

ZIOMYCIN®

Azithromycin Tablets 250 mg

Azithromycin Tablets 500 mg

Composition

Each film coated tablet contains;

Azithromycin dihydrate 262.05 mg equivalent to Azithromycin USP 250 mg

Azithromycin dihydrate 524.10 mg equivalent to Azithromycin USP 500 mg

Excipients: Microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulphate, povidone, isopropyl alcohol, purified talc, magnesium stearate, opadry yellow 04B520005 and purified water.

PRODUCT DESCRIPTION

Yellow colored, capsule shaped film-coated tablets with engraved “A250/A500” on one side and plain on other side.

PHARMACEUTICAL FORM: Film coated tablets

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties:

Pharmacotherapeutic group: Macrolides, ATC code J01FA

Mode of action

Azithromycin is the first of a subclass of macrolide antibiotics, known as azalides, and is chemically different from erythromycin. Chemically it is derived by insertion of a nitrogen atom into the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy- 9a-aza-9a- methyl-9a-homoerythromycin A. The molecular weight is 749.0.

Azithromycin binds to the 23S rRNA of the 50S ribosomal subunit. It blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

Cardiac electrophysiology

Co-administration of azithromycin increased the QTc interval in a dose- and concentration-dependent manner.

Mechanism of resistance

The two most frequently encountered mechanisms of resistance to macrolides, including azithromycin, are target modification (most often by methylation of 23S rRNA) and active efflux. The occurrence of these resistance mechanisms varies from species to species and, within a species, the frequency of resistance varies by geographical location.

The most important ribosomal modification that determines reduced binding of macrolides is post-transcriptional (N6) -dimethylation of adenine at nucleotide A2058 (Escherichia coli numbering system) of the 23S rRNA by methylases encoded by erm (erythromycin ribosome methylase) genes. Ribosomal modifications often determine cross-resistance (MLSB phenotype) to other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin), and the streptogramins B (which include, for example, the quinupristin component of quinupristin/dalfopristin). Different *erm* genes are present in

different bacterial species, in particular streptococci and staphylococci. Susceptibility to macrolides can also be affected by less frequently encountered mutational changes in nucleotides A2058 and A2059, and at some other positions of 23S rRNA, or in the large subunit ribosomal proteins L4 and L22.

Efflux pumps occur in a number of species, including gram-negatives, such as *Haemophilus influenzae* (where they may determine intrinsically higher minimal inhibitory concentrations [MICs]) and staphylococci. In streptococci and enterococci, an efflux pump that recognizes 14- and 15-membered macrolides (which include, respectively, erythromycin and azithromycin) is encoded by *mef* (A) genes.

Antibacterial spectrum:

The prevalence of acquired resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive isolates. As discussed above, some ribosomal modifications determine cross-resistance with other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin), and the streptogramin B (which include, for example, the quinupristin component of quinupristin/dalfopristin). A decrease in macrolide susceptibility over time has been noted in particular in *Streptococcus pneumoniae* and *Staphylococcus aureus*, and has also been observed in viridans streptococci and *Streptococcus agalactiae*.

Organisms that are commonly susceptible to azithromycin include:

Aerobic and facultative gram-positive bacteria (erythromycin-susceptible isolates): *S. aureus*, *Streptococcus agalactiae*,* *S. pneumoniae*,* *Streptococcus pyogenes*,* other β -hemolytic streptococci (Groups C, F, G) and viridans streptococci. Macrolide-resistant isolates are encountered relatively frequently among aerobic and facultative gram-positive bacteria, in particular among methicillin-resistant *S. aureus* (MRSA) and penicillin-resistant *S. pneumoniae* (PRSP).

Aerobic and facultative gram-negative bacteria: *Bordetella pertussis*, *Haemophilus ducreyi*,* *Haemophilus influenzae*,* *Haemophilus parainfluenzae*,* *Legionella pneumophila*, *Moraxella catarrhalis*,* and *Neisseria gonorrhoeae*.* *Pseudomonas* spp. and most *Enterobacteriaceae* are inherently resistant to azithromycin, although azithromycin has been used to treat *Salmonella enterica* infections.

