storage:

Prior to reconstitution, store between 5 and 30 °C (41 and 86 °F) in a tight container.
After reconstitution, the pediatric oral suspension should be stored between 5 and 30 °C (41 and 86 °F).

Preparation of dosage form:

For the pediatric suspension¾Add the indicated volume of water to the bottle and shake well 1.

Azithromycin content	Final concentration added	Total volume of water to be
300 mg	100 mg/5 mL	9 mL

600 mg	200 mg/5 mL	9 mL
900 mg	200 mg/5 mL	12 mL
1200 mg	200 mg/5 mL	15 mL

For the adult single dose packets-Empty the entire contents of the packet into a glass containing 2 ounces (approximately 60 mL) of water and mix thoroughly. The suspension should be consumed immediately. Add an additional 2 ounces of water to the glass, mix, and drink to assure complete consumption of the dose. This packet should not be used to administer doses other than 1000 mg of azithromycin. 1

Auxiliary labeling:

For the pediatric suspension¾· Refrigerate.
· Shake well.
· Do not take with food.
· Continue medicine for full time of treatment.
· For the adult single dose packets¾· Reconstitute before taking.

AZITHROMYCIN TABLETS

Usual adult and adolescent dose

Bronchitis, bacterial exacerbations or
Pharyngitis, streptococcal or
Pneumonia, due to Chlamydia pneumoniae * , Haemophilus influenzae , Mycoplasma pneumoniae * , or Streptococcus pneumoniae or
Skin and soft tissue infections or
Tonsillitis, streptococcal¾Adults and adolescents 16 years of age and older: Oral, 500 mg as a single dose on the first day, then 250 mg once a day on days two through five 1.

Adolescents up to 16 years of age: Safety and efficacy have not been established 1.

Cervicitis, nongonococcal or
Urethritis, nongonococcal¾Adults and adolescents 16 years of age and older: Oral, 1000 mg as a single dose 1.

Adolescents up to 16 years of age: Safety and efficacy have not been established 1.

Mycobacterium avium complex (MAC) disease, disseminated, prophylaxis *¾Adults and adolescents 16 years of age and older: Oral, 1200 mg once a week, alone or in combination with an approved dosing regimen of rifabutin 1.

Adolescents up to 16 years of age: Safety and efficacy have not been established 1.

Usual pediatric dose

Children up to 16 years of age¾Safety and efficacy have not been established 1.

Strength(s) usually available

U.S.¾250 mg (Rx)[Zithromax (scored) (lactose)] 1

600 mg (Rx)[Zithromax (lactose)] 1

Canada¾250 mg (Rx)[Zithromax (scored) (lactose)] 3

Packaging and storage:

Store between 5 and 30 °C (41 and 86 °F).

Auxiliary labeling:

· Continue medicine for full time of treatment.

Parenteral Dosage Form

AZITHROMYCIN FOR INJECTION

Note: Azithromycin for injection should be infused at a concentration of 1 mg per mL over a 3-hour period, or 2 mg per mL over a 1-hour period 2.

Azithromycin should not be administered by bolus or intramuscular injection 2.

Usual adult and adolescent dose

Pelvic inflammatory disease *¾Adults and adolescents 16 years of age and older: Intravenous infusion, 500 mg as a single dose once a day for the first one or two days of a seven-day course of therapy 2.

Adolescents up to 16 years of age: Safety and efficacy have not been established 2.

Note: After the one- or two-day infusion therapy is complete, an oral dose of 250 mg should be administered once a day to complete the seven-day course of therapy 2.

Pneumonia *, due to Chlamydia pneumoniae , Haemophilus influenzae , Legionella pneumophila , Moraxella catarrhalis , Mycoplasma pneumoniae , Staphylococcus aureus , or Streptococcus pneumoniae¾Adults and adolescents 16 years of age and older: Intravenous infusion, 500 mg as a single dose once a day for at least the first two days of a seven- to ten-day course of therapy 2.

Adolescents up to 16 years of age: Safety and efficacy have not been established 2.

Note: After the infusion therapy is complete, an oral dose of 500 mg should be administered once a day to complete the seven- to ten-day course of therapy 2.

Usual pediatric dose

Children up to 16 years of age¾Safety and efficacy have not been established 2.