

AZIMEX

Capsules & Powder

Composition

Azimex 250 Capsules

Each capsule contains Azithromycin (as dihydrate) 250 mg

Azimex 500 mg Capsules

Each capsule contains Azithromycin (as dihydrate) 500 mg

Azimex Powder

Each 5 ml contains Azithromycin (as dihydrate) 200 mg

Action

Azithromycin acts by binding to the 50S ribosomal subunit of susceptible organisms and thus interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by in vitro incubation techniques. Using such methodology, the ratio of intracellular to extra cellular concentration was > 30 after one-hour incubation. In vivo studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues. Azithromycin has been shown to be active against most strains of the following organisms – both in vitro and in clinical infections.

Gram-positive aerobes

Staphylococcus aureus

Streptococcus pneumoniae

Streptococcus agalactiae

Streptococcus pyogenes

NOTE: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains. Most strains of *Enterococcus faecalis* and methicillin-resistant staphylococci are resistant to Azithromycin.

Gram-negative aerobes

Haemophilus influenzae

Moraxella catarrhalis

Other organisms

Chlamydia trachomatis

Beta-lactamase production should have no effect on Azithromycin activity.

Azithromycin exhibits in vitro minimum inhibitory concentrations of 2.0 µg/ml or less against most strains of the following organisms. The safety and efficacy of Azithromycin in treating infections due to these organisms have not been established in adequate and well-controlled trials. The following in vitro data are available; however, their clinical significance is unknown.

Gram-positive aerobes

Streptococci (Groups C, F, G)

Viridans group streptococci

Gram-negative aerobes

Bordetella pertussis

Campylobacter jejuni

Haemophilus ducreyi

Legionella pneumophila

Anaerobic bacteria

Bacteroides bivius

Peptostreptococcus species

Other organisms

Borrelia burgdorferi

Mycoplasma pneumoniae

Treponema pallidum

Ureaplasma urealyticum

Indications

Azimec is indicated for the treatment of patients with mild to moderate infections (pneumonia: caused by susceptible strains of the designated microorganisms in the specific conditions listed below. As recommended dosages, duration's of therapy, and applicable patient populations vary among these infections.

Lower Respiratory Tract

Acute bacterial exacerbations of chronic obstructive pulmonary disease due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*.

Community-acquired pneumonia of mild severity due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients appropriate for outpatient oral therapy.

NOTE: Azithromycin should not be used in patients with pneumonia who are judged inappropriate for outpatient oral therapy because of moderate to severe illness or risk factors such as any of the following:

- Patients with nosocomially acquired infections.
- Patients with known or suspected bacteremia,
- Patients requiring hospitalization,
- Elderly or debilitated patients, or

Patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional aspienia).

Upper Respiratory Tract

Streptococcal pharyngitis / tonsillitis-As an alternative to first line therapy of acute Pharyngitis / tonsillitis due to *Streptococcus Pyogenes* occurring in individuals who cannot use first line therapy.

NOTE: Penicillin is the usual drug of choice in the treatment of *Streptococcus Pyogenes* infections and the prophylaxis of rheumatic fever. Azimec is often effective in the eradication of susceptible strains of *Streptococcus Pyogenes* from the nasopharynx. Because some strains are resistant to Azimec, susceptibility tests should be performed when patients are treated with Azimec. Data establishing efficacy of Azithromycin in subsequent prevention of rheumatic fever are not available.

Skin and Skin Structure

Uncomplicated skin and skin structure infections due to *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Streptococcus agalactiae*. Abscesses usually require surgical drainage.

Sexually Transmitted Diseases

Non-gonococcal urethritis and cervicitis due to chlamydia trachomatis.

Azimec, at the recommended dose, should not be relied upon to treat gonorrhea or syphilis. Antimicrobial agents used in high doses for short periods to treat non –gonococcal urethritis may mask or delay the symptoms of incubating gonorrhea or syphilis. All patients with sexually transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate cultures

for gonorrhoea performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to Azithromycin. Therapy with Azimex may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

Contraindications

Azithromycin is contraindicated in patients with known hypersensitivity to Azithromycin, erythromycin, or any macrolide antibiotic.

Warnings

Rare serious allergic reactions, including angioedema and anaphylaxis, have been reported in patients on Azithromycin therapy. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further Azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment.

The relationship of these episodes to the long tissue half-life of Azithromycin and subsequent prolonged exposure to antigen is unknown at present.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms might occur when symptomatic therapy is discontinued.

In the treatment of pneumonia, Azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia of mild severity due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients appropriate for outpatient oral therapy.

Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for outpatient oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia). Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity 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.

Treatment with antibacterial agents alters 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 the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone.

In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Adverse Reactions

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Patients, who discontinued Azithromycin therapy because of treatment related side effects, were related to the gastrointestinal tract, e.g. nausea,

vomiting, diarrhea, or abdominal pain. Rare but potentially serious side effects were angioedema and cholestatic jaundice.

Clinical

Multiple dose regimens

Overall, the most common side effects in patients receiving the multiple dose regimen of Azithromycin were related to the gastrointestinal system with diarrhea / loose stools (5%) nausea (3%) and abdominal pain (3%) being the most frequently reported. No other side effects occurred with a frequency of 1% or less included the following:

Cardiovascular: Palpitations chest pain.

Gastrointestinal: Dyspepsia, flatulence, vomiting, melena, and cholestatic jaundice.

Genitourinary: Monilia, vaginitis, and nephritis.

Nervous system: Dizziness, headache, vertigo, and somnolence.

General: Fatigue.

Allergic: Rash, photosensitivity, and angioedema.

Single 1-gram dose regimen; Overall, the most common side effects in patients receiving a single - dose regimen of 1 gram of Azithromycin were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple- dose regimen.

Side effects that occurred in patients on the single one-gram dosing regimen of Azimex with a frequency of 1 % or greater included diarrhea / loose stools (7%) nausea (5%) vomiting (2%) and vaginitis (2%).

Laboratory abnormalities, Significant abnormalities (irrespective of drug, relationships occurring during the clinical trials were reported as follows:

With an incidence of 1-2% elevated serum creatinine phosphokinase, potassium, ALT (SGPT) GGT, and AST (SGOT) with an incidence of less than 1 % leukopenia, neutropenia decreased platelet count elevated serum alkaline phosphate.

When follow up was provided, changes in laboratory tests appeared to be reversible. In multiple-dose clinical trials involving more than 3000 patients, 3 patients discontinued therapy because of treatment related liver enzyme abnormalities and because of a renal function abnormality.

Precautions

Hepatotoxicity

No dose adjustment is recommended for patients with mild to moderate hepatic impairment (GFR 10 – 80 mL/min). Nonetheless, since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Caution should be exercised when azithromycin is administered to patients with severe renal impairment.

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.

Prolongation of the QT interval

Ventricular arrhythmias associated with prolonged QT interval, including ventricular tachycardia and torsades de pointes have been reported with macrolide products including azithromycin.

Azithromycin should be used with caution in patients:

- predisposed to QT interval prolongation;

- taking other medications known to prolong the QT interval such as antiarrhythmics of classes IA and III; antipsychotic agents; antidepressants; and fluoroquinolones;
- with electrolyte disturbance, particularly in cases of Hypokalaemia and hypomagnesaemia;
- with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency;
- Elderly: elderly patients may be more susceptible to drug-associated effects on the QT interval.

Pregnancy

Category B

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Nursing Mothers

It is not known whether Azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Azithromycin is administered to a nursing woman.

Pediatric Use

Acute Otitis Media (dosage regimen: 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5): Safety and effectiveness in the treatment of children with otitis media less than 6 months of age have not been established

Community-Acquired Pneumonia (dosage regimen: 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5). Safety and effectiveness in the treatment of children with community-acquired pneumonia less than 6 months of age have not been established.

Safety and effectiveness for pneumonia due to *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* were documented in pediatric clinical trials.

Safety and effectiveness for pneumonia due to *Haemophilus influenzae* and *Streptococcus pneumoniae* were not documented bacteriologically in the pediatric clinical trial due to difficulty in obtaining specimens.

Use of Azithromycin for these two microorganisms is supported, however, by evidence from adequate and well-controlled studies in adults Pharyngitis/tonsillitis (dosage regimen: 12 mg/kg on Days 1-5): Safety and effectiveness in the treatment of children with pharyngitis/tonsillitis under 2 years of age have not been established.

Studies evaluating the use of repeated courses of therapy have not been conducted.

Geriatric Use

Pharmacokinetic parameters in older volunteers (65-85 years old) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen.

Information for Patients

Patients should be cautioned to take this medication at least one hour prior to a meal or at least two hours after a meal. This medication should not be taken with food.

Patients should also be cautioned not to take aluminium- and magnesium-containing antacids and Azithromycin simultaneously.

The patient should be directed to discontinue Azithromycin immediately and contact a physician if any signs of an allergic reaction occur.

Drug Interactions

Ergot derivatives

Because of the theoretical possibility of ergotism, Azithromycin, and ergot derivatives should not be co-administered.

