

ZIOX 250/500

(Azithromycin Tablets)

DESCRIPTION

Azithromycin is an azalide, a subclass of macrolide antibiotics. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring.

COMPOSITION - ZIOX-250

Each film coated tablet contains:

Azithromycin IP equivalent to Azithromycin (anhydrous) 250 mg

COMPOSITION - ZIOX-500

Each film coated tablet contains:

Azithromycin IP equivalent to Azithromycin (anhydrous) 500 mg

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption

Following oral administration, azithromycin is rapidly absorbed and widely distributed throughout the body. Rapid distribution of azithromycin into tissues and high concentration within cells result in significantly higher azithromycin concentrations in tissues than in plasma or serum.

With a regimen of 500 mg on Day 1 and 250 mg/day on Days 2–5, C_{min} and C_{max} remains essentially unchanged from Day 2 through Day 5 of therapy. However, without a loading dose, azithromycin C_{min} levels requires 5 to 7 days to reach steady state.

When azithromycin tablets is administered with food, the rate of absorption (C_{max}) may be reduced by 52% and the extent of absorption (AUC) by 43%.

Distribution

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 $\mu\text{g/mL}$ to 7% at 2 $\mu\text{g/mL}$. Following oral administration, azithromycin is widely distributed with an apparent steady state volume of distribution of 31.1 L/kg.

Elimination

Plasma concentrations of azithromycin following single 500 mg oral dose declines in a polyphasic pattern resulting in a terminal elimination half-life of 68 hours. The prolonged half-life is due to extensive uptake and subsequent release of drug from tissues. Azithromycin is mainly excreted in bile as unchanged drug. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

Renal Insufficiency: Following the oral administration of Azithromycin the mean C_{max} and AUC_{0-120} increased 61% and 35%, respectively in subjects

with end-stage renal disease (GFR <10 mL/min) compared to subjects with normal renal function (GFR >80 mL/min).

Hepatic Insufficiency: The pharmacokinetics of azithromycin in subjects with hepatic impairment has not been established.

Mechanism of Action

Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis.

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by in vitro incubation techniques. The ratio of intracellular to extracellular concentration is >30 after one hour incubation. In vivo studies suggest that

concentration in phagocytes may contribute to drug distribution to inflamed tissues.

Microbiology

Azithromycin has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections:

Aerobic Gram-Positive Microorganisms

Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic Gram-Negative Microorganisms

Haemophilus influenzae
Haemophilus ducreyi
Moraxella catarrhalis
Neisseria gonorrhoeae

"Other" Microorganisms

Chlamydia pneumoniae
Chlamydia trachomatis
Mycoplasma pneumoniae

N.B. Beta-lactamase production should have no effect on azithromycin activity.

INDICATIONS AND USAGE

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-LRTI:

Community acquired pneumonias, acute bacterial exacerbations of chronic bronchitis, chronic obstructive pulmonary disease due to Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae or Chlamydia pneumoniae.

Upper respiratory tract infections-URTI (including ENT infections):

Tonsillitis, sinusitis, otitis media and pharyngitis due to Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae or Streptococcus pyogenes.

Uncomplicated Skin and skin structure infections-SSTI:

Folliculitis, furuncles, carbuncles, impetigo, pyoderma, skin ulcer, dermatitis, cellulitis and erysipelas due to Staphylococcus aureus, Streptococcus pyogenes or Streptococcus agalactiae.

Genitourinary tract infections (including sexually transmitted diseases):

Urethritis, prostatitis, cervicitis, cervico-vaginitis and salpingitis due to Neisseria gonorrhoeae, Chlamydia trachomatis, or Haemophilus ducreyi.

DOSAGE & ADMINISTRATION

Mild to moderate LRTI, URTI and uncomplicated SSTI:

Adults: 500 mg as a single dose on the first day followed by 250 mg once daily on days 2 to 5 for a total dose of 1.5 g or 500 mg once daily for 3 days.

Children under 12 years:

The usual dose for children is 10 mg/kg body weight orally, once a day for 3 days. Alternatively after a 10 mg/kg body weight of loading dose on the first

day, therapy can be continued at a dose of 5 mg/kg body weight on four subsequent days.

Sexually transmitted diseases:

- 1) Gonorrhoea: 2 gm as a stat dose
- 2) Chancroid: 1 gm as a stat dose
- 3) Non-gonococcal urethritis & cervicitis due to *C. trachomatis* - 1 gm as a stat dose
- 4) Syphilis: 1 gm daily for 5 days or 500 mg daily for 10 days.

N.B. Azithromycin tablets may be taken without regard to food

Renal Insufficiency

No dosage adjustment is recommended for subjects with renal impairment (GFR \leq 80mL/min). The mean AUC 0–120 was similar in subjects with GFR 10–80 mL/min compared to subjects with normal renal function, whereas it increased 35% in subjects with GFR $<$ 10mL/min compared to subjects with normal renal function. Caution should be exercised when azithromycin is administered to subjects with severe renal impairment.

Hepatic Insufficiency

The pharmacokinetics of azithromycin in subjects with hepatic impairment has not been established. No dosage adjustment recommendations can be made in patients with impaired hepatic function

CONTRAINDICATIONS

Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin, any macrolide or ketolide antibiotic.

WARNINGS

Rare serious allergic reactions, have been reported rarely in patients on azithromycin therapy. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy instituted.

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Caution should be exercised when azithromycin is administered to subjects with severe renal impairment.

PRECAUTIONS

General

Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function.

Prolonged cardiac repolarization 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 repolarization.

Pregnancy

Pregnancy Category B: No evidence of impaired fertility or harm to the fetus due to azithromycin was found. There are, however, 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.

Nursing Mothers

It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman.

Geriatric Use

Pharmacokinetic parameters in older volunteers (65–85 years old) were similar to those in younger volunteers (18–40 years old) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function.

DRUG INTERACTIONS

Human clinical and pharmacokinetic studies have shown no major drug-drug interactions between azithromycin and numerous other agents: theophylline, midazolam, terfenadine, cetirizine, atorvastatin, Trimethoprim/Sulfamethoxazole, sildenafil, zidovudine, fluconazole or cimetidine. The extent of absorption of azithromycin was unaffected by concurrent administration of antacids.

ADVERSE REACTIONS

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Approximately 0.7% of the patients from the multiple-dose clinical trials discontinued azithromycin therapy because of treatment-related side effects. Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain. Rarely but potentially serious side effects were angioedema and cholestatic jaundice.

PRESENTATION

ZIOX-250 is available in blister of 6 tablets

ZIOX-500 is available in blister of 3 tablets