FRONT SIDE

dose of 500 mg is approximately 0.4 µg/ml.
Distribution: Orally administered azithromycin is widely distributed throughout the body.
Concentrations of azithromycin measured in tissues are noticeably higher (up to 50 times the maximum observed concentration in plasma) than those measured in plasma. This indicates that the agent strongly binds to tissues (steady-state distribution volume approx. 31 l/kg).
Three days after administration of 500 mg as a single dose or in partial doses concentrations of 1,3-4,8 µg/g, 0,6-2,3 µg/g, 2,0-2,8 µg/g and 0-0,3 µg/ml have been measured in resp. lung, prostate, tonsil and serum. Binding of azithromycin to serum proteins is variable and varies from 52% at 0,05 mg/l to 18% at 0,5 mg/l, depending on the serum concentration.
Elimination: The terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days.

5.3 Preclinical safety data
In animal studies using exposures 40 times those achieved at the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule there were no associated toxicological consequences. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown.
Electrophysiological investigations have shown that azithromycin prolongs the QT interval.
Carcinogenic potential:
Long-term studies in animals have not been performed to evaluate carcinogenic potential.
Mutagenic potential:
There was no evidence of a potential for genetic and chromosome mutations in in-vivo and in-vitro test models.
Reproductive toxicity:
Teratogenic effects were not observed in rat reproductive toxicity studies. In rats, azithromycin dosages of 100 and 200 mg/kg body weight/ day led to mild retardation in foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats mild retardations in physical and reflex development were noted following treatment with 50 mg/kg/day azithromycin and above.

6 Pharmaceutical Particulars
6.1 List of excipients
Colloidal Anhydrous Silica
Maize Starch
Lactose Monohydrate
Sodium Starch Glycolate (Type A)
Povidone
MagnesiumStearate
Purified Talc
Croscarmellose Sodium
Opadry White

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
36 Months from the date of manufacture.

6.4. Special precautions for storage
Store at a temperature not exceeding 30°C, protect from moisture.
Keep out of the reach and sight of children.

6.5 Nature and contents of container
1 x 3 Tabletsin Alu-PVC Blister pack.

6.6 Specialprecautions for disposal and other handling
No special requirements.

7. Manufactured by :
ZIM LABORATORIES LIMITED
B-21/22, MIDC Area,
Kalmeshwar, Nagpur 441501,
Maharashtra State, India

8. Marketing Authorization Number(S)
NA

9. Date of First Authorization/Renewal of the Authorization
NA

10. Date of Revision of the Text
04 Jun. 2019

*PB367/X/XX/XX

Azithromycin Tablets USP 500 mg

ZITO-500

1. Name of the Finished Pharmaceutical Product
1.1 Trade Name : ZITO-500 (Azithromycin Tablets USP 500 mg)
1.2 Strength : 500 mg
1.3 Pharmaceutical Form : *Film coated Tablet*
2. Qualitative And Quantitative Composition
Each film coated tablet contains:
Azithromycin Dihydrate USP
Eq to Azithromycin 500 mg
'For full list of excipients, see section 6.1'.

3. Pharmaceutical Form
'Film coated Tablet
White, caplet shaped, film coated tablets having break line on one side and plain on other side.

4. Clinical Particulars
4.1 Therapeutic indications
Azithromycin is indicated for the following bacterial infections induced by micro-organisms susceptible to azithromycin:
Acute bacterial sinusitis (adequately diagnosed), Acute bacterial otitis media (adequately diagnosed), Pharyngitis, tonsillitis, Acute exacerbation of chronic bronchitis (adequately diagnosed), Mild to moderately severe community acquired pneumonia, Infections of the skin and soft tissues of mild to moderate severity e.g. folliculitis, cellulitis, erysipelas, Uncomplicated Chlamydia trachomatis urethritis and cervicitis
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Posology
Azithromycin should be given as a single daily dose. Duration of the treatment for the different infection diseases is given below.
Adults, children and adolescents with a body weight of 45 kg or over: The total dose is 1500 mg, administered as 500 mg once daily for 3 days. Alternatively, the same total dose (1500 mg) can be administered in a period of 5 days, 500 mg on the first day and 250 mg on day 2 to 5. In the case of uncomplicated *Chlamydia trachomatis* urethritis and cervicitis, the dosage is 1000 mg as a single oral dose.
Children and adolescents with a body weight below 45 kg: Azithromycin tablets are not suitable for patients under 45 kg body weight. Other dosage forms are available for this group of patients.
Elderly patients: 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 torsaces de pointes.

Method of administration
Oral Administration
Azithromycin can be taken with or without food. The tablets should be taken with ½ glass of water.

4.3 Contraindication
Hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipient used in formulation.

4.4 Special warnings and special precautions for use
As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.
If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.
Use of azithromycin should be undertaken with caution in patients with significant hepatic disease.
In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/ investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.
Theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered
Superinfections: As with any antibiotic preparation, it is recommended to pay attention to signs of superinfection with non-susceptible micro-organisms like fungi. A superinfection may require an interruption of the azithromycin treatment and initiation of adequate measures.
Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridium difficile*. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
Following situations may lead to an increased risk for ventricular

240 mm

140 mm

BACK SIDE

arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:

With congenital or documented acquired QT prolongation, Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin, With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia, With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

The following should be considered before prescribing azithromycin:

Azithromycin is not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed. The selection of azithromycin to treat an individual patient should take into account the appropriateness of using a macrolide antibacterial agent based on adequate diagnosis to ascertain the bacterial etiology of the infection in the approved indications and the prevalence of resistance to azithromycin or other macrolides.

