Front

Back

240 mm

120 mm

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only .

Azithromycin for Injection USP 500 mg

Ozitop

Injection **500 mg**

FOR I.V. INFUSION ONLY

Composition :
Each vial contains :
Azithromycin Dihydrate (Sterile) IP
Eq. to Anhydrous
Azithromycin 500mg

Powder for intravenous (IV) infusion only

THERAPEUTIC INDICATION

To reduce the development of drug-resistant bacteria and maintain the effectiveness of azithromycin and other antibacterial drugs, azithromycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Azithromycin for infusion BP is a macrolide antibacterial drug indicated for the treatment of patients with infections caused by susceptible strains of the microorganisms in the conditions as directed by the Physician.

Azithromycin for infusion BP should be followed by azithromycin by the oral route as required.

DOSAGE AND ADMINISTRATION

Posology

As directed by the Physician.

Method of administration: For IV infusion only. Once Azithromycin (azithromycin as powder for solution for infusion) is constituted and diluted is intended to be administered by intravenous infusion. Azithromycin for infusion BP should not be administered as a intravenous bolus or as an intramuscular injection. The concentration of the solution for infusion and the infusion rate of azithromycin as powder for solution for infusion should be 1 mg/ml for 3 hours or 2 mg/ml for 1 hour.

Preparation of the solution for intravenous administration: Prepare the initial solution of azithromycin Injection by adding 5 mL of Sterile Water for Injection to the 500 mg vial. Shake the vial until the entire drug is dissolved. Transfer the entire 5 mL of the above into either 500 ml/250 ml of the diluents.

For concentration of 1mg/ml, add 500 ml of the diluent to 5 ml of azithromycin solution.

For concentration of 2 mg/ml, add 250 ml of the diluent to 5 ml of the azithromycin solution.

	Azithromycin solution	Amount of diluent	Infusion period
1 mg/ ml	5 ml	500 ml	Over 3 hours
2 mg/ ml	5 ml	250 ml	Over 1 hour

The constituted solution can be diluted with: Normal saline (0.9% Sodium Chloride), Half of normal saline (0.45% Sodium Chloride), 5% Dextrose in water, Lactated Ringer's solution, 5% Dextrose in half of normal saline (0.45% Sodium Chloride) with 20 mEq KCl, 5% Dextrose in Lactated Ringer's solution, 5% Dextrose in one-third of normal saline (0.3% Sodium Chloride), 5% Dextrose in half of normal saline (0.45% Sodium Chloride).

It is recommended that a 500 mg dose of Azithromycin for infusion BP, diluted as above, be infused over a period of not less than 60 minutes or as mentioned above.

Parenteral drug products should be inspected visually for particulate matter prior to administration. If particulate matter is evident in constituted fluids, the drug solution should be discarded.

CONTRAINDICATIONS

Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic. Azithromycin is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin. Azithromycin should not be co-administered with ergot derivatives because of the theoretical possibility of ergotism.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity: As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalised 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 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.

Hepatotoxicity: 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.

Ergot derivatives: In patients receiving ergotamine derivatives, ergotism has been precipitated by co-administration 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 co-administrated.

Prolongation of the QT interval: 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 QT prolongation.

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

With electrolyte disturbance, particularly in case of hypokalaemia and hypomagnesaemia.

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

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

Clostridium difficile associated diarrhoea: *Clostridium difficile* associated diarrhoea (Pseudomembranous colitis - 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 antibiotics alters the normal flora of the colon allowing an overgrowth of *C. difficile*. Strains of *C. difficile* producing hypertoxin A and B 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. Therefore, CDAD must be considered in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Discontinuation of therapy with azithromycin and the administration of specific treatment for *C. difficile* should be considered.

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.

