4.75 inches

Suspension/Capsule/Injection/Tablet

Zithrocin

(A z i t h r o m y c i n)

زیتھروسن سسپنشن / کیپسول / انجکشن / ٹیبلٹ

(ازیتھرومائیسین)

COMPOSITION

ZITHROCIN Injection 500mg: Each vial contains:
Azithromycin (as dihydrate) powder for reconstitution.....500mg
(Innovator's specifications)
ZITHROCIN Capsule 250mg: Each capsule contains:
Azithromycin (as dihydrate).....250mg
(BP Specifications)
ZITHROCIN suspension 200mg/5ml: Each 5ml (after reconstitution) contains:
Azithromycin (as dihydrate).....200mg
(BP Specifications)
ZITHROCIN Tablet 250mg: Each film coated tablet contains:
Azithromycin dihydrate eq. to Azithromycin.....250mg
(USP Specifications)
ZITHROCIN Tablet 500mg: Each film coated tablet contains:
Azithromycin (as dihydrate) 500mg
(USP Specifications)

DESCRIPTION

Azithromycin is an azalide, derived from the macrolide class of antibiotics. Azithromycin helps to escape of many disorders associated with inflammation. When used in high concentrations, it has bactericidal effect,it demonstrates activity in vitro, against a wide range of Gram-positive and Gram-negative bacteria including Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes (Group A) and other Streptococcal species; Haemophilus influenzae and para- influenzae; Moraxella catarrhalis; anaerobes including Bacteroides fragilis; Escherichia coli; Bordetella pertussis; Bordetella para pertussis; Borrelia burgdorferi; Haemophilus ducreyi; Neisseria gonorrhoeae and Chlamydia trachomatis. Azithromycin also demonstrates in-vitro activity against Legionella pneumophila, Mycoplasma pneumoniae and hominis, Campylobacter spp, Toxoplasma Gondi and Treponema pallidum.

MECHANISM OF ACTION

Azithromycin usually is bacteriostatic, although the drug may be bactericidal in high concentrations against selected organisms. Bactericidal activity has been observed in vitro against Streptococcus pyogenes, S. pneumoniae, and Haemophilus influenzae. Azithromycin inhibits protein synthesis in susceptible organisms by penetrating the cell wall and binding to 50S ribosomal subunits, thereby inhibiting translocation of aminoacyl transfer-RNA from one side of the ribosome to the other and inhibiting polypeptide synthesis. The site of action of azithromycin appears to be the same as that of the macrolides (i.e., erythromycin, clarithromycin), clindamycin, lincomycin, and chloramphenicol. The antimicrobial activity of azithromycin is reduced at low pH.

INDICATIONS

Azithromycin is indicated for infections caused by susceptible organisms; in lower respiratory tract infections including bronchitis and pneumonia, in upper respiratory tract infections including otitis media, pharyngitis/tonsillitis and sinusitis, skin and soft tissue infections and acne, mild to moderate typhoid fever caused by multi-drug resistant strains.
In sexually transmitted diseases in men and women, azithromycin is indicated in the treatment of uncomplicated genital infections due to Chlamydia trachomatis.
Azithromycin is indicated as second line therapy for typhoid fever caused by s.typhi and s.paratyphi.
Intravenous injection is used for the treatment of community-Acquired Pneumonia and Pelvic Inflammatory Disease.

DOSAGE AND ADMINISTRATION

Azithromycin should be administered as single dose, and as common with many other antibiotics, should be taken at least 1 hour before or 2 hours after food.

✧ **Oral Dose**

➢ **Adults:**

For respiratory tract infections and skin and soft tissue infections the total dose is 1.5 g which should be given as 500 mg as a single dose daily for 3 days. Alternatively, an initial dose of 500 mg in the first day may be followed by 250 mg daily for further 4 days.
For sexually transmitted diseases caused by Chlamydia trachomatis the dose is 1 g given as a single dose. For typhoid fever, the dose is 500 mg to 1000 mg once daily for 5-7 days.

➢ **Use in children**

There is no information on children under six months of age. The dose in children is 10mg/kg as a single daily dose for 3 days. For typhoid fever therapy, should be given for 7 days.