In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other antibiotics.

In bacterial pharyngitis the use of azithromycin is recommended only in cases where first line therapy with beta-lactams is not possible.

Skin and soft tissue infections: The main causative agent of soft tissue infections, *Staphylococcus aureus*, is frequently resistant to azithromycin. Therefore, susceptibility testing is considered a precondition for treatment of soft tissue infections with azithromycin.

Infected burn wounds: Azithromycin is not indicated for the treatment of infected burn wounds.

Sexually transmitted disease: In case of sexually transmitted diseases a concomitant infection by *T. pallidium* should be excluded.

Neurological or psychiatric diseases: Azithromycin should be used with caution in patients with neurological or psychiatric disorders.

Contain Lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids: Azithromycin must be taken at least 1 hour before or 2 hours after antacids.

Digoxin (P-gp substrates): Possibility of elevated serum concentrations of the substrate should be considered while taking with Azithromycin.

Zidovudine: Administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

Ergotamine derivatives: the concurrent use of azithromycin with ergot derivatives is not recommended.

Astemizole, alfentanil: Because of the known enhancing effect of these medicines when used concurrently with the macrolid antibiotic erythromycin caution should be taken.

Cisapride: Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsades de pointes.

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: If coadministration 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.

4.6 Pregnancy and lactation

Pregnancy: Azithromycin should only be used during pregnancy if the benefit outweighs the risk.

Breast-feeding: Nursing should be discontinued during treatment with Azithromycin. Among other things diarrhoea, fungus infection of the mucous membrane as well as sensitisation is possible in the nursed infant. It is recommended to discard the milk during treatment and up until 2 days after discontinuation of treatment. Nursing may be resumed thereafter.

4.7 Effects on ability to drive and use machines

No data are available regarding the influence of azithromycin on a patient's ability to drive or operate machinery. However, the possibility of undesirable effects like dizziness and convulsions should be taken into account when performing these activities.

4.8 Undesirable effects

Like other medicine Azithromycin has also some undesirable effects. 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); and Not known (cannot be estimated from the available data).

Very Common: Diarrhoea, abdominal pain, nausea, flatulence

Common: Dizziness, headache, paraesthesia, dysgeusia, Visual impairment, Deafness, Vomiting, dyspepsia, Rash, pruritus, Arthralgia, Fatigue, Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased, basophils increased, monocytes increased, neutrophils increased.

Uncommon: Candidiasis, oral, candidiasis, vaginal infection, pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, respiratory disorder, rhinitis, Leukopenia, neutropenia, eosinophilia, Angioedema, hypersensitivity, Nervousness, insomnia, Hypoaesthesia, somnolence, Ear disorder, vertigo, hearing impaired, tinnitus, Palpitations, Hot flush, Dyspnoea, epistaxis, Gastritis, constipation, dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion, Hepatitis, Stevens-Johnson syndrome, photosensitivity reaction, urticaria, dermatitis, dry skin, hyperhidrosis, Osteoarthritis, myalgia, back pain, neck pain, Dysuria, renal pain, Metrorrhagia, testicular disorder, Chest pain, face oedema, pyrexia, peripheral pain, oedema, malaise, asthenia, Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal, blood alkaline phosphatase increased, chloride increased, glucose increased, platelets increased, hematocrit decreased, bicarbonate increased, abnormal sodium, Post procedural complications.

Rare: Agitation, depersonalisation, Hepatic function abnormal, jaundice cholestatic, Allergic reactions including angioneurotic oedema, Acute generalised exanthematous pustulosis (AGEP), Renal failure acute, nephritis interstitial.

Not known: Pseudomembranous colitis, Thrombocytopenia, haemolytic anaemia, Anaphylactic reaction, Aggression, anxiety, delirium, hallucination, Syncope, convulsion, psychomotor, hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis, arrhythmia including ventricular tachycardia, Hypotension, Pancreatitis, tongue and teeth discoloration.

4.9 Overdose

Symptoms: The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea.

Treatment: In the event of overdose, general symptomatic and supportive measures are indicated as required.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group :Antibacterials for systemic use, macrolides.

ATC code : J01FA10.

Azithromycin is a macrolide antibiotic belonging to the azalide group.

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.

Pharmacokinetic/pharmacodynamic relationship: For azithromycin the AUC/MIC is the major PK/PD parameter correlating best with the efficacy of azithromycin.

Mechanism of resistance: There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.

Complete cross resistance exists among *Streptococcus pneumoniae*, betahaemolytic streptococcus of group A, *Enterococcus faecalis* and *Staphylococcus aureus*, including methicillin resistant *S. aureus* (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

Breakpoints

	MIC breakpoint (mg/L)	
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	≤ 0.125	> 4
Moraxella catarrhalis	≤ 0.25	> 0.5
Neisseria gonorrhoeae	≤ 0.25	> 0.5

Susceptibility: **Commonly susceptible species.**

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*

5.2 Pharmacokinetic properties

Absorption: Bioavailability of azithromycin after oral administration is approximately 37%. Peak plasma concentrations are attained after 2-3 hours. The mean maximum concentration observed (Cmax) after a single

240 mm

140 mm