130x190 mm

Didanosine: Coadministration of daily doses of 1200mg azithromycin with didanosine in 6 subjects did not appear to affect the pharmacokinetics of didanosine as compared with the placebo.
Rifabutin: Coadministration 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 .

Pregnancy and lactation:
Use In pregnancy: Animal reproduction studies have demonstrated that azithromycin crosses the placenta, but have revealed no evidence of harm to the foetus. There are no adequate and well controlled studies in pregnant woman. Since animal studies are not always predictive of human response. Azithral should be used during pregnancy only if adequate alternatives are not available.
Use in lactation: No data on secretion of azithromycin in breast milk are available, so that Azithral should only be used in lactating women where adequate alternatives are not available.

Side effects
Azithral is well tolerated with a low incidence of side effects.
Blood and lymphatic system disorders
Rare
Thrombocytopenia
There have been occasional reports of periods of transient, mild neutropenia. However, a causal relationship with azithromycin treatment has not been confirmed.
Psychiatric disorders
Rare
Agressiveness, agitation, anxiety and nervousness
Nervous system disorders
Uncommon
Dizziness/vertigo, somnolence, headache, convulsions (which have also been found to be caused by other macrolides), taste perversions, syncope
Rare

Paraesthesia and asthenia
Insomnia and hyperactivity
Ear and labyrinth disorders
Rare
Macrolide antibiotics have been reported to have caused hearing damage. In some patients receiving azithromycin impaired hearing, deafness and ringing in the ears have been reported. Many of these cases relate to experimental studies in which azithromycin was used at large doses over prolonged periods. According to available follow-up reports, the majority of these problems however were reversible.
Cardiac disorders
Rare
Palpitations and arrythmias including ventricular tachycardia (as seen with macrolides) have been reported. There have been rare reports of OT prolongation and torsades de pointes.
Vascular disorders
Rare
Hypotension
Gastrointestinal disorders
Common
Nausea, vomiting, diarrhoea, abdominal discomfort (pain/cramps)
Uncommon
Loose stools, flatulence, digestive disorders, anorexia, dyspepsia
Rare
Constipation, discoloration of the tongue, pancreatitis
Pseudomembranous colitis has been reported
Infantile hypertrophic pyloric stenosis have been reported
Hepato-biliary disorders
Rare
Hepatitis and cholestatic jaundice have been reported, including abnormal liver function test values, as well as rare instances of hepatic necrosis and hepatic dysfunction, which in rare instances have resulted in death
Skin and subcutaneous tissue disorders
Uncommon
Allergic reactions including pruritus and rash
Rare
Allergic reactions including angioneurotic oedema, urticaria and photosensitivity; serious skin reactions such as erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis
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 generalised exanthematous pustulosis (AGEP).
Musculoskeletal, connective tissue and bone disorders
Uncommon
Arthralgia
Renal and urinary disorders
Rare
Interstitial nephritis and acute renal failure
Reproductive system and breast disorders
Uncommon
Vaginitis
General disorders
Rare
Anaphylaxis including oedema (leads in rare cases to death), candidiasis, fatigue, malaise
Symptoms and treatment of overdose:
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 protected from light at a temperature not exceeding 30°C
Shelf life: 36 months from the date of manufacture
Presentation:
For Unimed's Azithral-250mg :
1 blister of 6 tablets are packed in a printed mono carton along with a package insert, 10 printed mono cartons are packed in a printed carton.
1 blister of 6 tablets are packed in a printed mono carton along with a package insert, 5 printed mono cartons are packed in a printed carton.
For Unimed's Azithral-500mg :
1 strip of 3 tablets are packed in a mono carton along with a package insert, 5 mono cartons are packed in a printed carton.

SCOTT-EDIL Enhancing Life

Manufactured in India by :
Scott Edil Pharmacia Ltd.
Unit-II, Plot No. 21/22, EPIP,
Phase I, Jharmajri, Baddi,
Dist. Solan, HP-173 205.
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and Imported by:
UNIMED SDN. BHD.
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Bandar Sri Damansara 52200,
Kuala Lumpur.