Age (years)	Weight	Dosage (10ml/kg)
0.5-2	4.5-12	1.5-3ml (45-120mg)
2.5-4	14-16	6.5-4ml (140-160mg)
4.5-6	17-20..5	4.5-5ml (170-205 mg)
6.5-8	21.5-25	5-6.5mal (215-250 mg)
8.5-10	26.5-31	6.5-8ml (265-310mg)
10.5-12	33-40	8.5-10.5ml (330-400mg)
12.5-14	41-50.5	11-12.5ml (410-505mg)
14.5-16	52-62	13.5-15.5ml (520-620mg)
16.5-18	64-69	16-17ml (640-690 mg)

✧ **Intravenous Dose**

The recommended dose of Azithromycin (azithromycin as powder for solution for infusion) for the treatment of adult patients with community-acquired pneumonia due to the indicated susceptible microorganisms is of 500 mg administered as a single intravenous daily dose for at least two consecutive days. The intravenous therapy should be followed by the oral administration of azithromycin in a single daily dose of 500 mg up to 7 to 10 days of treatment. Transition to oral therapy should be carried out when indicated by the doctor and according to the clinical response.
The recommended dose of Azithromycin (azithromycin as powder for solution for infusion) for the treatment of adult patients with pelvic inflammatory disease (PID) due to the indicated susceptible microorganisms is of 500 mg administered as a single intravenous daily dose for one or two days. The intravenous therapy should be followed by the oral administration of azithromycin in a single daily dose of 250 mg up to 7 days of treatment. Transition to oral therapy should be carried out when indicated by the doctor and according to the clinical response.

➢ ***Use in the elderly***

No dose adjustment is required in elderly patients that require therapy with azithromycin.

➢ ***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.

➢ ***Use in children***

The efficacy and safety of azithromycin as powder for solution for infusion for the treatment of infections in children and adolescents has not been established.

✧ **Method of Administration**

Once Azithromycin (azithromycin as powder for solution for infusion) is reconstituted and diluted is intended to be administered by intravenous infusion. It should not be administered as an intravenous bolus or 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**

• **Reconstitution**

The initial solution of azithromycin is prepared by adding 4.8 ml of sterile water for injections to the 500 mg vial and shaking the vial until all the drug is dissolved. It is recommended that a standard 5 ml (non-automated) syringe be used to ensure that the exact volume of 4.8 ml of sterile water for injections is dispensed. Each ml of reconstituted solution contains azithromycin dihydrate equivalent to 100 mg azithromycin (100 mg/ml).
Parenteral administration drugs should be inspected visually for particulate in suspension prior to administration, If particulate in suspension is evident in reconstituted solution, the drug solution should be discarded.
The reconstituted solution must be further diluted prior to administration as instructed below.

• **Dilution**

To provide azithromycin over a concentration range of 1.0 - 2.0 mg/ml, transfer 5 ml of the 100 mg/ml azithromycin solution to the appropriate amount of any of the diluents.

Final infusion solution concentrtion	Amount of diluent (ml)
1.0mg/ml	500 ml
2.0 mg/ml	250 ml

PHARMACOKINETIC PROPERTIES

➢ **Absorption**

The biological availability of azithromycin after oral administration is approximately 37%. Peak plasma levels are achieved 2-3 hours after taking the medicinal product.

➢ **Distribution**

After oral administration, azithromycin is distributed throughout the entire body. Pharmacokinetic studies have shown clearly higher azithromycin levels in the tissues than in the plasma (up to 50 times the maximum observed concentration in plasma). This indicates that the substance is bound in the tissues in considerable quantities.
Concentrations in the infected tissues, such as lungs, tonsil and prostate are higher than the MRC90 of the most frequently occurring pathogens after a single dose of 500 mg.
The protein binding of azithromycin in serum is variable and varies, depending on the serum concentration, from 52% at 0.05 mg/l to 12% at 0.5 mg/l. The steady state distribution volume is 31.1 l/kg.

➢ **Metabolism**

The principal route of biotransformation involves N-demethylation of the desosamine sugar or at the 9a position on the macrolide ring. Other metabolic pathways include O-demethylation and hydrolysis and/or hydroxylation of the cladinose and desosamine sugar moieties and the macrolide ring.

➢ **Elimination·**

The terminal plasma-elimination half-life closely follows the tissue depletion half-life from 2 to 4 days.

PRECAUTIONS AND WARNINGS

As with any antibiotic, observation for signs of superinfection with non-susceptible organisms, including fungi is recommended. As with erythromycin and other macrolides, serious allergic reactions, including antineurotic edema and anaphylaxis, have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a long period of observation and treatment.

