ZEZOT®

(Azithromycin)

Capsules / Suspension / Tablets

زیزوٹ

(ایزیتھرومائیسن)

کیپسولز / سسپینشن / ٹیبلیٹس

QUALITATIVE AND QUANTITATIVE COMPOSITION

Zezot 250mg Capsules

Each capsule contains:
Azithromycin USP 250mg
as Azithromycin dihydrate
(Product Specs.: BP)
"Product contains lactose"

Zezot 500mg Tablets

Each film coated tablet contains:
Azithromycin USP 500mg
as Azithromycin dihydrate
(Product Specs.: USP)

Zezot 200mg/5mL Suspension

Each 5mL contains:
Azithromycin USP 200mg
as Azithromycin dihydrate
(Product Specs.: USP)

PHARMACEUTICAL FORM

Powder for Oral Suspension, Capsules, Film Coated Tablets.

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS:

Zezot can be indicated for the treatment of the following infections.

- Acute bacterial sinusitis/ Acute bacterial otitis media (adequately diagnosed)
- Pharyngitis, tonsillitis,
- Acute exacerbation of chronic bronchitis (adequately diagnosed)
- Mild to moderately severe community acquired pneumonia
- Skin and soft tissue infections
- Uncomplicated *Chlamydia trachomatis* urethritis and cervicitis

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Zezot (capsules/ tablets/suspension) should be given as a single daily dose. In common with many other antibiotics, it should be taken at least 1 hour before or 2 hours after food.

Children over 45kg body weight and adults, including elderly patients

The total dose is 1500mg which should be given over three days (500mg once daily).

- In uncomplicated genital infections due to *Chlamydia trachomatis*, the dose is 1000mg as a single oral dose. For susceptible *Neisseria gonorrhoea* the recommended dose is 1000mg or 2000mg of azithromycin in combination with 250mg or 500mg ceftriaxone according to guidelines.

- For patients who are allergic to penicillin and/or cephalosporins, consult the treatment guidelines

- Capsules and Tablets are not suitable for children under 45kg.

Children and adolescents (< 18years)

The total dose in children aged 1 year and older is 30mg/kg administered as 10mg/kg once daily for three days, or over a period of five days starting with a single dose of 10mg/kg on the first day, followed by doses of 5mg/kg per day for the following 4days.

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10 - 80mL/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR < 10mL/min)

Hepatic impairment

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.

Reconstitution directions for Oral Suspension

Add a small quantity of pre-boiled cool water in the bottle and shake, after this add more water upto the mark given on the label and shake vigorously to make suspension which should be used within 10 days.

CONTRAINDICATIONS:

Hypersensitivity to the active substance, erythromycin, any macrolide or ketolide antibiotic, lactose.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Product contains Lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Hypersensitivity

If an allergic reaction occurs, the product should be discontinued and appropriate therapy should be instituted.

Hepatotoxicity
In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy. Azithromycin administration should be stopped immediately.

Infantile Hypertrophic Pyloric Stenosis (IHPS)
Following the use of azithromycin in neonates (treatment up to 42 days of life), Infantile Hypertrophic Pyloric Stenosis (IHPS) has been reported. Parents should be informed to contact their physician if vomiting or irritability with feeding occurs.

Pseudomembranous colitis
Pseudomembranous colitis has been reported with the use of macrolide antibiotics.

Ergot derivatives
Because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered.

Cross resistance
Concomitant use of several medicinal products from the same or related group of antibacterial agents is not recommended. e.g. erythromycin, clarithromycin, lincosamide.

Cardiovascular events
Azithromycin should be used with caution in patients with ongoing pro-arrhythmic conditions (especially women and elderly patients).

Clostridium difficile associated diarrhea (CDAD)
CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antimicrobial agents.

Myasthenia gravis
Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy

Paediatric population
Safety and efficacy for the prevention or treatment of *Mycobacterium avium* Complex in children have not been established.

The following should be considered before prescribing azithromycin:
Skin and soft tissue infections: *Staphylococcus aureus*, is frequently resistant to azithromycin. Therefore, susceptibility testing is considered.
Sexually transmitted disease: In case of sexually transmitted diseases a concomitant infection by *T. pallidum* should be excluded.
Neurological or psychiatric diseases: Azithromycin should be used with caution in patients with neurological or psychiatric disorders.
Superinfection: As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms, including fungi is recommended.
Renal impairment: In patients with severe renal impairment (GFR < 10mL/min) a 33% increase in systemic exposure to azithromycin was observed.

Interaction with other medicinal products and other forms of interaction
Effects of other medicinal products on azithromycin
Antacids: In patients receiving both azithromycin and antacids, it should not be taken simultaneously, but with an interval of about 2 hours.
Fluconazole: Total exposure and half-life of azithromycin were unchanged by the co-administration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed.
Terfenadine, Cimetidine & Nelfinavir: No clinically significant adverse effects were observed and no dose adjustment is required.

