ZITRO

200 mg/5 ml

DRY POWDER FOR ORAL SUSPENSION

Each 5 mL suspension, prepared by reconstitution of dry powder with previously boiled and cooled water, contains 200 mg Azithromycin as Azithromycin dehydrate.
Sucrose, saccharin sodium, banana flavour and raspberry flavour are used as excipients.

PHARMACOLOGICAL PROPERTIES:
Pharmacodynamic Properties:
Azithromycin is an antibiotic from the azalide group of the macrolide class, distinguished from the other members of this class by the substitution of a carbon atom in the 15-member lactone ring by a nitrogen atom with an attached methyl group. Important properties of Azithromycin can be summarized as follows:
High tissue penetration, concentration at sites of infection, concentration in macrophages and neutrophils followed by transport to sites of infection, prolonged terminal half life with consequent short treatment period, high stability in acid environment resulting in increased absorption and bioavailability and extended antibacterial spectrum.
Like other macrolide antibiotics, Azithromycin is bound to 50S unit of bacterial ribosomes and inhibits protein synthesis without affecting nucleic acid synthesis.
Azithromycin is active against the following microorganisms both in vitro and in clinical infections:
Gram positive aerobes:
Staphylococcus aureus
Streptococcus pyogenes
Streptococcus pneumoniae
Streptococcus agalactiae
Enterococcus faecalis and most of the methicillin-resistant strains of Staphylococci are also resistant to Azithromycin.
Gram negative aerobes:
Haemophilus ducreyi
Haemophilus influenzae
Moraxella (Branhamella) catarrhalis
Neisseria gonorrhoeae
Other microorganisms:
Chlamydia pneumoniae
Chlamydia trachomatis
Mycoplasma pneumoniae
Activity of Azithromycin is not decreased in the presence of beta-lactamase-producing bacteria.
Azithromycin is active against the following microorganisms in vitro:
Gram positive aerobes:
Streptococci (group C, F, G)
Viridans group streptococci
Gram negative aerobes:
Bordatella pertussis
Legionella pneumophila
Anaerobic microorganisms:
Peptostreptococcus species
Prevotella bivia
Other microorganisms:
Ureaplasma urealyticum
Borrelia burgdorferi (Causative agent of the Lyme disease)
Mycobacterium avium intracellulare (MAC)
Campylobacter species
Listeria monocytogenes

Pharmacokinetic Properties:
Following oral administration, Azithromycin is rapidly absorbed. It diffuses from blood into tissues. Concentrations in tissues are higher than those in the blood. Absolute bioavailability of tablet form is 34 %. Administration with food increases Cmax by 23 %, but AUC does not change. Following administration of Azithromycin 500 mg initially, followed by 250 mg per day for days 2 - 5, the following pharmacokinetic parameters have been found:

	1st Day	5st Day
Peak plasma level (Cmax, µg/mL)	0.41	0.24
Time to reach Cmax (Tmax, hour)	2.5	3.2
Area Under the Curve (AUC_{0-24} µg. st/mL)	2.6	2.1
Lowest plasma level (Cmin, µg/mL)	0.05	0.05
Urinary elimination (% of dose)	4.5	6.5

Azithromycin rapidly diffuses from blood into tissues. Tissue concentrations are higher than blood levels. Azithromycin is concentrated mainly in phagocytes and fibroblasts. Distribution volume at the steady state is 31.1 L/kg. Protein binding depends on concentration, being 51.2 % at 0.02 µg/mL, 7 % at 2 µg/mL. Azithromycin is eliminated mainly through biliary tract in unchanged form. In addition to main molecule, 10 other metabolites formed by N- and D-demethylation, hydroxylation and conjugation have been reported. Metabolites have no antibacterial activity. About 6 % of Azithromycin is excreted in the urine as unchanged molecule. Its plasma clearance is 630 mL/min. Following administration of a 500 mg dose, mean terminal elimination half life is 68 hours. Azithromycin pharmacokinetics is not different in adults and elderly. Its pharmacokinetics has not been studied in patients with decreased renal and hepatic functions.

Pharmacokinetic Properties in Pediatric Patients:
Following administration of Azithromycin as oral suspension in doses of 10 mg/kg for the first day and then 5 mg/kg per day from day 2 to day 5, the following pharmacokinetic parameters have been found:

	1 - 5 years of age	1 - 5 years of age
Peak plasma level (Cmax, µg/mL)	0.216	0.383
Time to reach Cmax (Tmax, hour)	1-3	2-4
Area Under the Curve (AUC0-24, µg.h/mL)	1.822	3.109

INDICATIONS:
Azithromycin is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below:
Lower Respiratory Tract Infections:
Acute bacterial exacerbations of chronic obstructive pulmonary disease caused by Haemophilus influenzae, Moraxella catarrhalis or Streptococcus pneumoniae.
For the treatment of community acquired (from home, school, work place) pneumonia of light severity due to Streptococcus pneumoniae and Haemophilus influenzae suitable for outpatient treatment by orally administered medication.
NOTE: Azithromycin should not be used in patients with moderate to severe pneumonia for whom ambulatory treatment in the outpatient department is not appropriate and in the presence of the risk factors listed below:
- Nosocomially acquired infection
- Bacteremia or its suspicion
- When hospitalization is necessary
- In the elderly and debile patients
- When body defence against infections is diminished (such as defective immunity or functional asplenia)

