AZIMEX

Powder

Composition
Each 5 ml contains Azithromycin (as dihydrate) 200 mg

Action
Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms 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 extracellular 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 microorganisms, both *in vitro* and in clinical infections as described in the indications section.

Aerobic gram-positive microorganisms
Staphylococcus aureus, Streptococcus agalactiae, Streptococcus pneumonia, 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.

Aerobic gram-negative microorganisms
Haemophilus ducreyi, Haemophilus influenza, Moraxella catarrhalis, Neisseria gonorrhea
"Other" microorganisms, *Chlamydia pneumonia, Chlamydia trachomatis, Mycoplasma pneumonia*

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

Aerobic gram-positive microorganisms
Streptococci (Groups C, F, G), Viridans group streptococci, anaerobic microorganisms, Peptostreptococcus species, *Prevotella bivia*, Aerobic gram-negative microorganisms, *Bordetella pertussis, Legionella pneumophila*, "Other" microorganisms, *Ureaplasma ureulyticum* Susceptibility Tests

Indications
Azimex 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.

Adults
Acute bacterial exacerbation is of chronic obstructive pulmonary disease due to *Haemophilus influenza, Moraxella catarrhalis*, or *Streptococcus pneumoniae*. Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenza*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* in patients appropriate for oral therapy.

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

Patients with cystic fibrosis, 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.

Pharyngitis/tonsillitis
Caused by Streptococcus Pyogenes as an alternative to first-line therapy in individuals who cannot use first line therapy.

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

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

Uretheritis and cervicitis due to *Chlamvdia trachomatis* or *Neisseria gonorrhoeae*.

Genital ulcer disease: in men due to haemophilus ducreyi (chancroid). Due to the small Dumber of women included in clinical trials, the efficacy of Azithromycin in the treatment of chancroid in women has not been established.

Azithromycin, at the recommended dose- should not be relied upon to treat syphilis. Antimicrobial agents used in high doses for short periods to treat non-gonococcal uretheritis may mask or delay the symptoms of incubating syphilis. All patients with sexually transmitted uretheritis or cervicitis should have a serologic test for syphilis and appropriate cultures for gonorrhea 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 Azithromycin may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

Acute otitis media caused by *Haemophilus influenzae, Moraxella catarrhalis* or *Streptococcus pneumoniae.*

Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae*. *Mycoplasma pneumoniae*, or *Streptococcus pneumonia* in patients appropriate for oral therapy.

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

Patients with cystic fibrosis, Patients with nosocomially acquired infections, Patients with known or suspected bacteremia, Patients requiring hospitalization, or patients with significant underlying health problems that may compromise their ability to respond to their illness, including immunodeficiency or functional asplenia

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to Azithromycin. Therapy with Azithromycin 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

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported rarely in patients on Azithromycin therapy. Although rare, fatalities have been reported. 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 may 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 due to Chlamydia pneumonia, Haemophilus influenzae. Mycoplasma pneumonia. or Streptococcus pneumonia in patients appropriate for oral therapy Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following patients with cystic fibrosis, 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 asplenial.

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 sub- sequent 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 (adults and children) who discontinued Azithromycin therapy because of treatment-related side effects were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain. Potentially serious side effects of angioedema and cholestatic jaundice were reported rarely.

Clinical

Adults Multiple-dose regimen

Overall the most common side effects in adult patients receiving a 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 in patients on the multiple-dose regimen of Azithromycin with a frequency greater than 1%. Side effects that 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.

Children
Multiple-dose regimens the types of side effects in children were comparable to those seen in adults, with different incidence rates for the two dosage regimens recommended in children

Acute Otitis Media
For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5, the most frequent side effects attributed to treatment were diarrhea loose stools (2%), abdominal pain (2%), vomiting (1%), and nausea (1%).

Community-Acquired Pneumonia
For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5, the most frequent side effects attributed to treatment were diarrhea noose stools (5.8%), abdominal pain, vomiting, and nausea (1.9% each), and rash (1.6%). Pharyngitis/tonsillitis: For the recommended dosage regimen of 12 mg/kg on Days 1-5, the most frequent side effects attributed to treatment were diarrhea loose stools (6%), vomiting (5%), abdominal pain (3%), nausea (2%), and headache (1%).

With either treatment regimen, no other side effects occurred in children treated with Azithromycin with a frequency greater than 1 %. Side effects that occurred with a frequency of 1% or less included the following:

Cardiovascular: Chest pain.

Gastrointestinal: Dyspepsia, constipation, anorexia, flatulence, and gastritis.

Nervous System: Headache (otitis media dosage), hyperkinesia, dizziness, agitation, nervousness, insomnia.

General: Fever, fatigue, malaise.

Allergic: Rash.

Skin and Appendages: Pruritus, urticaria

Special Senses: Conjunctivitis.

Post-Marketing Experience
Adverse events reported with Azithromycin during the post marketing period in adult and/or pediatric patients for which a causal relationship may not be established include:

Allergic: Arthralgia, edema, urticaria.

Cardiovascular: Arrhythmias including ventricular tachycardia.

Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting /diarrhea rarely resulting in dehydration.

General: Asthenia, paraesthesia.

Genitourinary: Interstitial nephritis and acute renal failure

liver/Biliary: Abnormal liver function including hepatitis and cholestatic jaundice.

Nervous System: Convulsions

Skin/Appendages: Rarely serious skin reactions including erythema multiforme, Stevens Johnson Syndrome, and toxic epidermal necrolysis.

Special Senses: Hearing disturbances including hearing loss, deafness, and/or tinnitus, rare reports of taste disturbances

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 antiarrythmics of classes IA and III; antipsychotic agents; antidepressants; and fluoroquinolones;
- with electrolyte disturbance, particularly in cases of Hypokalaemia and hypomagnesemia;
- 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

There are no adequate and well-controlled studies in pregnant women. Azithromycin should be used during pregnancy only if clearly needed.

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 influenza* 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
Pharmacokinetics parameters in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 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.

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

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/TONSILITIS
(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.

Weight		**200 mg/5 ml**	**Total ml per Treatment Course**
Kg	***lbs***	***Day 1-5***	
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.

Presentation
Bottle contains powder for preparing 22.5 ml suspension