



AZITHROMYCIN DIHYDRATE

AZIK®

250 mg Film-Coated Tablet
500 mg Film-Coated Tablet
Antibacterial (Macrolide)

Formulation:

Each film-coated tablet contains:

Azithromycin dihydrate equivalent to Azithromycin USP 250/500 mg

Pharmacokinetics:

Absorption

After oral administration the bioavailability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours (C_{max} after a single dose of 500 mg orally was approximately 0.4 mg/l).

Distribution

Kinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the active substance is heavily tissue bound (steady state distribution volume of approximately 31 l/kg). Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC_{50} for likely pathogens after a single dose of 500 mg. In experimental *in vitro* and *in vivo* studies azithromycin accumulates in the phagocytes, freeing is stimulated by active phagocytosis. In animal studies this process appeared to contribute to the accumulation of azithromycin in the tissue. In serum the protein binding of azithromycin is variable and depending on the serum concentration varies from 50% in 0.05 mg/l to 12% in 0.5 mg/l.

Metabolism

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. The identified metabolites (formed by N- and O- demethylising, by hydroxylising of the desosamine and aglycone rings, and by the splitting of the cladinose conjugate) are microbiologically inactive.

Elimination

About 12% of an intravenously administered dose is excreted in the urine unchanged over a period of 3 days; the majority in the first 24 hours. Biliary excretion of azithromycin, predominantly in unchanged form, is a major route of elimination. After a 5 day treatment slightly higher (29%) AUC values were seen in the elderly volunteers (>65 years of age) compared to the younger volunteers (< 45 years of age).

Pharmacokinetics in special populations

Renal insufficiency

Following a single oral dose of azithromycin 1 g, mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renal function (GFR> 80 ml/min). In subjects with severe renal impairment, the mean C_{max} and AUC_{0-120} increased 61% and 33% respectively compared to normal.

Hepatic insufficiency

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

Elderly

The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred.

Infants, toddlers, children and adolescents

Pharmacokinetics have been studied in children aged 4 months – 15 years taking capsules, granules or suspension. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the C_{max} achieved is slightly lower than adults with 224 ug/l in children aged 0.6-5 years and after 3 days dosing and 383 ug/l in those aged 6-15 years. The $t_{1/2}$ of 36 h in the older children was within the expected 1/2 range for adults.

Indications:

Azithromycin tablets can be applied in situations where micro-organisms sensitive to azithromycin have caused:

- upper respiratory tract infections: sinusitis, pharyngitis, tonsillitis
- acute otitis media
- lower respiratory tract infections: acute bronchitis and mild to moderately severe community acquired pneumonia
- skin and soft tissue infections
- uncomplicated *Chlamydia trachomatis* urethritis and cervicitis

Considerations should be given to official guidance on the appropriate use of antibacterial agents.

Dosage and Administration:

Azithromycin tablets should be given as a single daily dose. The tablets may be taken with food.

Adults

In uncomplicated *Chlamydia trachomatis* urethritis and cervicitis the dosage is 1000 mg as a single oral dose. For all other indications the dose is 1500 mg, to be administered as 500 mg per day for three consecutive days. As an alternative the same total dose (1500 mg) can also be administered over a period of five days with 500 mg on the first day and 250 mg on the second to the fifth day.

Elderly patients

The same dose range as in younger patients may be used in the elderly.

Children

Azithromycin tablets should only be administered to children weighing more than 45 kg, normal adult dose should be used. For children under 45 kg, other pharmaceutical forms of Azithromycin, e.g. suspensions may be used.

In patients with renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min)

In patients with hepatic impairment

Dose adjustment is not necessary for patients with mild to moderately impaired liver function.

Adverse Effects:

The table below lists the adverse reactions identified through clinical experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. The frequency grouping is defined using the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency group, undesirable effects are listed in order of decreasing seriousness.

Adverse reactions possibly or probably related to azithromycin based on clinical trial experience and post-marketing surveillance.

Infections and infestations:

Uncommon: Candidiasis, oral candidiasis, vaginal infection

Blood and lymphatic system disorders:

Common: Lymphocyte count decreased, eosinophil count increased

Uncommon: Leukopenia, neutropenia

Rare: Thrombocytopenia, haemolytic anaemia

Immune system disorders:

Uncommon: Angioedema, hypersensitivity

Metabolism and nutrition disorders:

Common: Anorexia

Psychiatric disorders:

Uncommon: Nervousness

Rare: Agitation, depersonalization

Nervous system disorders:

Common: Dizziness, headache, paraesthesia, dysgeusia

Uncommon: Hypoaesthesia, somnolence, insomnia

Eye disorders:

Common: Visual impairment

Ear and labyrinth disorders:

Common: Deafness

Uncommon: Hearing impaired, tinnitus

Rare: Vertigo

Cardiac disorders:

Uncommon: Palpitations

Gastrointestinal disorders:

Very common: Diarrhoea, abdominal pain, nausea, flatulence

Common: Vomiting, dyspepsia

Uncommon: Gastritis, constipation

Hepatobiliary disorders:

Uncommon: Hepatitis, aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubine increased

Rare: Hepatic function abnormal

Skin and subcutaneous tissue disorders:

Common: Rash, pruritus

Uncommon: Steven-Johnson syndrome, photosensitivity reaction, urticaria

Musculoskeletal and connective tissue disorders:

Common: Arthralgia

Renal and urinary disorders:

Uncommon: Blood urea increased

Rare: Renal failure acute, nephritis interstitial

General disorders and administration site conditions:

Common: Fatigue

Uncommon: Chest pain, oedema, malaise, asthenia

Investigations:

Common: Blood bicarbonate decreased

Uncommon: Blood potassium abnormal

Overdose:

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of over dosage general symptomatic and general supportive measures are indicated as required.

