Zelinz

Tablets
Suspension
Capsules

(AZITHROMYCIN)

ذِی لنز

ٹیبلیٹس/سسپنشن/کیپسولز

(ایزیتھرومائیسن)

Description:
Zelinz contain the active ingredient azithromycin, a macrolide antibacterial drug, for oral administration. Azithromycin has the chemical name (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-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xy lo-hexopyranosyl]oxy]-1¬ oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12}$•$2H_2O$ and a molecular weight of 785.0.

Composition:
Each Zelinz 250mg Tablet contains:
Azithromycin dihydrate eq. to
Azithromycin U.S.P. 250mg
(Product Specs.: U.S.P.)

Each Zelinz 500mg Tablet contains:
Azithromycin dihydrate eq. to
Azithromycin U.S.P. 500mg
(Product Specs.: U.S.P.)

Each Zelinz 250mg Capsule contains:
Azithromycin dihydrate eq. to
Azithromycin U.S.P. 250mg
(Product Specs.: U.S.P.)

Each 5ml of Zelinz Suspension 100mg contains:
Azithromycin dihydrate eq. to
Azithromycin U.S.P.....100mg
(Product Specs.: U.S.P.)

Each 5ml of Zelinz Suspension 200mg contains:
Azithromycin dihydrate eq. to
Azithromycin U.S.P.....200mg
(Product Specs.: U.S.P.)

Clinical Pharmacology:
Pharmacodynamic Properties:
Pharmacotherapeutic group: Antibacterials for systemic use, macrolides.
ATC code: J01FA10.

Mechanism of Action:
Azithromycin acts by binding to the 23S rRNA of the 50S ribosomal subunit of susceptible microorganisms inhibiting bacterial protein synthesis and impeding the assembly of the 50S ribosomal subunit.

Microbiology:
Gram-Positive Bacteria:
- Staphylococcus aureus
- Streptococcus agalactiae
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Beta-hemolytic streptococci (Groups C, F, G)
- Viridans group streptococci

Gram-Negative Bacteria:
- Haemophilus ducreyi
- Haemophilus influenzae
- Moraxella catarrhalis
- Neisseria gonorrhoeae
- Bordetella pertussis
- Legionella pneumophila

Anaerobic Bacteria:
- Prevotella bivia
- Peptostreptococcus species

Other Bacteria
- Chlamydophila pneumoniae
- Chlamydia trachomatis
- Mycoplasma pneumonia
- Ureaplasma urealyticum

Mycobacteria
- Mycobacterium avium

• Mycobacterium intracellulare

Pharmacokinetic Properties
Absorption:
The absolute bioavailability of azithromycin 250 mg capsules is 38%. The 1 gram single-dose packet is bioequivalent to four 250 mg azithromycin capsule. When the oral suspension of azithromycin was administered with food, the Cmax increased by 46% and the AUC by 14%. Peak serum concentrations were achieved approximately 2.5 hr later following Zelinz administration.

Distribution:
The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 mcg/mL to 7% at 2 mcg/mL. Following oral administration, azithromycin is widely distributed throughout the body with an apparent steady-state volume of distribution of 31.1 L/kg. Azithromycin has been shown to penetrate into human tissues, including skin, lungs, tonsil, and cervix. Following a regimen of 500 mg of azithromycin tablets on the first day and 250 mg daily for 4 days, only very low concentrations were noted in cerebrospinal fluid (less than 0.01 mcg/mL) in the presence of non-inflamed meninges.

Elimination:
Plasma concentrations of azithromycin following single 500 mg oral doses declined in a polyphasic pattern resulting in a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hr. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues. Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

Specific Populations
Renal Impairment
Following the oral administration of a single 1.0 g dose of azithromycin (4 x 250 mg capsules), mean Cmax and AUC0-120 increased by 5.1% and 4.2%, respectively. The mean Cmax and AUC0-120 increased 61% and 35%, respectively.

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

Pediatrics:
Pharmacokinetics in children aged 4 months – 15 years taking capsules, granules or suspension. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the Cmax achieved is slightly lower than in adults, with 224 µg/l in children aged 0.6-5 years and after 3 days dosing, and 383 µg/l in those aged 6-15 years. The half-life of 36 h in the older children was within the expected range for adults.