Anaerobes: *Clostridium perfringens*, *Peptostreptococcus* spp. and *Prevotella bivia*.

Other bacterial species: *Borrelia burgdorferi*, *Chlamydia trachomatis*, *Chlamydophila pneumoniae*,* *Mycoplasma pneumoniae*,* *Treponema pallidum*, and *Ureaplasma urealyticum*.

Opportunistic pathogens associated with HIV infection: Eukaryotic microorganisms *Pneumocystis jirovecii* and *Toxoplasma gondii*.

* The efficacy of azithromycin against the indicated species has been demonstrated

Pharmacokinetic properties:

Absorption

Following oral administration in humans, azithromycin is widely distributed throughout the body; bioavailability is approximately 37%. The time taken to peak plasma levels is 2 to 3 hours.

Distribution

It is shown markedly higher azithromycin levels in tissues than in plasma (up to 50 times the maximum observed concentration in plasma), indicating that the drug is heavily tissue bound. Concentrations in target tissues, such as lung, tonsil and prostate, exceed the MIC₉₀ for likely pathogens after a single dose of 500 mg.

Elimination

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. Approximately 12% of an intravenously administered dose is excreted in the urine over 3 days as the parent drug, the majority in the first 24 hours. Biliary excretion of azithromycin is a major route of elimination for unchanged drug following oral administration. Very high concentrations of unchanged drug have been found in human bile, together with 10 metabolites, formed by N- and O- demethylation, hydroxylation of the desosamine and aglycone rings, and cleavage of the cladinose conjugate. Comparison of HPLC and microbiological assays in tissues suggests that metabolites play no part in the microbiological activity of azithromycin.

Pharmacokinetics in special patient groupsElderly

In elderly (>65 years), slightly higher AUC values were seen after a 5-day regimen than in young volunteers (<40 years), but these are not considered clinically significant, and hence no dose adjustment is recommended.

Renal Impairment

The pharmacokinetics of azithromycin in subjects with mild to moderate renal impairment (GFR 10 - 80 ml/min) were not affected following a single 1 gram dose of immediate-release azithromycin. Statistically significant differences in AUC₀₋₁₂₀ (8.8 µg.h/ml vs. 11.7 µg.h /ml), C_{max} (1.0 µg/ml vs. 1.6 µg/ml) and CL_r (2.3 ml/min/kg vs. 0.2 ml/min/kg) were observed between the group with severe renal impairment (GFR <10 ml/min) and the group with normal renal function.

Hepatic Impairment

In patients with mild (Class A) to moderate (Class B) hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. In these patients, urinary clearance of azithromycin appears to increase, perhaps to compensate for reduced hepatic clearance.

INDICATIONS

Azithromycin is indicated for infections caused by susceptible organisms; in lower respiratory tract infections including bronchitis and pneumonia, in skin and soft tissue infections, in acute otitis media and in upper respiratory tract infections including sinusitis and pharyngitis/ tonsillitis. (Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. Azithromycin is generally effective in the eradication of streptococci from the oropharynx, however, data establishing the efficacy of azithromycin and the subsequent prevention of rheumatic fever are not available at present.)

In sexually transmitted diseases in men and women, azithromycin is indicated in the treatment of uncomplicated genital infections due to *Chlamydia trachomatis*. It is also indicated in the

treatment of chancroid due to *Haemophilus ducreyi*; and uncomplicated genital infection due to non-multiresistant *Neisseria gonorrhoea*; concurrent infection with *Treponema pallidum* should be excluded.

DOSAGE & ADMINISTRATION

- Azithromycin tablets can be taken with or without food.
- Oral azithromycin should be administered as a single daily dose. The period of dosing with regard to infection is given below.

Adults

- For the treatment of sexually transmitted diseases caused by *Chlamydia trachomatis* and *Haemophilus ducreyi* or susceptible *Neisseria gonorrhoea*, the dose is 1000 mg as a single oral dose. For patients who are allergic to penicillin and/or cephalosporins, prescribers should consult local treatment guidelines.
- For patients who are allergic to penicillin and/or cephalosporins, prescribers should consult local treatment guidelines.
- For all other indications in which the oral formulation is administered, the total dosage of 1500 mg should be given as 500 mg daily for 3 days. As an alternative, the same total dose can be given over 5 days with 500 mg given on Day 1, then 250 mg daily on Days 2 to 5.