Contraindications:

The use of azithromycin is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients.

Precautions:

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 azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment. Azithromycin tablets contain soya lecithin which might be a source of soya protein and should therefore not be taken in patients allergic to soya or peanut due to the risk of hypersensitivity reactions.

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. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with Azithromycin. Liver function tests/investigations should be performed in cases where signs and symptoms of liver dysfunction occur such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy.

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

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. Therefore caution is required when treating patients:

- With congenital or documented acquired QT prolongation.

- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA and III, cisapride and terfenadine.

- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia

- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea 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 diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antimicrobial agents. In case of CDAD anti-peristaltics are contraindicated.

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.

Safety and efficacy for the prevention or treatment of MAC in children have not been established.

The following should be considered before prescribing azithromycin:

Azithromycin tablets are not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.

In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other antibiotics. As for other macrolides, high resistance rates of *Streptococcus pneumoniae* (> 30 %) have been reported for azithromycin in some European countries. This should be taken into account when treating infections caused by *Streptococcus pneumoniae*.

Pharyngitis/ tonsillitis

Azithromycin is not the substance of first choice for the treatment of pharyngitis and tonsillitis caused by *Streptococcus pyogenes*. For this and for the prophylaxis of acute rheumatic fever penicillin is the treatment of first choice.

Sinusitis

Often azithromycin is not the substance of first choice for the treatment of sinusitis.

Acute otitis media

Often azithromycin is not the substance of first choice for the treatment of acute otitis media.

Skin and soft tissue infections

The main causative agent of soft tissue infections, *Staphylococcus aureus*, is frequently resistant to azithromycin. Therefore, susceptibility testing is considered a precondition for treatment of soft tissue infections with azithromycin.

Infected burn wounds

Azithromycin is not indicated for the treatment of infected burn wounds.

Sexually transmitted disease

In case of sexually transmitted diseases a concomitant infection by *T. palladium* should be excluded.

Neurological or psychiatric disorders

Azithromycin should be used with caution in patients with neurological or psychiatric disorders.

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

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

Interactions:

Antacids:

In a pharmacokinetic study investigating the effects of simultaneous administration of antacids and azithromycin, no effect on the total bio-availability was seen, although the peak serum concentrations were reduced by approximately 25%. Azithromycin must be taken at least 1 hour before or 2 hours after the antacids.

Fluconazole:

Coadministration 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 coadministration of fluconazole, however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed.

Nelfinavir:

Coadministration 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:

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.

Terfenadine:

Pharmacokinetic 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.

Cimetidine:

In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Effect of azithromycin on other medicinal products:

Ergotamine derivatives:

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

Digoxin:

It is known that some macrolide antibiotics limit the metabolism of digoxin (in the gut). In patients treated concomitantly with azithromycin and digoxin the possibility of increased digoxin levels should be borne in mind and digoxin levels monitored.

Coumarin-Type Oral Anticoagulants:

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15-mg 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.

Cyclosporin:

In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting cyclosporin C_{max} and AUC_{0-6} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Theophylline:

There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers. As interactions of other macrolides with theophylline have been reported, alertness to signs that indicate a rise in theophylline levels is advised.

Trimethoprim/sulfamethoxazole:

Coadministration 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. Azithromycin serum concentrations were similar to those seen in other studies.

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.

Astemizole, alfentanil:

There are no known data on interactions with astemizole or alfentanil. Caution is advised in the co-administration of these medicines with azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolid antibiotic erythromycin.

Atorvastatin:

Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay).

Carbamazepine: In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

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.

Cetirizine:

In healthy volunteers, 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.

Didanosins (Dideoxyinosine):

Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Efavirenz:

Coadministration 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.

Indinavir:

Coadministration 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: In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Midazolam:

In healthy volunteers, 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.

Sildenafil:

In normal healthy male volunteers, 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.

Triazolam:

In 14 healthy volunteers, co administration of azithromycin 500 mg on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

Storage Condition: Store at temperatures not exceeding 30°C.

Caution: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

“For suspected adverse drug reaction, report to the FDA: www.fda.gov/ph”

Please seek medical attention immediately at the first sign of any adverse drug reaction shall appear.

Availability:

250 mg: Clear PVC/PVDC- Alu Blister Pack of 10’s (Box of 50’s).

500 mg: Clear PVC/PVDC- Alu Blister Pack of 10’s (Box of 50’s)

Clear PVC/PVDC- Alu Blister Pack of 3’s (Box of 3’s)

Manufactured by:

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