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For Hospital or Medical Practitioner or Laboratory

UNIMED'S AZITHRAL

UNIMED'S AZITHRAL-250 (Azithromycin Tablets USP 250mg)
UNIMED'S AZITHRAL-500 (Azithromycin Tablets USP 500mg)

Description and composition:
UNIMED'S AZITHRAL-250
Round, biconvex, light yellow to yellow color film coated tablets plain on both sides.
Each film coated tablet contains:
Azithromycin (As dihydrate) USP
Eq. to Anhydrous Azithromycin 250 mg
Excipient q.s.
Colour: Approved colour used.

UNIMED'S AZITHRAL-500
Capsule shaped, biconvex light yellow to yellow colour film coated tablets plain on both sides.
Each film coated tablet contains:
Azithromycin (As dihydrate) USP
Eq. to Anhydrous Azithromycin 500 mg
Excipient q.s.
Colour: Approved colour used.

Pharmacodynamics:
Mode of action:
Azithral is a macrolide antibiotic belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoeyrthromycin A. The molecular weight is 749.0. The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50s sub-unit and inhibition of peptide translocation.

Mechanism of resistance:
Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic

Complete cross resistance exists among Streptococcus pneumoniae, betahaemolytic streptococcus of group A, Enterococcus faecalis and Staphylococcus aureus, including methicillin resistant S. aureus (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

Break points
Azithromycin susceptibility breakpoints for typical bacterial pathogens are:
NCCLS:
- Susceptible 2mg/L; resistant 8mg/l
- Haemophilus spp.; susceptible 4mg/l
- Streptococcus pneumoniae and Streptococcus pyogens: Susceptible 0.5mg/l; resistant 2mg/l

Susceptibility
The prevalence of acquired resistant 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.

130x190 mm

Table: Antibacterial spectrum of Azithromycin

Commonly susceptible species
Aerobic Gram-positive microorganisms
Staphylococcus aureus Methycillin-susceptible
Streptococcus pneumoniae Penicillin-susceptible
Streptococcus pyogenes **(Group A)**
Aerobic Gram-negative microorganisms
Haemophilus influenzae *Haemophilus parainfluenzae*
Legionella pneumophila
Moraxella catarrhalis
Pasteurella multocida
Anaerobic microorganisms
Clostridium perfringens
Fusobacterium spp.
Prevotella spp.
Porphyromonas spp.
Other microorganisms
Chlamydia trachomatic
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Streptococcus pneumoniae *Penicillin-intermediate* *Penicillin-resistant*
Inherently resistant organisms
Aerobic Gram-positive microorganisms
Enterococcus faecalis
Staphylococci **MRSA, MRSE** *
Anaerobic microorganisms
Bacteroides fragilis group

*Methycillin-resistant staphylococci have a very high prevalence of acquired resistance to macrolides and have been placed here because they are rarely susceptible to azithromycin.

Pharmacokinetics:
Absorption: Bioavailability after oral administration is approximately 37%. Peak plasma concentrations are attained 2-3 hours after taking the medicinal product.

Distribution: Orally administered azithromycin is widely distributed throughout the body. In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues.
Binding to serum proteins varies according to plasma concentration and ranges from 12% at 0.5 microgram/ml up to 52% at 0.05 microgram azithromycin/ml serum. The mean volume of distribution at steady state (VVss) has been calculated to be 31.1l/kg.

Elimination: The terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days.
Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following three days. Particularly high concentrations of unchanged azithromycin have been found in human bile. Also in bile, ten metabolites were detected, which were formed through N- and O-demethylation, hydroxylation of desosamine and aglycone rings and cleavage of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses has shown that the metabolites of azithromycin are not microbiologically active.
In animal tests, high concentrations of azithromycin have been found in phagocytes. It has also been established that during active phagocytosis higher concentrations of azithromycin are released from inactive phagocytes. In animal models this results in high concentrations of azithromycin being delivered to the site of infection.