Special administration advised with the following:

Antacids

In patients receiving Azithromycin and antacids, Azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

Cimetidine

a single dose of cimetidine administered 2 hours before Azithromycin had no effect on the pharmacokinetics of azithromycin.

Special precautionary monitoring advised with the following

Cyclosporin

some of the related macrolide antibiotics interfere with the metabolism of cyclosporine. In the absence of pharmacokinetic studies or clinical data investigating potential interaction between Azithromycin and cyclosporine, caution should be exercised before co-administration of these two drugs. If co-administration is necessary, cyclosporine levels should be monitored and the dose adjusted accordingly.

Digoxin

some of the macrolide antibiotics have been reported to impair the metabolism of digoxin (in the gut) in some patients. Therefore, in patients receiving concomitant Azithromycin, a related azalide antibiotic, and digoxin the possibility of raised digoxin levels should be borne in mind.

Warfarin

In a pharmacokinetic interaction study, Azithromycin did not alter the anticoagulant effect of a single 15 mg dose of warfarin administered to healthy volunteers. Azithromycin and warfarin may be co-administered, but monitoring of the prothrombin time should be continued as routinely performed.

Terfenadine

There have been less frequent reports of an interaction in patients receiving Azithromycin and terfenadine where the possibility of such an interaction could not be entirely excluded

Dosage and Administration

Azimex 250 mg capsules

Azimex should be given at least 1 hour before or 2 hours after a meal.

The recommended dose of Azimex for the treatment of individuals 16 years of age and older with mild to moderate acute bacterial exacerbation's of chronic obstructive pulmonary disease pneumonia pharyngitis / tonsillitis (as second - line therapy) and uncomplicated skin and skin structure infections due to the indicated organisms is 500 mg as a single dose on the first day followed by 250 mg once daily on days 2 through 5 for a total dose of 1.5 grams of Azimex.

The recommended dose of Azimex for the treatment of non-gonococcal urethritis and cervicitis due to *C. trachomatis* is a single 1-gram (1000 mg) dose of Azimex.

Azimex 500 mg capsules

Adult

For all indications other than sexually transmitted disease, the total dose is 1.5 g which should be given as 500 mg daily for three days.

For sexual transmitted diseases caused by *Chlamydia trachomatis*, the dose is 1 g given as a single dose.

Use in elderly

Normal adult dose is recommended.

Use in children

Children over 45 Kg – dose as per adult.

This formulation is not suitable for children under 45 kg.

Azimex Powder

Acute Otitis Media and Community-Acquired Pneumonia

The recommended dose of Azimex suspension for the treatment of children with acute otitis media and community-acquired pneumonia is 10 mg/kg as a single 1 dose on the first day (not to exceed 500 mg/day) followed by 5 mg/kg on days 2 through 5 (not to exceed 250 mg/day)

Azimex suspension should be given at least 1 hour before or 2 hours after a meal.

Azimex suspension should not be taken with food.

Pharyngitis/Tonsillitis

The recommended dose for children with Pharyngitis/tonsillitis is 12 mg/kg once a day for 5 days (not to exceed 500 mg/day).

Azimex suspension should be given at least 1 hour before or 2 hours after a meal.

Azimex suspension should not be taken with food.

PEDIATRIC DOSAGE GUIDELINES FOR PHARYNGITIS/TONSILLITIS

(Age 2 years and above-pediatric Use)

Based on Body Weight

Pharyngitis /Tonsillitis

Dosing Calculated on 12 mg/kg once daily Days 1 to 5.

<u>Weight</u>		<u>200 mg/5 ml</u>	<u>Total ml per Treatment Course</u>
<u>Kg</u>	<u>lbs</u>	<u>Day 1-5</u>	
8	18	2.5 ml (1\2 tsp)	12.5 ml
17	37	5 ml (1 tsp)	25 ml
25	55	7.5 ml (1 1\2 tsp)	37.5 ml
33	73	10 ml (2 tsp)	50 ml
40	88	12.5 ml (2 1\2 tsp)	62.5 ml

Shake well before each use. Oversized bottle provides shake space. Keep tightly closed. After mixing, store at 5° to 30° C and use within 10 days. Discard after full dosing is completed.

Over Dosage

There are no data on over dosage with Azithromycin. Typical symptoms of over dosage with macrolide antibiotics include hearing loss; severe nausea, vomiting and diarrhea.

Gastric lavage and general supportive measures are indicated.

Presentation

Azimex 250 & 500 capsules

Box of 6 capsules.

Azimex Powder

Bottle contains powder for preparing 22.5 ml suspension