Upper Respiratory Tract Infections:
Acute pharyngitis and tonsillitis due to Streptococcus pyogenes. Azithromycin eradicates the Streptococci from the nasopharynx.
Acute bacterial exacerbations of acute otitis media and chronic bronchitis.
Skin and Soft Tissue Infections:
For the treatment of uncomplicated skin and skin structure infections due to Staphylococcus aureus, Streptococcus pyogenes and Streptococcus agalactiae. In general, abscess require surgical drainage.
Genital infections (Sexually Transmitted Diseases - STD):
For the treatment of non-gonococcal urethritis and cervicitis caused by Chlamydia trachomatis and Chancroid (Ulcus molle) due to Haemophilus ducreyi. In these patients because of the possibility of co-existing syphilis and gonorrhoea, microbiological cultures and serological tests should be performed.
Gynecologic Infections:
For the treatment of cervicitis, endometritis and salpingo-ovaritis (P.I.D. - Pelvic Inflammatory Disease) due to susceptible strains of Chlamydia trachomatis, Mycoplasma hominis, Neisseria gonorrhoeae.

CONTRAINDICATIONS:
Azithromycin is contraindicated in patients with a history of hypersensitivity to any one of the macrolide antibiotics, erythromycin and Azithromycin.
WARNINGS / PRECAUTIONS:
Warnings:
Serious allergic reactions, angioedema and anaphylaxis have been reported rarely during Azithromycin therapy. Although they may respond to symptomatic therapy, recurrences are possible on discontinuing the therapy. These patients should be observed and treated for prolonged periods of time. These reactions may occur due to prolonged presence of Azithromycin in the body.
Almost with all antibiotics, pseudomembraneous enterocolitis associated with Clostridium difficile has been reported. In such a situation, Azithromycin should be discontinued and appropriate therapy with electrolytes, protein supplements and an antibiotic effective against Clostridium difficile should be instituted.

Azithromycin may induce Long QT Syndrome / Torsades de Pointes. For this reason, Azithromycin should not be used in patients with diagnosed or suspected Congenital Long QT Syndrome or Torsades de Pointes. Risk of causing Torsades de Pointes in women can be much higher rather than in men.

Precautions:
1- Azithromycin is eliminated mainly by biliary excretion. ZITRO should be used with caution in patients with impaired hepatic function.
2- Experience with use of Azithromycin in patients with kidney disease has been limited. ZITRO should be used with caution in these patients.
3- ZITRO Suspension can be taken with meals or between two meals. If taken with meals, it is tolerated better.
4- Azithromycin should not be taken concurrently with magnesium and aluminium containing antacids.
5- Patients should be advised to consult their physician immediately on the appearance of the first sign of an allergic reaction.

Use in Pregnancy and Lactation:
Use in Pregnancy: Pregnancy category B.
Studies did not reveal evidence of teratogenic or embryotoxic effect of Azithromycin. However, adequate and well-controlled studies in pregnant women have not been done.
ZITRO should be used during pregnancy only when it is clearly needed.
Use in Lactation: It is not known whether Azithromycin is distributed into human milk. However, since many drugs are excreted in the human milk, ZITRO should be used with caution in nursing mothers.

Geriatric Patients: Pharmacokinetic properties of Azithromycin in elderly patients are not different from those found in younger people. Dose adjustment is not necessary.

Effects on Ability to Drive and use Machines:
Azithromycin does not affect skills and performance required for driving and operating machinery.

SIDE EFFECTS / ADVERSE REACTIONS:
Most of the side effects reported during clinical studies are light and moderate severity and have disappeared on discontinuation of medication. About 0.7 % of the patients discontinued treatment because of side effects.

Side effects with a frequency above 1 % : Diarrhea, nausea, abdominal pain.

Side effects with a frequency less than 1 % :
Cardiovascular: Palpitations, chest pain.
Gastrointestinal: Dyspepsy, flatulence, vomiting, melena and cholestatic jaundice.
Genitourinary: Monilia, vaginitis, nephritis.
Nervous System: Dizziness, headache, vertigo, somnolence.
General: Fatigue.
Allergic: Skin rash, photosensitivity, angioedema.
Laboratory Test Abnormalities:
In clinical studies the following test abnormalities with a frequency of 1 % - 2 % have been reported. Their causal relation to therapy has not been established: Serum creatine, phosphokinase, potassium, ALT (SGPT), GGT, AST (SGOT) elevations. Test abnormalities with a frequency of less than 1 % : Leukopenia, neutropenia, thrombocytopenia and alkaline phosphatase, bilirubin BUN, creatinine, glucose, LDH, phosphate elevations.

IN THE EVENT OF AN UNEXPECTED REACTION CONSULT YOUR PHYSICIAN.

