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ZITRO 500 mg FILM COATED TABLET

COMPOSITION : Each film coated tablet contains ;
500 mg Azithromycin as azithromycin trihydrate
Colouring agent : Titanium dioxide

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 summerized 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 binds to 50S unit of bacterial rhibosomes 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 livia
Other microorganisms :
Ureaplasma urealyticum
Borrelia burgdorferi (Causative agent of the *Lyme disease*). *Mycobacterium avium intracellulare (MAC). Campylobacter species* and *Listeria monocytogenes.*

Pharmacokinetic properties :
After oral administration azithromycin is rapidly absorbed ; from blood it diffuses into body tissues. Absolute bioavailability of tablet form is 34 %. Administration with food increases Cmax by 23 %, 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.

	1. Day	5. 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 (AUC0-24, µg.h/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 parent 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.

INDICATIONS :
ZITRO is indicated for the treatment of the following mild-to-moderate infections caused by the susceptible microorganisms :
Lower respiratory tract infections :
Acute bacterial exacerbations of the chronic obstructive pulmonary disease caused by *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae.*
Mild cases of community-acquired pneumonia due to *Streptococcus pneumoniae* and *Haemophilus influenzae,* suitable for ambulatory treatment.
NOTE : Azithromycin should not be used in patients with medium-to-severe pneumonia for whom ambulatory treatment is not appropriate and in the presence of the following risk factors :
nosocomially acquired infection
bacteremia or its suspicion
when hospitalization is necessary
elderly and debile patients
when body defenses to infection are diminished (defective immunity or functional asplenia)
Upper respiratory tract infections :
Acute pharyngitis and tonsillitis : For the treatment of acute pharyngitis / tonsillitis caused by *Streptococcus pyogenes.* Azithromycin eradicates Streptococci from nasopharynx.
For the treatment of acute otitis media, acute exacerbations of 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, abscesses require surgical drainage.
Genital infections. Sexually transmitted disease (STD) :
Non-gonococcal urethritis and cervicitis caused by *Chlamydia trachomatis,* and chancroid (ulculs molle) due to *Haemophilus ducrei.* These patients should have serologic tests for syphilis and cultures for gonorrhea performed at the time of diagnosis.
Gynecologic infections :
Cervicitis, endometritis and salpingo-ovaritis (P.I.D. – Pelvic Inflammatory Disease) due to susceptible strains of *Chlamydia trachomatis, Mycoplasma hominis* and *Neisseria gonorrhoeae.*

CONTRAINDICATIONS :
Azithromycin is contraindicated in patients with a history of hypersensitivity to any one of the macrolide antibiotics, erythromycin and azithromycin.

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WARNINGS / PRECAUTIONS :
Warnings :
Rarely serious allergic reactions, angioedema and anaphylaxis have been reported during azithromycin therapy.
Although they may respond to symptomatic therapy, recurrences are possible on discontinuing the treatment. These patients should be observed and treated for prolonged periods of time. These reactions may be due to prolonged residence of azithromycin in the body. Almost with all antibiotics, pseudomembraneous enterocolitis associated with Clostridium infection has been reported. In such situations azithromycin should be discontinued and appropriate therapy with electrolytes, protein supplements and an antibiotic effective against *Clostridium difficile* should be instituted.
Azythromycin may lead to prolonged QT Syndrome/ Torsades de Pointes. For this reason it should not be administed to patients with diagnosed or suspected congenital prolonged QT Syndrome/ Torsades de Pointes. The risk of Torsades de Pointes in women is higher than 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 may be taken during meals or between meals. However, it is tolerated better if taken with meals.
4- ZITRO 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 first sign of an allergic reaction.

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.

SIDE EFFECTS / ADVERSE REACTIONS :
Most of the side effects reported during clinical studies have been of light and medium severity and have disappeared on discontinuation of medication. About 0.7 % of 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, alkaline phosphatase, bilirubin BUN, creatinine, glucose, LDH and 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 :
Recommended dosage for treatment of skin and respiratory tract infections in patients older than 16 years of age is 500 mg initially (1 film coated tablet), and 250 mg (1/2 film coated tablet) daily for the following 4 days. (Total dose for 5 day treatment is 1.5 g or 3 film coated tablet)
For treatment of non-gonococcal urethritis or cervicitis due to Chlamydia trachomatis a single dose of 1000 mg azithromycin (2 film coated tablets) is recommended.
For treatment of gonococcal cervicitis and urethritis a single dose of 2 g azithromycin is recommended.

OVERDOSE AND IT'S TREATMENT :
In the event of 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.

HOW SUPPLIED :
ZITRO 500 mg Film Tablet, blister packs containing 3 film tablets.

OTHER PHARMACEUTICAL DOSAGE FORMS AVAILABLE :
ZITRO 200 mg/5 ml, Dry powder in 15 ml bottles for pediatric oral suspension
ZITRO 200 mg/5 ml, Dry powder in 30 ml bottles for oral suspension

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