AZIC 250
Azithromycin Tablets USP 250 mg

COMPOSITION:
Each Film Coated Tablet Contains:
Azithromycin Dihydrate USP
Eq. to Azithromycin (Anhydrous) 250 mg
Excipients q.s.
Colour: Titanium Dioxide BP

DESCRIPTION:
AZIC 250 (Azithromycin Tablets USP 250 mg) contains Azithromycin as an active.

PHARMACODYNAMICS:
Pharmacodynamic properties
Therapeutic class: Antibacterial for systemic use, macrolides; (**ATC code:** J01FA10).

Mechanism of Action:
Azithromycin is an azalide, a sub-class of the macrolide antibiotics. By binding to the 50S ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

Pharmacokinetic Properties
Absorption:
Bioavailability of azithromycin after oral administration is approximately 37%. Peak plasma concentrations are attained after 2-3 hours. The mean maximum concentration observed (C_{max}) after a single dose of 500 mg is approximately 0.4 µg/ml.
Distribution:
Orally administered azithromycin is widely distributed throughout the body.
Pharmacokinetic studies have demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (up to 50 times the maximum observed concentration in plasma) than those measured in plasma. This indicates that the agent strongly binds to tissues (steady-state distribution volume approx. 31 l/kg).
At the recommended dose no accumulation appears in the serum. Accumulation appears in tissues where levels are much higher than in serum. Three days after administration of 500 mg as a single dose or in partial doses concentrations of 1,3-4,8 µg/g, 0,6-2,3 µg/g, 2,0-2,8 µg/g and 0-0,3 µg/ml have been measured in resp. lung, prostate, tonsil and serum.
These concentrations are higher than the MIC90 of the most common pathogens.
In experimental in vitro and in vivo studies azithromycin accumulates in phagocytes.
Release is mediated by active phagocytosis. In animal models this process contributes to the accumulation of azithromycin in tissue.
Binding of azithromycin to serum proteins is variable and varies from 50% at 0,05 mg/l to 18% at 0,5 mg/l, depending on the serum concentration.
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 is excreted in unchanged form with the urine over a period of 3 days; the major proportion in the first 24 hours. Concentrations of up to 237 µg/ml azithromycin, 2 days after a 5-day course of treatment, have been found in human bile. Ten metabolites have been identified (formed by N and O demethylation, by hydroxylation of the desosamine and aglycone rings, and by splitting of the cladinose conjugate). Investigations suggest that the metabolites do not play a role in the microbiological activity of azithromycin.

THERAPEUTIC INDICATIONS:
AZIC 250 (Azithromycin Tablets USP 250 mg) is indicated in treatment of:
Azithromycin is indicated for the following bacterial infections induced by microorganisms susceptible to azithromycin
- Acute bacterial sinusitis (adequately diagnosed)
- Acute bacterial otitis media (adequately diagnosed)
- Pharyngitis, tonsillitis
- Acute exacerbation of chronic bronchitis (adequately diagnosed)
- Mild to moderately severe community acquired pneumonia
- Infections of the skin and soft tissues of mild to moderate severity e.g. folliculitis, cellulitis, erysipelas
- Uncomplicated Chlamydia trachomatis urethritis and cervicitis

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

POSOLOGY AND METHOD OF ADMINISTRATION:
Posology
Azithromycin should be given as a single daily dose. Duration of the treatment for the different infection diseases is given below.
Children and adolescents with a body weight above 45 kg, adults and the elderly
The total dose is 1500 mg, administered as 500 mg once daily for 3 days. Alternatively, the same total dose (1500 mg) can be administered in a period of 5 days, 500 mg on the first day and 250 mg on day 2 to 5.
In the case of uncomplicated Chlamydia trachomatis urethritis and cervicitis, the dose is 1000 mg as a single oral dose.
Children and adolescents with a body weight below 45 kg
Azithromycin tablets are not suitable for patients under 45 kg body weight. Other dosage forms are available for this group of patients.
Elderly patients
For elderly patients the same dose as for adults can be applied. Since elderly patients can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes.
Patients with 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).
Patients with hepatic impairment
Dose adjustment is not required for patients with mild to moderate hepatic dysfunction.
Method of administration
Azithromycin should be given as a single daily dose. The tablets can be taken with or without food. The tablets should be taken with ½ glass of water.

CONTRAINDICATION:
Hypersensitivity to the active substance, erythromycin, any macrolide, ketolide antibiotic, or to any of the excipient.