Effect of azithromycin on other medicinal products
Ergot derivatives: Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended
Digoxin and colchicine (P-gp substrates): Azithromycin and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.
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.
Cyclosporin: Caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.
Theophylline: As interactions of other macrolides with theophylline have been reported, alertness to signs that indicate a rise in theophylline levels is advised.
Zidovudine: Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.
Astemizole, alfentanil: Caution is advised in the co-administration of these medicines with azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolide antibiotic erythromycin.
Cisapride: Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsades de pointes.
Hydroxychloroquine: Azithromycin should be used with caution in patients receiving medicines known to prolong the QT interval with potential to induce cardiac arrhythmia,
Medicinal products known to prolong the QT interval: Azithromycin should not be used co-administered with other medicinal products, known to prolong the QT interval
Cetirizine: No significant changes in the QT interval.
Pharmacokinetics interaction with other medicines: In a pharmacokinetic interaction, no significant effect was observed on the plasma levels of Trimethoprim/sulfamethoxazole, Methylprednisolone, Sildenafil, Didanosine (Dideoxyinosine), Triazolam, Midazolam, Efaverinz and Indinavir or its active metabolite in patients receiving concomitant azithromycin.

FERTILITY, PREGNANCY AND LACTATION
Pregnancy
Azithromycin should only be used during pregnancy if the benefit outweighs the risk.

Lactation
Azithromycin is excreted in breast milk. A decision should be taken whether breastfeeding is discontinued or that treatment with azithromycin is discontinued/initiated or not, taking into account the benefit of breastfeeding for the child and the benefit of treatment for the woman.

Fertility
The relevance of this finding to humans is unknown.

Effects on ability to drive and use machines
There is no evidence to suggest that azithromycin may have an effect on a patient's ability to drive or operate machinery. Visual impairment and vision blurred may have an effect on a patient's ability to drive or operate machinery.

UNDESIRABLE EFFECTS:

Adverse reactions identified from post-marketing experience are included in italics. The frequency grouping is defined using the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known.

System organ class	Adverse reaction	Frequency
Infections and infestations	Candidiasis, oral candidiasis, vaginal infection	Uncommon
	Pseudomembranous colitis	Not known
Blood and lymphatic system disorders	Leukopenia, neutropenia	Uncommon
	Thrombocytopenia, haemolytic anaemia	Not known
Immune system disorders	Angioedema, hypersensitivity	Uncommon
	Anaphylactic reaction	Not known
Metabolism and nutrition disorders	Anorexia	Common
Psychiatric disorders	Nervousness	Uncommon
	Agitation	Rare
	Aggression, anxiety	Not known
Nervous system disorders	Dizziness, headache, paraesthesia, dysgeusia	Common
	Hypaesthesia, somnolence, insomnia	Uncommon
	Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis	Not known
Eye disorders	Visual impairment	Common
Ear and labyrinth disorders	Deafness	Common
	Hearing impaired, tinnitus	Uncommon
	Vertigo	Rare
Cardiac disorders	Palpitations	Uncommon
	Torsades de pointes arrhythmia including ventricular tachycardia	Not known
Vascular disorders	Hypotension	Not known
Gastrointestinal disorders	Diarrhoea, abdominal pain, nausea, flatulence	Very common
	Vomiting, dyspepsia	Common
	Gastritis, constipation	Uncommon
	Pancreatitis, tongue discolouration	Not known
Hepatobiliary disorders	Hepatitis	Uncommon
	Hepatic function abnormal	Rare
	Hepatic failure, hepatitis fulminant, hepatic necrosis, jaundice cholestatic	Not known
Skin and subcutaneous tissue disorders	Pruritus and rash	Common
	Stevens-Johnson syndrome (SJS), photosensitivity reaction, urticaria	Uncommon
	Acute Generalised Exanthematous Pustulosis (AGEP)	Rare
	Drug reaction with eosinophilia and systemic symptoms (DRESS)	Very Rare
	Toxic epidermal necrolysis (TEN), erythema multiforme	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Common
Renal and urinary disorders	Renal failure acute, nephritis interstitial	Not known
General disorders and administration site conditions	Pain and inflammation on the local injection site, fatigue	Common
	Chest pain, oedema, malaise, asthenia	Uncommon

OVERDOSE

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

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antibacterial for systemic use; macrolides; azithromycin,
ATC code: J01FA10

Mechanism of action

Azithromycin is an azalide, a sub-class of the macrolide antibiotics. By binding to the 50S-ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

