Zetro™

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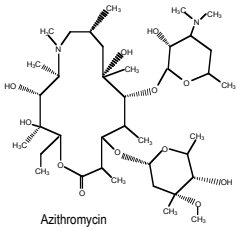
[Azithromycin]

250mg Capsules, 500mg Tablets

200mg/5mL Suspension

DESCRIPTION

ZETRO (Azithromycin) is nitrogen containing macrolide or azalide for oral administration. Chemically azithromycin is (*2R, 3S, 4R, 5R, 8R, 10R, 11R, 12S, 13S, 14R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-*L*-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-hepta methyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-*D*-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopenta decan-15-one.The molecular formula is $C_{38}H_{72}N_2O_{12}$ and the structural formula is:



Azithromycin

QUALITATIVE & QUANTITATIVE COMPOSITION

ZETRO (Azithromycin) is available for oral administration as:

1. ZETRO Capsules 250mg
   Each capsule contains:
   Azithromycin USP....250mg
   (as dihydrate)
2. ZETRO Tablets 500mg
   Each film-coated tablet contains:
   Azithromycin USP....500mg
   (as dihydrate)
3. ZETRO Suspension 200mg/5mL
   Each 5mL contains:
   Azithromycin USP....200mg
   (as dihydrate)

CLINICAL PHARMACOLOGY

Mechanism of Action

Azithromycin exerts it antibacterial action by binding to the 50s ribosomal subunit of susceptible organisms and thus interfering with microbial protein synthesis and inhibition of peptide translocation. Nucleic acid synthesis is not effected.

Pharmacokinetics

Following oral administration about 40% of the dose of azithromycin is bioavailable. Absorption from the capsule formulation is reduced by food but there is no significant effect on the bioavailability of tablet formulation even after a high fat meal.Peak plasma concentrations are achieved 2 to 3 hours after a dose but azithromycin is extensively distributed to the tissues and tissue concentration subsequently remain much higher than those in blood. High concentrations are taken up into white blood cells. Small amount of azithromycin are demethylated in liver and it is excreted in bile as unchanged drug and metabolites. About 20% of the amount in the systemic circulation is excreted in the urine. The terminal elimination half-life is probably in excess of 40 hours.

Special Populations

Renal Insufficiency

Following a single dose of azithromycin 1g orally, the pharmacokinetics in subjects with mild to moderate renal impairment (GFR 10 - 80mL/min) were not effected. Significant differences in AUC, C_{max} and Cl_{cr} were observed between subjects with severe renal impairment (GFR < 10mL/min) and subjects with normal renal function.

Hepatic Insufficiency

In patients with mild (Class A) to moderate (Class B) hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function.

Microbiology:

Azithromycin has been shown to be active against most isolates of the following micro-organisms, both *in vitro* and in clinical infections.

Aerobic and facultative gram-positive organisms.

Streptococcus pneumoniae, penicillin-resistant, penicillin-intermediate, *Streptococcus pyogenes, Staphylococcus aureus, Streptococcus agalactiae, Streptococci (Groups C, F, G) Viridans group streptococci, Corynebacterium diptheriae.* Azithromycin demonstrates cross-resistance with erythromycin-resistant Gram-positive strains, including *Streptococcus faecalis (entrococcus)* and most strains of methicillin-resistant staphylococci.

Aerobic and facultative gram-negative organisms.

Haemophilus ducreyi, Haemophilus influenzae, Moraxella catarrhalis, Neisseria gonorrhoeae, Bordetella pertussis, Legionella pneumophila, Haemophilus parainfluenzae, Acinetobacter species, Yersinia species, Shigella species, Pasteurella species, *Vibrio cholerae* and *parahaemolyticus, Plesiomonas shigelloides.*

Anaerobic micro-organisms

Peptostreptococcus species, *Prevotella bivia, Bacteroides fragilis* and Bacteroides species, *Clostridium perfringens,* Peptococcus species, *Fusobacterium necrophorum* and *Propionibacterium acnes.*

Others

Chlamydia pneumoniae, Chlamydia trachomatis, Mycoplasma pneumoniae, Ureaplasma urealyticum, Escherichia coli, Salmonella, Shigella spp., *Mycobacterium avium, Mycobacterium intracellulare,Toxoplasma gondii, Plasmodium falciparum.*

THERAPEUTIC INDICATIONS

ZETRO (Azithromycin) is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated micro-organisms in the specific conditions listed below:

- Lower respiratory tract infections (acute bacterial bronchitis and community acquired pneumonia in patients suitable for outpatient oral treatment and in patients who require initial intravenous therapy).
- Upper respiratory tract infections (acute sinusitis, acute streptococcal pharyngitis/tonsillitis and acute otitis media in children).
- Uncomplicated skin and skin structure infections.
- Sexually transmitted diseases (uncomplicated urethritis and cervicitis). Antimicrobial agents used in high doses for short periods of times to treat non-gonococcal urethritis may mask or delay the symptoms of incubating gonorrhea or syphilis. All patients with sexually-transmitted urethritis or cervictitis should have a serologic test for syphilis and appropriate cultures for gonorrhea performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.
- Pelvic inflammatory disease in patients who require initial intravenous therapy.
- Chlamydia trachomatis conjunctivitis and trachoma in adults and in children 12 months or older.
- Prophylaxis and treatment of disseminated mycobacterium avium complex (MAC) disease in adults and children aged more than 12 years.

DOSAGE AND ADMINISTRATION

ZETRO (Azithromycin) tablets and oral suspension can be taken with or without food. The capsule formulation should be given at least an hour before or 2 hours after meals.

Adults:

For all indications except for those given below, the usual adult dose of ZETRO (Azithromycin) is 500mg as a single dose daily for 3 days. Alternatively, an initial dose of 500mg maybe followed by 250mg daily for a further 4 days.