Elderly:
The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred.

Therapeutic Indications:
Zelinz (azithromycin) is a macrolide antibacterial drug 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.

Adult Patients
- Acute bacterial exacerbations of chronic bronchitis
- Acute bacterial sinusitis
- Community-acquired pneumonia
- Pharyngitis/tonsillitis
- Uncomplicated skin and skin structure infections
- Urethritis and cervicitis
- Genital ulcer disease in men

Pediatric Patients
- Acute otitis media (>6 months of age)
- Community-acquired pneumonia (>6 months of age)
- Pharyngitis/tonsillitis (>2 years of age)

Dosage and Administration:
Adult Patients:

Infection	Recommended Dose/ Duration of Therapy
Community-acquired pneumonia Pharyngitis/tonsillitis (second-line therapy) Skin/skin structure (uncomplicated)	500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5
Acute bacterial exacerbations of chronic obstructive pulmonary disease	500 mg once daily for 3 days OR 500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5
Acute bacterial sinusitis	500 mg once daily for 3 days
Genital ulcer disease (chancroid)	One single 1 gram dose
Non-gonococcal urethritis and cervicitis	One single 1 gram dose
Gonococcal urethritis and cervicitis	One single 2 gram dose

Zelinz tablets can be taken with or without food
Pediatric Patients:

Infection	Recommended Dose/ Duration of Therapy
Acute otitis media	30 mg/kg as a single dose or 10 mg/kg once daily for 3 days or 10 mg/kg as a single dose on Day 1 followed by 5 mg/kg/day on Days 2 through 5.
Acute bacterial sinusitis	10 mg/kg once daily for 3 days.
Community-acquired pneumonia	10 mg/kg as a single dose on Day 1 followed by 5 mg/kg once daily on Days 2 through 5.
Pharyngitis/tonsillitis	12 mg/kg once daily for 5 days.

Elderly:
For elderly patients the same dose as for adults can be applied. Since elderly patients can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes.

Patients with Renal Impairment:
Dose adjustment is not required 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).
Patients with Hepatic Impairment:
Since azithromycin is metabolised in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease.

Contraindications:
- Zelinz is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drug.
- Zelinz is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.

Warnings and Precautions:
Hypersensitivity
Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported in patients on azithromycin therapy.
Fatalities and Cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that allergic symptoms may reappear when symptomatic therapy has been discontinued.

Hepatotoxicity
Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.

Infantile Hypertrophic Pyloric Stenosis (IHPS)
Following the use of azithromycin in neonates, IHPS has been reported. Direct parents and caregivers to contact their physician if vomiting or irritability with feeding occurs.

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.

Providers should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:
- Patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure
- Patients on drugs known to prolong the QT interval
- Patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.

Elderly patients may be more susceptible to drug-associated effects on the QT interval.

Clostridium difficile-Associated Diarrhea (CDAD)
Clostridium difficile-associated diarrhea has been reported with use of Zelinz, and may range in severity from mild diarrhea to fatal colitis.
C.difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antibacterial therapy and may require colectomy. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued.

Exacerbation of Myasthenia Gravis
Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy.

Use in Sexually Transmitted Infections
Antibacterial agents used to treat non-gonococcal urethritis may mask or delay the symptoms of incubating syphilis. All patients with sexually transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate testing for gonorrhea performed at the time of diagnosis.

Development of Drug-Resistant Bacteria
Prescribing Zelinz 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.

Drug Interactions:
Nelfinavir
Co-administration of nelfinavir at steady-state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known adverse reactions of azithromycin.

Warfarin
Concomitant administration of azithromycin may potentiate the effects of oral anticoagulants such as warfarin, although the prothrombin time was not affected in the dedicated drug interaction study with azithromycin and warfarin. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.

Potential Drug-Drug Interaction with Macrolides
Drug interactions have been observed with other macrolide products, when digoxin, colchicine or phenytoin are used with azithromycin careful monitoring of patients is advised.

