ZEVLEN®

Azithromycin Tablets and Oral Suspension

DESCRIPTION

ZEVLEN® (azithromycin tablets and azithromycin for oral suspension) contains the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration.

ZEVLEN® is supplied for oral administration as film coated, round tablets containing azithromycin dihydrate equivalent to 250 mg azithromycin and the following inactive ingredients: dibasic calcium phosphate, pregelatinized starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, and iron oxide (yellow, red and black).

ZEVLEN® for oral suspension is supplied in bottles containing azithromycin dihydrate powder equivalent to 600 mg or 900 mg azithromycin per bottle and the following inactive ingredients: sucrose, sodium phosphate tribasic , hydroxypropyl cellulose, xanthan gum , saccharin sodium, banana, cherry and vanilla flavors. After reconstitution, each 5 ml of suspension contains 200 mg of azithromycin.

INDICATIONS AND USAGE

Azithromycin is indicated for the treatment of patients with mild to moderate infections (pneumonia: see WARNINGS) caused by susceptible strains of the designated microorganisms in the specific conditions listed below. **As recommended dosages, durations of therapy, and applicable patient populations vary among these infections, please see DOSAGE AND ADMINISTRATION for specific dosing recommendations.**

Adults:

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

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

NOTE: 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 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.

Urethritis and cervicitis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

Genital ulcer disease in men due to *Haemophilus ducreyi* (chancroid). Due to the small number 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 of time to treat non-gonococcal urethritis may mask or delay the symptoms of incubating syphilis. All patients with sexually-transmitted urethritis 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.

Children: (see **Pediatric Use**) (for specific dosage recommendation, see **DOSAGE AND ADMINISTRATION**).

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 pneumoniae* in patients appropriate for oral therapy.

NOTE: azithromycin should not be used in pediatric 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, 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.

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 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. (See **CONTRAINDICATIONS**). 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 pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, or Streptococcus pneumoniae* 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 asplenia).

Pseudomembranous colitis has been reported with nearly all antibacterial agents and many 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.

PRECAUTIONS

General: because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. There are no data regarding azithromycin usage in patients with renal impairment; thus, caution should be exercised when prescribing azithromycin in these patients.

The following adverse events have not been reported in clinical trials with azythromycin, an azalide; however, they have been reported with macrolide products: ventricular arrhythmias, including ventricular tachycardia and *torsade de pointes*, in individuals with prolonged QT intervals.

There has been a spontaneous report from the post-marketing experience of a patient with previous history of arrhythmias who experienced *torsade de pointes* and subsequent myocardial infarction following a course of azithromycin therapy.

Information for Patients: azithromycin tablets and oral suspension can be taken with or without food (PDR® 2005).

Patients should also be cautioned not to take aluminum- 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: aluminum and magnesium- containing antacids reduce the peak serum levels (rate) but not the AUC (extent) of azithromycin absorption.

Administration of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin absorption.

Azithromycin did not affect the plasma levels or pharmacokinetics of theophylline administered as a single intravenous dose. The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline administered in multiple doses resulting in therapeutic steady-state levels of theophylline is not known. However, concurrent use of macrolides and theophylline has been associated with increases in the serum concentrations of theophylline. Therefore, until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving azithromycin and theophylline concomitantly.

Azithromycin did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

The following drug interactions have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products. Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised:

-Digoxin: elevated digoxin levels.

-Ergotamine or dihydroergotamine: acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

-Triazolam: decreases the clearance of triazolam and thus may increase the pharmacologic effect of triazolam.

-Drugs metabolized by the cytochrome P450 system: elevations of serum carbamazepine, cyclosporine, hexobarbital, and phenytoin levels.

Laboratory Test Interactions: there are no reported laboratory test interactions.

Pregnancy: category B. 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: (see INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION).

Acute Otitis Media (dosage regimen: 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5 or 10 mg/Kg once daily for three days): safety and effectiveness in the treatment of children with otitis media under 6 months of age have not been established.

Community-Acquired Pneumonia (dosage regimen:10 mg/kg on Day1 followed by 5 mg/kg on Days 2-5): safety and effectiveness in the treatment of children with community-acquired pneumonia under 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 effectivness for pneumonia due to *Haemophilus influenzae* and *Streptococcus pneumoniae* were not documented bacteriologically in pediatric clinical trials 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 once daily for 5 days): 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) 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.

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. Approximately 0.7% of the patients (adults and children) from the multiple-dose clinical trials discontinued azithromycin therapy because of treatment-related side effects. Most of the side effects leading to discontinuation 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.

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 azithromycin with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%), and vaginitis (1%).

Single 2-gram dose regimen: overall, the most common side effects in patients receiving a single 2-gram dose of azithromycin were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%), and dizziness (1%). The majority of these complaints were mild in nature.

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/loose 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, flatuence, 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, angiodema.

Cardiovascular: arrhythmias including ventricular tachycardia.

Gastrointestinal: anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis and rare reports of tongue discoloration.