Sexually transmitted uncomplicated urethritis and cervicitis: 1g as a single dose.

Conjunctivitis and trachoma due to Chlamydia trachomatis: 1g either as a single dose or once weekly for up to 3 weeks.

Treatment of community acquired pneumonia following IV therapy: 500mg as a single daily dose to complete a 7 to 10 day course of therapy.

Treatment of pelvic inflammatory disease following IV therapy: 250mg as a single daily dose to complete a 7 day course of therapy.

Prevention of disseminated Mycobacterium avium complex (MAC) disease in adults with HIV Infection: 1200mg taken as a single dose once weekly, either alone, or in combination with rifabutin, at its recommended dosage.

Treatment of disseminated Mycobacterium avium complex (MAC) disease in adults with HIV Infection: ZETRO (Azithromycin) should be taken at a daily dose of 600mg, in combination with ethambutol at the recommended daily dose of 15mg/kg.

Children
ZETRO (Azithromycin) should be used for children under 45kg. The dose in children is 10mg/kg as a single daily dose for 3 days. Alternatively, 10mg/kg as a single dose on the first day followed by 5mg/kg/day on days 2-5.

Conjunctivitis and trachoma due to Chlamydia trachomatis in children 12 months or older: 20mg/kg either as a single dose or once weekly for up to three weeks.

Prevention of disseminated Mycobacterium avium complex (MAC) disease in children aged more than 12 years with HIV Infection:
1200mg taken as a single dose once weekly, either alone, or in combination with rifabutin, at its recommended dosage.

Streptococcal pharyngitis and tonsillitis: 20mg/kg once daily for 3 consecutive days providing a total dose of 60mg/kg over a 3 day treatment period. Do not exceed a daily dose of 500mg (or 12.5mL of the reconstituted powder for oral suspension).

Acute Otitis Media: Total dose of 30mg/kg given as 30mg/kg as a single dose or 10mg/kg once daily for 3 days or 10mg/kg as a single dose on the first day followed by 5mg/kg/day on days 2-5.

Acute Bacterial Sinusitis:
The recommended dose of ZETRO (Azithromycin) for oral suspension for the treatment of pediatric patients with acute bacterial sinusitis is 10mg/kg once daily for 3 days.

Community-Acquired Pneumonia:
The recommended dose of ZETRO (Azithromycin) for oral susension for the treatment of pediatric patients with community-acquired pneumonia is 10mg/kg as a single dose on the first day followed by 5mg/kg on days 2 through 5.

Directions for Preparing Oral Suspension
To prepare 15mL suspension add 7.5mL boiled cooled water to the powder by using the given measureing device and shake well to dissolve the powder. Discard any unused portion after 10 days.

ADVERSE REACTIONS
Very Common
Diarrhea, abdominal pain, nausea and flatulence.

Common
Lymphocyte count decreased, eosinophil count increased, anorexia, dizziness, headache, paraesthesia, dysgeusia, deafness, vomiting, dyspepsia, rash, pruritus, arthralgia, fatigue and blood bicarbonate decreased.

Uncommon
Candidiasis, oral candidiasis, vaginal infection, leukopenia, neutropenia, angioedema, hypersensitivity, nervousness,hypoaesthesia, somnolence, insomnia, hearing impaired, tinnitus, palpitations, gastritis, constipation, hepatitis, aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubine increased, Steven-Johnson syndrome, photosensitivity reaction, urticaria, blood urea increased, chest pain, oedema, malaise, asthenia and blood potassium abnormal.

Rare
Thrombocytopenia, hemolytic anemia, agitation, depersonalisation,vertigo, hepatic function abnormal, renal failure acute and nephritis interstitial.

CONTRAINDICATIONS
Azithromycin is contraindicated:
- In patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotics.
- In patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.
- To use concurrently with ergot derivatives.

PRECAUTIONS
- Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of risk factors such as:
  - Patients with cystic fibrosis.
  - Patients with nosocomially acquired infections.
  - Patients with known or suspected bacteremia.
  - Patients requiring hospitalization.
  - Elderly or debilitated patients.
  - Patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).
- No dose adjustment is needed in patients with mild or moderate renal impairment.
- Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR < 10mL/min).
- Since azithromycin is metabolized in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease.
- As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms including fungi, is recommended.
- Venticular arrythmias associated with prolonged QT interval, including ventricular tachycardia and torsades de pointes have been reported with macrolide products. Azithromycin should be used with caution in patients predisposed to QT interval prolongation or in patients taking other medications known to prolong the QT interval.
- Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin and may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued.

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Therefore, azithromycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether azithromycin is excreted into human milk. Azithromycin should only be used in lactating women where adequate alternatives are not available.

Drug Interactions
Antacids: In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously. Azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

Cyclosporine: Caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporine levels should be monitored and the dose adjusted accordingly.

Theophylline: Theophylline levels may be increased in patients taking azithromycin.

Coumarin-type oral anticoagulants: Consideration should be given to the frequency of monitoring prothrombin time, when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Digoxin: In patients receiving concomitant azithromycin, a related azalide antibiotic and digoxin, the possibility of raised digoxin levels should be borne in mind.

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 diarrhea. In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

STORAGE
Store at 25°C (Excursions permitted between 15°C -30°C)
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
- ZETRO (Azithromycin) Capsules 250mg are available in blister pack of 10's.
- ZETRO (Azithromycin) Tablets 500mg are available in blister pack of 3's.
- ZETRO (Azithromycin) Suspension 200mg/5mL is available in pack size of 15mL.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

Getz pharma (PVT) LIMITED
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L01-200006712