➢ **Hypersensitivity**

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens-Johnson Syndrome, and toxic epidermal necrolysis have been reported in patients on azithromycin therapy.

➢ **QT Prolongation**

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen with treatment with macrolides, including azithromycin.

➢ **Clostridium Difficile-Associated Diarrhea**

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all atibacterial agents, including ZITHROCIN (azithromycin for injection), 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.

➢ **Exacerbation of Myasthenia Gravis**

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

➢ **Infusion Site Reactions**

ZITHROCIN for injection should be reconstituted and diluted as directed and administered as an intravenous infusion over not less than 60 minutes. Local IV site reactions have been reported with the intravenous 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 hr (1 mg/mL as 500 mL infusion)

➢ **Development of Drug-Resistant Bacteria**

Prescribing ZITHROCIN in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

➢ **Pregnancy**

There are no adequate data from the use of azithromycin in pregnant women.

➢ **Breastfeeding**

Azithromycin passes into breast milk. Because it is not known whether azithromycin may have adverse effects on the breast-fed infant, nursing should be discontinued during treatment with Azithromycin.

➢ **Use in renal impairment:**

No dosage adjustment is needed in patients with mild renal impairment (Creatinine Clearance >40 ml/min.)

➢ **Use in hepatic impairment:**

As liver is the principal route of excretion of azithromycin, it should not be used in patients with hepatic disease.

SIDE-EFFECTS

Side effects on various organs and systems are given below:

➢ **Allergic:**

Arthralgia, edema, urticaria and angioedema.

➢ **Cardiovascular:**

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

➢ **Gastrointestinal:**

Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea, pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, and reports of tongue discoloration.

➢ **General:**

Asthenia, paraesthesia, fatigue, malaise and anaphylaxis (including fatalities).

➢ **Genitourinary:**

Interstitial nephritis and acute renal failure and vaginitis.

➢ **Hematopoietic:**

Thrombocytopenia.

➢ **Liver/biliary:**

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure.

➢ **Nervous system:**

Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation and syncope.

➢ **Psychiatric:**

Aggressive reaction and anxiety.

➢ **Skin/appendages:**

Pruritus, serious skin reactions including, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS.

➢ **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:
Elevated ALT (SGPT), AST (SGOT), creatinine (4 to 6%)
Elevated LDH, bilirubin (1 to 3%)
Leukopenia, neutropenia, decreased platelet count, and elevated serum alkaline phosphatase (less than 1%)
When follow-up was provided, changes in laboratory tests appeared to be reversible.

DRUG INTERACTIONS

➢ **Antacids:**

In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with oral azithromycin, no effect on overall bioavailability was seen, although peak serum concentrations were reduced by approximately 25%. In patients taking azithromycin by oral administration, azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

➢ **Cetrizine:**

In healthy volunteers, co-administration 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 *(Dideoxyinosine)*:**

Co-administration 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.

➢ **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.

➢ **Ergot derivatives *(Ergotamine)*:**

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 (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.

➢ **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 post-marketing period of potentiated anticoagulation subsequent to co-administration of azithromycin and coumarin-type oral anticoagulants.

➢ **Ciclosporin:**

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 ciclosporin, the resulting ciclosporin Cmax and AUC were found to be significantly elevated (by 24% and 21% respectively),Azithromycin also shows interactions with efavirenz, fluconazole, indinavir, methylprednisolone etc.

CONTRAINDICATIONS

➢ ZITHROCIN is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drugs

➢ It is also 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.

OVERDOSAGE

Typical symptoms of over dosage with macrolide antibiotics include hearing loss, severe nausea/ vomiting and diarrhea. Gastric lavage and general supportive measures are indicated.

STORAGE & INSTRUCTIONS

Store between 15-25°C. Protect from heat, sunlight and moisture.
Keep away from the reach of children.
To be sold on the prescription of a registered medical practitioner only.

HOW SUPPLIED

ZITHROCIN Injection 500mg
Ivial + 5ml sterile water for injection.
ZITHROCIN Capsule 250mg
10's Capsules.
ZITHROCIN suspension 200mg/5ml
15ml bottle.
ZITHROCIN Tablet 250mg
6's Tablets.
ZITHROCIN Tablet 500mg
6's Tablets.

خوراک وطریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۱۵-۳۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔
دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

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PHARMASOL
PRIVATE LIMITED
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Lahore, Pakistan.

6.75 inches