Microbiology

Aerobic Gram-negative Microorganisms: *Haemophilus influenzae, Moraxella catarrhalis*
Other Microorganisms: *Chlamydophila pneumoniae, Chlamydia trachomatis, Legionella pneumophila, Mycobacterium avium, Mycoplasma pneumonia*
Species for which acquired resistance may be a problem.
Aerobic Gram-positive Microorganisms: *Staphylococcus aureus, Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus pyogenes* Other microorganisms *Ureaplasma urealyticum* Inherently resistant organisms.
Aerobic Gram-positive Microorganisms: *Staphylococcus aureus* – methicillin resistant and erythromycin resistant strains *Streptococcus pneumoniae* – penicillin resistant strains
Aerobic Gram-negative Microorganisms: *Escherichia coli, Pseudomonas aeruginosa, Klebsiella spp.*
Anaerobic Gram-negative Microorganisms: *Bacteroides fragilis*-group

Break Points:

Pathogens	Susceptible (mg/L)	Resistant (mg/L)
Staphylococcus spp.	≤ 1	> 2
Streptococcus spp. (Group A,B,C,G)	≤ 0.25	> 0.5
Streptococcus pneumoniae	≤ 0.25	> 0.5
Haemophilus influenzae	Note[2]	Note[2]
Moraxella catarrhalis	≤ 0.25	> 0.5
Neisseria gonorrhoeae	Note[3]	Note[3]

1. Erythromycin can be used to determine susceptibility to azithromycin.
2. Clinical evidence for the efficacy of macrolides in *H.influenzae* respiratory infections is conflicting due to high spontaneous cure rates.
3. Azithromycin is always used in conjunction with another effective agent

PHARMACOKINETIC PROPERTIES

Absorption

The biological availability of azithromycin after oral administration is approximately 37%. Peak plasma levels are achieved 2-3 hours after taking the medicinal product.

Distribution

After oral administration, azithromycin is distributed throughout the entire body. The protein binding of azithromycin in serum is variable and varies, depending on the serum concentration, from 52% at 0.05mg/L to 12% at 0.5mg/L. The steady state distribution volume is 31.1L/kg.

Elimination

The terminal plasma-elimination half-life closely follows the tissue depletion half-life from 2 to 4 days.

Pharmacokinetics in special populations:

Renal insufficiency

Following a single oral dose of azithromycin 1g mean Cmax and AUC_{0-120} increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80mL/min) compared with normal renal function (GFR >80mL/min).

Hepatic insufficiency

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

Elderly

The pharmacokinetics of azithromycin in elderly men was similar to that of young adults.

Paediatric Population

Pharmacokinetics have been studied in children aged 4 months – 15 years taking capsules, granules or suspension

PHARMACEUTICAL PARTICULARS

Incompatibilities

Not applicable.

Shelf life

Tablets and Suspension: 2 years
(Reconstituted powder for oral suspension: 10 days).
Capsules: 3 years

Nature and content of container/Presentation

Zezot 250mg Capsules: Alu Alu pack of 6 capsules.
Zezot 500mg Tablets: Alu Alu pack of 6 tablets.
Zezot 200mg/5mL Suspension: Powder for oral suspension available in 15mL (after reconstitution).
Zezot 200mg/5mL Suspension: Powder for oral suspension available in 30mL (after reconstitution).

Special precautions for storage and instructions

Suspension: Protect from heat, sunlight and moisture, store below 30°C.
Do not take if seal is broken.
Shake well before use. For oral use only.
Reconstituted suspension to be used within 10 days. Discard any unused suspension. Close the bottle properly after use.
Capsules & Tablets: Protect from heat, sunlight and moisture.
Store below 25°C.
The expiration date refers to the product correctly stored at the required condition.
Keep out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.

MARKETING AUTHORISATION HOLDER / REGISTRATION HOLDER
Head Office:
Bosch Pharmaceuticals (Pvt.) Ltd.,
8, Modern Society, Tipu Sultan Road, Karachi-Pakistan.

Manufacturer:
Bosch Pharmaceuticals (Pvt.) Ltd.
221-223, Sector 23, Korangi Industrial Area, Karachi-Pakistan.

REGISTRATION / MARKETING AUTHORIZATION NUMBER
Zezot 200mg/5mL Suspension: 027161
Zezot 250mg Capsules: 027162
Zezot 500mg Tablets: 067514

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Zezot 200mg/5mL Suspension: 24-07-2001 / 23-07-2021
Zezot 250mg Capsules: 24-07-2001 / 23-07-2021
Zezot 500mg Tablets: 05-04-2011 / 04-04-2021

DATE OF REVISION OF THE TEXT
05-03-2024

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

استعمال سے پہلے دوا کو اچھی طرح ہلا لیں۔ کھلی سیل والی بوتل نہ لیں۔

صرف پینے کیلئے استعمال کریں۔

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

استعمال کے بعد ڈھکن کو اچھی طرح بند رکھیں۔

کیپسولز اور ٹیبلیٹس:

دھوپ، گرمی اور نمی سے محفوظ ۲۵ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔

Manufactured by:
Bosch Pharmaceuticals (Pvt.) Ltd.
221-223, Sector 23, Korangi Industrial Area,
Karachi - Pakistan

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