Indication
Azithromycin is indicated for infections caused by susceptible organisms : lower respiratory tract infections including bronchitis and pneumonia – skin and soft tissue infections – acute otitis media – 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.

Recommended dose:
Azithral should be given as a single dose. In common with many other antibiotics.
Azithral tablets should be taken at least 1 hour before or 2 hours after food.
Azithral suspension can be taken with food.
Children over 45kg body weight and adults, including elderly patients: The total dose of azithromycin is 1500mg which should be given over three days (500mg once daily). In uncomplicated genital infections due to Chlamydia trachomatis, the dose 1000mg as a single oral dose.
Renal failure: No dose adjustment is necessary in patients with mild to moderate (GFR 10-80ml/min) or severe (GFR <10 ml/min) renal impairment.
Hepatic failure: Since azithromycin is metabolised in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease. No studies have been conducted regarding treatment of such patients with azithromycin.

Route of administration: Azithral is administered orally.

Contraindication:
Azithral is contra-indicated in patients with a known hypersensitivity to azithromycin or any other macrolide antibiotics. Because of the theoretical possibility of ergotism, Azithral and ergot derivatives should not be coadministered.

Warning and precaution:
As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions with Azithral have resulted in recurrent symptoms and acquired a longer period of observation and treatment. 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)], [UNIMED'S Azithral - 250/500] should be discontinued immediately and appropriate treatment should be urgently initiated.

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarisation.
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.
As with any antibiotic preparation, there is a possibility that superinfections could occur (e.g. fungal infections).
Streptococcal infections: Penicillin is usually the first choice for treatment of pharyngitis/tonsillitis due to Streptococcus pyogenes and also for prophylaxis of acute rheumatic fever. Azithromycin is in general effective against streptococcus in the oropharynx, but no data are available that demonstrate the efficacy of azithromycin in preventing acute rheumatic fever.
In patients with severe renal impairment (GFR < 10ml/min) a 33% increase in systemic exposure to azithromycin was observed.

Interaction with other medicaments
Antacids: In patients receiving Azithral and antacids, Unimed's Azithral should be taken at least 1 hour before or 2 after the antacid.
Carbamazepine: In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite.
Cimetidine: A single dose of cimetidine administered 2 hours before Unimed's Azithral had no effect on the pharmacokinetics of azithromycin.
Cyclosporin: In a pharmacokinetic study with healthy volunteers that were administered a 500mg/day oral dose of cyclosporin, the resulting cyclosporin Cmax and AUC0-5 were found to be significantly elevated (by 24% and 21% respectively), however no significant changes were seen in AUC0-.
Consequently caution should be exercised before considering coadministration of these two drugs. If coadministration is necessary, cyclosporin 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 Unimed's Azithral and digoxin the possibility of raised digoxin levels should be borne in mind, and digoxin levels monitored.
Ergot derivatives: Because of the theoretical possibility of ergotism, Unimed's Azithral and ergot derivatives should not be coadmininstered.
Methylprednisolone: In a pharmacokinetic interaction study in healthy volunteers, Unimed's Azithral had no significant effect on the pharmacokinetics of methylprednisolone.
Terfenadine: Because of the occurrence of serious dysrhythmias secondary to prolongation of the QTc interval in patients receiving other anti-infectives in conjunction with terfenadine, pharmacokinetic interaction studies have been performed. These studies have reported no evidence of an interaction between azithromycin and terfenadine. 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. As with other macrolides, Unimed's Azithral should be administered with caution in combination with terfenadine.
Theophylline: Theophylline levels may be increased in patients taking Unimed's Azithral.
Coumarin-Type Oral Anticoagulants: In a pharmacodynamic interaction study, Unimed's Azithral did not alter the anticoagulant effect of a single 15mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration 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.
Zidovudine: Single 1000mg doses and multiple 1200mg or 600mg doses of azithromycin did not affect 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.