SPECIAL WARNING AND PRECAUTION FOR USE:
Hypersensitivity: As with erythromycin and other macrolides, rare serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalized exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.
If an allergic reaction occurs, the medicinal product 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.
Hepatic impairment: Since the 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. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.
In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/ investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.
Infantile hypertrophic pyloric stenosis
Following the use of azithromycin in neonates (treatment up to 42 days of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.
Ergot alkaloids and azithromycin
In patients receiving ergot derivatives, ergotism has been precipitated by co-administration 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.
Superinfections:
As with any antibiotic preparation, it is recommended to pay attention to signs of superinfection with nonsusceptible microorganisms like fungi. A superinfection may require an interruption of the azithromycin treatment and initiation of adequate measures.
Clostridium difficile associated diarrhoea (CDAD) has been reported with 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 antibacterial agents. In case of CDAD anti-peristaltics are contraindicated.
Renal impairment
In patients with severe renal impairment (GFR < 10 ml/min) a 33% increase in systemic exposure to azithromycin was observed.
Cardiovascular events
QT Prolongation
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, including azithromycin. Therefore, as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:
- With congenital or documented acquired QT prolongation.
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including azithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing azithromycin.
Myasthenia gravis
Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.
Paediatric population
Safety and efficacy for the prevention or treatment of Mycobacterium avium complex in children have not been established.
The following should be considered before prescribing azithromycin:
Azithromycin is not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.
The selection of azithromycin to treat an individual patient should take into account the appropriateness of using a macrolide antibacterial agent based on adequate diagnosis to ascertain the bacterial etiology of the infection in the approved indications and the prevalence of resistance to azithromycin or other macrolides.
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. pallidium should be excluded.
Neurological or psychiatric diseases:
Azithromycin should be used with caution in patients with neurological or psychiatric disorders.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:
Antacids:
In a pharmacokinetic study investigating the effects of simultaneous administration of antacids with azithromycin, no effect on overall bioavailability was seen, although peak serum levels were reduced by approximately 25%. In patients receiving both azithromycin and antacids, the medicinal products should not be taken simultaneously. Azithromycin must be taken at least 1 hour before or 2 hours after antacids.
Co-administration of azithromycin prolonged-release granules for oral suspension with a single 20 ml dose of comagaldrox (aluminium hydroxide and magnesium hydroxide) did not affect the rate and extent of azithromycin absorption.
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.
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 HIVpositive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.
Digoxin (P-gp substrates) and colchicine:
Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.
Zidovudine:
Single 1000 mg doses and multiple doses of 600 mg or 1200 mg 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.
Ergotamine derivatives: Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended.
Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.
Astemizole, alfentanil
There are no known data on interactions with astemizole or alfentanil. Caution is advised in the coadministration of these medicines with Azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolide 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). However, postmarketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.
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.
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.
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 postmarketing 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
Cmax and AUC0-5 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.
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.
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 halflife of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed.
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, coadministration 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: 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 medicinal product. 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: In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and Cmax of sildenafil or its major circulating metabolite.
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.
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.
Triazolam: In 14 healthy volunteers, coadministration 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.
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.

PREGNANCY, BREAST-FEEDING AND FERTILITY
Pregnancy
There are no adequate data from the use of azithromycin in pregnant women. In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed . The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore azithromycin should only be used during pregnancy if the benefit outweighs the risk.
Breastfeeding
Azithromycin has been reported to be secreted into human breast milk. The limited information available from published literature indicates azithromycin is present in human milk at an estimated maximum mean daily dose of 0.1 to 0.7 mg / kg / day. No serious side effects have been observed by azithromycin in breast-fed infants.
A decision should be taken whether breastfeeding is discontinued or that treatment with azithromycin is discontinued/initiated or not, taking into account the benefit of breastfeeding for the child and the benefit of treatment for the woman.
Fertility
In fertility studies conducted in rat, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

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

UNDESIRABLE EFFECTS:
The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency.

The frequency grouping is defined using the following convention: Common. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Adverse reactions possibly or probably related to azithromycin based on clinical trial experience and post marketing surveillance:

SYSTEM ORGAN CLASS	very common ≥ 1/10	common ≥ 1/100 to < 1/10
Metabolism and nutrition disorders		*Anorexia*
Nervous system disorders		*Headache* Dizziness Dysgeusia Paraesthesia
Eye disorders		Visual impairment
Ear and labyrinth disorders		Deafness
Gastrointestinal disorders	Diarrhoea Abdominal pain, Nausea, flatulence	*Vomiting*
Skin and subcutaneous tissue disorders		Pruritus Rash
Musculoskeletal and connective tissue disorders		Arthralgia

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

SHELF LIFE:
36 Months

PACKAGING:
6 Tablets are packed in Alu-PVC Blister & such 10 Blisters are packed in printed carton along with pack insert.

STORAGE CONDITION:
Stored at a temperature not exceeding 30°C. Protect from light and moisture.
Keep the medicine out of reach of children.

Product of :
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MANUFACTURED BY :
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