Adverse Effects:
Very Common:
Diarrhoea, abdominal pain, nausea, flatulence

Common:
Anorexia, Dizziness, headache, paraesthesia, dysgeusia, Visual impairment, Deafness, Vomiting, dyspepsia, Rash, pruritus, Arthralgia, Fatigue

Uncommon:
Candidiasis, oral candidiasis, vaginal infection, Leukopenia, neutropenia, Angioedema, hypersensitivity, Nervousness, Hypoaesthesia, somnolence, insomnia, Hearing impaired, tinnitus, Palpitations, Gastritis, constipation, Hepatitis, Stevens-Johnson syndrome, photosensitivity reaction, urticaria, Chest pain, oedema, malaise, asthenia.

Rare:
Agitation, Vertigo, Hepatic function abnormal, Acute generalised exanthematous pustulosis (AGEP), DRESS (Drug reaction with eosinophilia and systemic symptoms).

Not Known:
Pseudomembranous colitis, Thrombocytopenia, haemolytic anaemia, Anaphylactic reaction, Aggression, anxiety, Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis, Torsades de pointes, arrhythmia including ventricular tachycardia, Hypotension, Pancreatitis, tongue discoloration, Hepatic failure, hepatitis fulminant, hepatic necrosis, jaundice cholestatic, Toxic epidermal necrolysis, erythema multiforme. Renal failure acute, interstitial nephritis,

Use In Pregnancy And Lactation:
Pregnancy:
There are no adequate data from the use of azithromycin in pregnant women. The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore Azithromycin should only be used during pregnancy if the benefit outweighs the risk.

Lactation:
Azithromycin is present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Zelinz and any potential adverse effects on the breastfed infant from Zelinz or from the underlying maternal condition.

Overdose:
Adverse reactions experienced at higher than recommended doses were similar to those seen at normal doses particularly nausea, diarrhea, and vomiting. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

Shelf Life
2 years.

Reconstitution Directions for Oral Suspension:
For reconstitution of 30ml suspension, add 20ml Biostatic water as diluent (available in the pack).
For reconstitution of 15ml suspension, add 10ml Biostatic water as diluent (available in the pack).

Storage and Instruction:
Protect from heat, sunlight & moisture. Store below 30°C.
Reconstituted Suspension used within 10 days. Discard any unused suspension.
The Expiration date refers to the product correctly stored at required condition.
Keep out of reach of the children
Patients and healthcare professionals can also report suspected adverse drug reaction at ade@linzpharma.com.
To be sold on prescription of a registered medical practitioner only.

Presentation:
Zelinz 250mg Tablets: Cold form cold seal Alu Alu pack of 6 tablets.
Zelinz 500mg Tablets: Cold form cold seal Alu Alu pack of 6 tablets.
Zelinz 250mg Capsules: Cold form cold seal Alu Alu pack of 6 Capsules.
Zelinz Suspension 100mg/5ml: Powder for oral suspension available in 30ml (after reconstitution) with 20ml biostatic water as diluent for suspension.
Zelinz Suspension 200mg/5ml: Powder for oral suspension available in 15ml (after reconstitution) with 10ml biostatic water as diluent for suspension.
Zelinz Suspension 200mg/5ml: Powder for oral suspension available in 30ml (after reconstitution) with 20ml biostatic water as diluent for suspension.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:۔

دھوپ، گرمی اور نمی سے محفوظ ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

تیار شدہ دوا ۱۰ دن کے اندر استعمال کرلیں۔ غیر استعمال شدہ دوا کو ضائع کر دیں۔

بچّوں کی پہنچ سے دُور رکھیں۔

صرف مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔

Suspension Manufactured by:
Bosch Pharmaceuticals (Pvt) Ltd.
221-223, Sector 23, Korangi Industrial Area, Karachi-Pakistan.
For LINZ Pharmaceuticals (Pvt) Ltd.
Plot # 31-G & 31-H Sector 15, K.I.A. Karachi, Pakistan.

Tablet & Capsule Manufactured by:
LINZ Pharmaceuticals (Pvt) Ltd.
Plot # 31-G & 31-H Sector 15, K.I.A. Karachi, Pakistan.