Children

- The maximum recommended total dose for any treatment is 1500 mg for children.
- In general, the total dose in children is 30 mg/kg. Treatment for pediatric streptococcal pharyngitis should be dosed at a different regimen (see below).
- The total dose of 30 mg/kg should be given as a single daily dose of 10 mg/kg daily for 3 days, or given over 5 days with a single daily dose of 10 mg/kg on Day 1, then 5 mg/kg on Days 2-5.
- As an alternative to the above dosing, treatment for children with acute otitis media can be given as a single dose of 30 mg/kg.
- For pediatric streptococcal pharyngitis, azithromycin given as a single dose of 10 mg/kg or 20 mg/kg for 3 days has been shown to be effective; however, a daily dose of 500 mg must not be exceeded.
- Penicillin is the usual drug of choice for the treatment of *Streptococcus pyogenes* pharyngitis, including prophylaxis of rheumatic fever.
- Azithromycin tablets should only be administered to children weighing more than 45 kg.

Elderly

- The same dosage as in adult patients is used in the elderly. Elderly patients may be more susceptible to the development of torsades de pointes arrhythmia than younger patients.

Renal Impairment

- No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10- 80 ml/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR <10 ml/min).

Hepatic Impairment

- The same dosage as in patients with normal hepatic function may be used in patients with mild to moderate hepatic impairment.

ROUTE OF ADMINISTRATION

Oral

CONTRAINDICATIONS

The use of this product is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotics or to any excipients.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], ZIOMYCIN[®] should be discontinued immediately and appropriate treatment should be urgently initiated.

Prolongation of the QT interval

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including azithromycin (see section 4.8). Prescribers should consider the risk of QT prolongation, which can be fatal, when weighing the risks and benefits of azithromycin for at-risk groups including:

- Patients with congenital or documented QT prolongation
- Patients currently receiving treatment with other active substances known to prolong QT interval, such as antiarrhythmics of Classes IA and III, antipsychotic agents, antidepressants, and fluoroquinolones
- Patients with electrolyte disturbance, particularly in cases of hypokalemia and hypomagnesemia
- Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency
- Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval

Infantile hypertrophic pyloric stenosis (IHPS) has been reported following the use of azithromycin in infants (treatment up to 42 days of life). Parents and caregivers should be informed to contact their physician if vomiting and/ or irritability with feeding occurs.

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.

In patients receiving ergot derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be coadministered.

As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms, including fungi is recommended.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of

antibacterial agents.

In patients with severe renal impairment (GFR <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed.

Effects on Ability to Drive and Use Machines

No data are available regarding the influence of azithromycin on a patient's ability to drive or operate machinery. However, the possibility of undesirable effects like dizziness and convulsions should be taken into account when performing these activities. Visual impairment and vision blurred may have an effect on a patient's ability to drive or operate machinery.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Antacids:

No effect on overall bioavailability was seen although peak serum concentrations were reduced by approximately 25%. In patients receiving both oral azithromycin and antacids, the drugs should not be taken simultaneously.

Cetirizine:

Coadministration of a 5-day regimen of azithromycin with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Didanosine:

Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Digoxin:

Some of the macrolide antibiotics have been reported to impair the microbial metabolism of digoxin in the gut in some patients. In patients receiving concomitant azithromycin, a related azalide antibiotic, and digoxin the possibility of raised digoxin levels should be borne in mind.

Zidovudine:

Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic drug interactions as seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

Ergot derivatives:

Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended.

Atorvastatin:

Co-administration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin.

Carbamazepine:

No significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

Cimetidine:

If a single dose of cimetidine given 2 hours before azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Coumarin-Type Oral Anticoagulants:

There have been reports of potentiated anticoagulation subsequent to co-administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Cyclosporin:

Caution should be exercised before considering concurrent administration of cyclosporin and azithromycin. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz:

Co-administration of a 600 mg single dose of azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

Fluconazole:

Co-administration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the co-administration of fluconazole, however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed.

Indinavir:

Co-administration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Methylprednisolone:

Azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Midazolam:

Co-administration of azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.