DRUG INTERACTIONS:
1- Magnesium and aluminium containing antacids decrease peak plasma concentrations of Azithromycin. Area under the curve does not change.
2- The effect of Azithromycin on plasma levels of theophylline and warfarin is not known. However, since macrolides may increase these levels, theophylline plasma concentrations and prothrombin time should be monitored when these drugs are used in combination with Azithromycin.
3- Plasma levels of the following drugs may be elevated by macrolides. Although this effect has not been reported with Azithromycin, it is recommended that the patients receiving these drugs and Azithromycin concurrently be monitored closely: Digoxin, ergotamine, triazolam, phenytoin, carbamazepine, cyclosporine, hexobarbital.
4- If warfarin is administered as a single dose to patients receiving the recommended dose of Azithromycin, prothrombin time does not change. However, the use of macrolides in combination with warfarin may potentiate anticoagulant effect. The patients receiving Azithromycin and warfarin concurrently should be observed closely.
5- The use of Azithromycin in conjunction with zidovudin and didanosin does not result in a clinically significant interaction.
6- Concurrent use of Azithromycin and rifabutin does not result in changes in serum concentrations of any one of the drugs.
7- Azithromycin absorption is not affected by cimetidine, taken two hours before Azithromycin administration.

DOSAGE AND ADMINISTRATION:
ZITRO Oral Suspension can be taken 1 hour before or 2 hours after having the meal.
Adults:
For the treatment of chronic obstructive pulmonary disease, acute bacterial infections, community acquired pneumonia, pharyngitis and tonsillitis, uncomplicated skin and soft tissue infections; on day 1, 500 mg of Azithromycin is administered as a single dose, then 250 mg Azithromycin is administered per day from days 2 to 5.
For the treatment of genital ulcers due to Haemophilus ducreyi and nongonococcal urethritis and cervicitis due to C. trachomatis, 1 g (1000 mg) of Azithromycin is administered as a single dose.
For the treatment of gonorrhea, 2 g (2000 mg) of Azithromycin is administered as a single dose.
Children:
Acute Otitis Media: Recommended dosage in children with acute otitis media is as follows: 30 mg/kg as single dose or 10 mg/kg/day for 3 days as single dose or 10 mg/kg/day on day 1, then 5 mg/kg/day from days 2 to 5.
Streptococcal Pharyngitis: 12 mg/kg/day for 5 days.
Other Indications : 10 mg/kg/day for 3 days or 10 mg/kg/day on day 1, then 5 mg/kg/day from days 2 to 5.

BODY WEIGHT (kg)	3 DAYS TREATMENT (Once a day)		5 DAYS TREATMENT (Once a day)	
	1st day	Days 2 and 3	1st day	Days 2 and 5
< 15 kg	2.5 ml (100 mg)	2.5 ml (100 mg)	2.5 ml (100 mg)	1.25 ml (50 mg)
15-25 kg	5 ml (200 mg)	5 ml (200 mg)	5 ml (200 mg)	2.5 ml (100 mg)
26-35 kg	7.5 ml (300 mg)	7.5 ml (300 mg)	7.5 ml (300 mg)	3.75 ml (150 mg)
36-45 kg	10 ml (400 mg)	10 ml (400 mg)	10 ml (400 mg)	5 ml (200 mg)
> 45 kg	Adult dose			

Preparation of the Suspension:
Tap the closed bottle gently several times to loosen the powder. Measure recommended amount of water by filling the measuring cup to the indicated level (measuring cup included in the box). Add all of water into the bottle, recap the bottle and shake the closed bottle well. After preparing the suspension wait for 5 minutes before administrating the initial dose. Shake the bottle well before each use.
By using the measuring spoon which has dosing lines, administrate the exact dose of suspension that your physician has prescribed.

OVERDOSE AND ITS TREATMENT:
In the event of an overdose, general symptomatic and supportive therapy is applied. There is no known antidote.

STORAGE:
Keep out of the reach of children. Store in original package at room temperature below 30°C before reconstitution. ZITRO Suspension is stable for 5 days at room temperature below 30°C after reconstitution.
HOW SUPPLIED:
Plastic bottle of 30 mL containing Azithromycin dihydrate equivalent to 200 mg Azithromycin in each 5 mL (1 measuring spoon) suspension, prepared by reconstitution of dry powder with previously boiled and cooled water, with a measuring cup (15 mL) and a measuring spoon (5 mL).

Pediatric Package: Plastic bottle of 15 mL containing Azithromycin dihydrate equivalent to 200 mg Azithromycin in each 5 mL (1 measuring spoon) suspension, prepared by reconstitution of dry powder with previously boiled and cooled water, with a measuring cup (7.5 mL) and a measuring spoon (5 mL).

OTHER PHARMACEUTICAL DOSAGE FORMS AVAILABLE:
ZITRO 500 mg Film Coated Tablet, in blister packages containing 3 film coated tablets.

PRODUCT LICENCE HOLDER :
The holder of trade mark and Marketing Authorization is
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