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

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

Infusion Site Reactions: Azithromycin for infusion BP should be constituted and diluted as directed and administered as an IV infusion over not less than 60 minutes. Local IV site reactions have been reported with the IV administration of azithromycin. The incidence and severity of these reactions were the same when 500 mg azithromycin was given over 1 hour (2 mg/mL as 250 mL infusion) or over 3 hours (1 mg/mL as 500 mL infusion). All volunteers who received infusate concentrations above 2.0 mg/mL experienced local IV site reactions and, therefore, higher concentrations should be avoided.

General: Azithromycin (azithromycin as powder for solution for infusion) should be constituted and diluted according to the instructions and should be administered as an intravenous infusion over at least 60 minutes. It should not be administered as an intravenous bolus or an intramuscular injection.

Patients should be cautioned not to take aluminum- and magnesium-containing antacids and azithromycin by the oral route simultaneously.

Safety and efficacy of azithromycin intravenous infusion for treatment of infections in children have not been established. Safety and efficacy for prevention or treatment of MAC in children have not been established.

Patients should be directed to discontinue azithromycin and contact a physician if any signs of an allergic reaction occur.

DRUG INTERACTION

Co-administration of nelfinavir at steady-state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted.

Azithromycin given by the oral route 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.

Drug interaction studies were performed with azithromycin and other drugs likely to be coadministered. When used in therapeutic doses, azithromycin had a modest effect on the pharmacokinetics of atorvastatin, carbamazepine, cetirizine, didanosine, efavirenz, fluconazole, indinavir, midazolam, rifabutin, sildenafil, theophylline (intravenous and oral), triazolam, trimethoprim/sulfamethoxazole or zidovudine. Co-administration with efavirenz or fluconazole had a modest effect on the pharmacokinetics of azithromycin. No dosage adjustment of either drug is recommended when azithromycin is coadministered with any of these agents.

Interactions with the drugs listed below 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 concentrations.

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

Terfenadine, cyclosporine, hexobarbital and phenytoin: elevated concentrations.

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

USE IN SPECIAL POPULATION

Pregnancy: Teratogenic Effects: Pregnancy Category B. However, there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Lactation: Azithromycin has been reported to be excreted in human breast milk in small amounts. Caution should be exercised when azithromycin is administered to a nursing woman.

Use in Children: Safety and effectiveness of azithromycin as powder for solution for infusion for the treatment of infections in children and adolescents has not been established.

Use in the Elderly: Pharmacokinetic studies with intravenous azithromycin have not been performed in older volunteers. Pharmacokinetics of azithromycin following oral administration in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5-day therapeutic regimen.

Use in Patients with Renal Impairment: No dose adjustment is recommended 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)

Use in Patients with Hepatic Impairment: Dose adjustment is not required for patients with mild-to-moderate hepatic dysfunction but the medicinal product should be used with caution in patients with significant hepatic diseases.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no evidence to suggest that azithromycin may have an effect on a patient's ability to drive or operate machinery.

UNDESIRABLE EFFECTS

Overall, the most common side effects associated with treatment in adult patients who received IV/PO azithromycin in studies of community-acquired pneumonia were related to the gastrointestinal system with diarrhea/loose stools (4.3%), nausea (3.9%), abdominal pain (2.7%), and vomiting (1.4%) being the most frequently reported. Approximately 12% of patients experienced a side effect related to the intravenous infusion; most common were pain at the injection site (6.5%) and local inflammation (3.1%).

The most common side effects associated with treatment in adult women who received IV/PO azithromycin in studies of pelvic inflammatory disease were related to the gastrointestinal system. Diarrhea (8.5%) and nausea (6.6%) were most commonly reported, followed by vaginitis (2.8%), abdominal pain (1.9%), anorexia (1.9%), rash and pruritus (1.9%). When azithromycin was coadministered with metronidazole in these studies, a higher proportion of women experienced side effects of nausea (10.3%), abdominal pain (3.7%), vomiting (2.8%), application site reaction, stomatitis, dizziness, or dyspnea (all at 1.9%).