Nelfinavir:

Co-administration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment is required.

Rifabutin:

Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either drug.

Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established.

Sildenafil:

There was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and C_{max}, of sildenafil or its major circulating metabolite.

Terfenadine:

No evidence of an interaction between azithromycin and terfenadine is reported. There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however there was no specific evidence that such an interaction had occurred.

Theophylline:

There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers.

Triazolam:

Co-administration of azithromycin with 0.125 mg triazolam had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

Trimethoprim/sulfamethoxazole:

Co-administration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with azithromycin 1200 mg on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole.

Cisapride

Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsades de pointes.

Astemizole, alfentanil

Caution is advised in the co-administration of astemizole or alfentanil with Azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolide antibiotic erythromycin.

PREGNANCY AND LACTATION:***Pregnancy***

The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Azithromycin should be used during pregnancy only if clearly needed.

Breast-feeding

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

UNDESIRABLE EFFECTS

Azithromycin is well tolerated with a low incidence of side effects.

Blood and Lymphatic System Disorders: Transient episodes of mild neutropenia have occasionally been observed

Ear and Labyrinth Disorders: Hearing impairment (including hearing loss, deafness and/or tinnitus) has been reported in some patients receiving azithromycin. Many of these have been associated with prolonged use of high doses. In those cases where follow-up information was available, the majority of these events were reversible.

Gastrointestinal Disorders: Infantile hypertrophic pyloric stenosis, Nausea, vomiting, diarrhea, loose stools, abdominal discomfort (pain/cramps), and flatulence.

Hepatobiliary Disorders: Abnormal liver function.

Skin and Subcutaneous Tissue Disorders: Allergic reactions including rash and angioedema.

General Disorders and Administration Site Conditions: Local pain and inflammation at the site of infusion.

In post-marketing experience, the following additional undesirable effects have been reported:

Infections and Infestations: Moniliasis and vaginitis.

Blood and Lymphatic System Disorders: Thrombocytopenia. *Immune System Disorders:* Anaphylaxis (rarely fatal) *Metabolism and Nutrition Disorders:* Anorexia.

Psychiatric Disorders: Aggressive reaction, nervousness, agitation, and anxiety.

Nervous System Disorders: Dizziness, convulsions, headache, hyperactivity, hypoesthesia, paresthesia, somnolence, and syncope.

There have been rare reports of taste/smell perversion and/or loss.

Ear and Labyrinth Disorders: Deafness, tinnitus, hearing impaired, and vertigo.

Cardiac Disorders: Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongations and torsades de pointes

Vascular Disorders: Hypotension.

Gastrointestinal Disorders: Vomiting/diarrhea (rarely resulting in dehydration), dyspepsia, constipation, pseudomembranous colitis, pancreatitis, and rare reports of tongue discoloration.

Hepatobiliary Disorders: Hepatitis and cholestatic jaundice have been reported, as well as rare cases of hepatic necrosis and hepatic failure, which have resulted in death

Skin and Subcutaneous Tissue Disorders: Allergic reactions including pruritus, rash, photosensitivity, edema, urticaria, and angioedema.

Frequency not known: severe cutaneous adverse reactions (SCARs) including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalized exanthematous pustulosis (AGEP).

Musculoskeletal and Connective Tissue Disorders: Arthralgia.

Renal and Urinary Disorders: Interstitial nephritis and acute renal failure.

General Disorders and Administration Site Conditions: Asthenia, fatigue, and malaise.

OVERDOSAGE AND TREATMENT:

- Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea.

- In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

STORAGE CONDITION:

Store at temperature below 30°C. Keep all medicines out of reach of children.

DOSAGE FORM AND PACKING AVAILABLE:

For 250 mg: PVD/PVDC/Alu blister of 6 tablets, each blister is packed in a carton along with pack insert.

For 500 mg: PVD/PVDC/Alu blister of 3 tablets, each blister is packed in a carton along with pack insert.

NAME AND ADDRESS OF MANUFACTURER:

Kusum Healthcare Pvt. Ltd.

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PRODUCT REGISTRATION HOLDER:

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DATE OF REVISION OF PACKAGE INSERT

March 2021