General: asthenia, paresthesia and anaphylaxis (rarely fatal).

Genitourinary: interstitial nephritis and acute renal failure, oral candidiasis, vaginitis.

Hematopoietic: thrombocytopenia.

Liver/Biliary: abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, some of which have resulted in death.

Nervous System: convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, and agitation.

Psychiatric: aggressive reaction and anxiety.

Skin/Appendages: pruritus, 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 perversion.

Laboratory Abnormalities:

Adults:

Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows: with an incidence of 1-2%: elevated serum creatine phosphokinase, potassium, ALT (SGPT), GGT, and AST (SGOT); with an incidence of less than 1%: leukopenia, neutropenia, decreased platelet count, elevated serum alkaline phosphatase, bilirubin, BUN, creatinine, blood glucose, LDH, and 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 1 because of a renal function abnormality.

Children:

Significant abnormalities (irrespective of drug relationship) occurring during clinical trials were all reported at a frequency of less than 1%, but were similar in type to the adult pattern. In multiple-dose clinical trials involving almost 3300 pediatric patients, no patients discontinued therapy because of treatment-related laboratory abnormalities.

DOSAGE AND ADMINISTRATION

Adults:

The recommended dose of azithromycin for the treatment of mild to moderate acute bacterial exacerbations of chronic obstructive pulmonary disease, community-acquired pneumonia of mild severity, 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.

Azithromycin tablets can be taken with or without food.

The recommended dose of azithromycin for the treatment of genital ulcer disease due to *Haemophilus ducreyi* (chancroid), non-gonococcal urethritis and cervicitis due to C. *trachomatis* is a single 1 gram (1000 mg) dose.

The recommended dose of azithromycin for the treatment of urethritis and cervicitis due to *Neisseria gonorrhoeae* is a single 2 gram (2000mg) dose.

Children:

Acute Otitis Media and Community-Acquired Pneumonia: the recommended dose of azithromycin for oral suspension for the treatment of children with acute otitis media and community-acquired pneumonia is 10 mg/kg as a single 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). (See chart below.)

Azithromycin for oral suspension can be taken with or without food.

The prior ingestion of food may ameliorate any gastrointestinal side effects caused by the administration of azithromycin.

PEDIATRIC DOSAGE GUIDELINES FOR OTITIS MEDIA AND COMMUNITY-ACQUIRED PNEUMONIA
(Age 6 months and above, see Pediatric Use)
Based on Body Weight
Dosing Calculated on 10 mg/kg on Day 1 dose, followed by 5 mg/kg on Days 2 to 5.

Weight		100mg/5 ml Suspension		200mg/5 ml Suspension		Total ml per Treatment Course
Kg	lbs	Day 1	Days 2-5	Day 1	Days 2-5	
10	22	5 ml (1 tsp)	2.5 ml(1/2 tsp)			15 ml
20	44			5 ml (1 tsp)	2.5 ml (1/2 tsp)	15 ml
30	66			7.5 ml (1 1/2 tsp)	3.75 ml (3/4 tsp)	22.5 ml
40	88			10 ml (2tsp)	5ml (1tsp)	30 ml

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). (See chart below).

Azithromycin for oral suspension can be taken with or without food.

The prior ingestion of food may ameliorate any gastrointestinal side effects caused by the administration of azithromycin.

PEDIATRIC DOSAGE GUIDELINES FOR PHARYNGITIS / TONSILLITIS
(Age 2 years and above, see pediatric Use)
Based on Body Weight
Dosing calculated on 12mg/Kg once daily days 1 to 5.

Weight		200mg/5 ml Suspension	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

Constituting instructions for Azithromycin Oral suspension 600 mg and 900 mg bottles. The table below indicates the volume of water to be used for constitution:

Amount of water to be added	Total volume after constitution (azithromycin content)	Azithromycin concentration after constitution
9 ml (600 mg)	15 ml (600 mg)	200 mg / 5 ml
12 ml (900 mg)	22.5 ml (900 mg)	200 mg / 5 ml

STORAGE CONDITIONS

Tablets: store in a dry place below 30°C, protected from light. Do not refrigerate.

Suspension: *prior to mixing*: store in a dry place below 30°C, protected from light. Do not refrigerate.

After mixing: store below 30°C. Keep tightly closed.

Discard after full dosing is completed. Discard any unused portion after 5 days.

PRESENTATION

ZEVLEN® tablets 250 mg is supplied in blister packs of 6's

ZEVLEN® Suspension 200 mg / 5 ml and 300 mg / 7.5 ml are supplied in bottles of 15 ml and 22.5 ml (total volume after reconstitution) equivalent to 600 mg and 900 mg / bottle respectively.

Do not use after expiry date.

keep medicaments out of reach of children.

This is a medicament

-A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

-Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

-The doctor and the pharmacist are experts in medicine, its benefits and risks.

-Do not by yourself interrupt the period of treatment prescribed.

-Do not repeat the same prescription without consulting your doctor.

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