No other side effects occurred in patients on the multiple doses IV/PO regimen of azithromycin in these studies with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

Gastrointestinal: dyspepsia, flatulence, mucositis, oral moniliasis, and gastritis.

Nervous System: headache, somnolence.

Allergic: bronchospasm.

Special Senses: taste perversion.

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 and angioedema.

Cardiovascular: Arrhythmias including ventricular tachycardia and hypotension. There have been rare reports of QT prolongation and torsades de pointes.

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

General: Asthenia, paresthesia, fatigue, malaise and anaphylaxis (rarely fatal).

Genitourinary: Interstitial nephritis and acute renal failure and 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, agitation and syncope.

Psychiatric: Aggressive reaction and anxiety.

Skin/Appendages: Pruritus, rarely serious skin reactions including erythema multiforme, Stevens - Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Special Senses: Hearing disturbances including hearing loss, deafness and/or tinnitus and reports of taste/smell perversion and/or loss.

Laboratory Abnormalities: Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:

- With an incidence of 4–6%, elevated ALT (SGPT), AST (SGOT), creatinine
- With an incidence of 1–3%, elevated LDH, bilirubin
- With an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, and elevated serum alkaline phosphatase.

When follow-up was provided, changes in laboratory tests appeared to be reversible.

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, general symptomatic treatment and supportive measures are indicated as required.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics Properties

Pharmacotherapeutic group: Antibacterials for systemic use, Macrolides.

Azithromycin is a broad-spectrum macrolide antibiotic with a long half-life and a high degree of tissue penetration. Macrolides stop bacterial growth by inhibiting protein synthesis and translation, treating bacterial infections.

Mechanism of action: Azithromycin 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-homoerythromycin 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.

Pharmacokinetic Properties

Absorption: In patients hospitalized with community-acquired pneumonia treated with a single daily intravenous infusion of 500 mg azithromycin, over one hour, in a solution with a concentration of 2 mg/ml, for 2 to 5 days, the mean Cmax ± D achieved was of 3.63 ± 1.60 µg/ml, while the trough levels concentration at 24 hours was 0.20 ± 0.15 µg/ml and the AUC24 of 9.60 ± 4.80 µg.h/ml. Mean Cmax, trough levels concentration at 24 hours and AUC24 values were of 1.14 ± 0.14 µg/ml, 0.18 ± 0.02 µg/ml and 8.03 ± 0.86 µg.h/ml, respectively, in normal volunteers receiving intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/ml, for 3 hours.

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. Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC90 for likely pathogen agents after a single dose of 500 mg. High azithromycin concentrations were detected in gynaecological tissue 96 hours after a single dose of 500 mg azithromycin.

Biotransformation/Elimination: The terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days.

In a multiple-dose study in 12 normal volunteers using a 500 mg (1 mg/ml) one-hour intravenous dosage regimen for five days, the amount of administered azithromycin dose excreted in urine in 24 hours was about 11% after the 1st dose and 14% after the 5th dose. These values are higher than the reported 6% as being excreted unchanged in urine after oral administration of azithromycin. 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 carried has shown that the metabolites do not contribute to azithromycin microbiological activity.

INCOMPATIBILITY

This medicinal product must not be mixed with other medicinal products except those mentioned in "Preparation of the solution for intravenous administration". Other intravenous substances, additives or other medications should not be added with azithromycin injection or infused simultaneously through the same intravenous line.

Concentrated solution after constitution (according to the instructions): azithromycin as powder for solution for infusion is chemically and physically stable during 24 hours, when stored below 25 °C.

Diluted solutions, prepared according to the instructions, are chemically and physically stable for 24 hours at or below 25°C, or for 72 hours if stored at 2-8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless the constitution/dilution has taken place in controlled and validated aseptic conditions.

Storage : Store in a cool, dry & dark plac

Keep out of reach of children.

PRESENTATION

Ozitop infusion is available in a vial & packed in mono carton with 5 ml Sterile Water for Injections IP.

Mfd. by : Protech Telelinks
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