AZEE–500

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AZEE–500

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only OR for Specialist Use only (as applicable)

AZEE–500 (Azithromycin Tablets 500 mg)

Composition
Each film-coated tablet contains
Azithromycin (anhydrous)...500 mg
(As Azithromycin Dihydrate USP)
Colour: Titanium Dioxide

Dosage Form
Tablet

Product Description
White to off-white film coated capsule shaped biconvex tablets plain on one side and central breakline on the other.

Pharmacology
Pharmacodynamics
Azithromycin is an azalide, derived from the macrolide class of antibiotics. The mode of action of azithromycin is inhibition of protein synthesis in bacteria by binding to the 50s ribosomal subunit and preventing translocation of peptides. Azithromycin is usually bacteriostatic. However, in high concentrations, azithromycin may be bactericidal against selected microorganisms. Azithromycin is active against many Gram-positive and Gram-negative aerobic and anaerobic bacteria and bacterial pathogens such as *Mycobacterium avium* complex, *Mycoplasma* spp., *Borrelia burgdorferi, Chlamydia* spp. and *Campylobacter* spp. In addition, azithromycin has activity against protozoan microorganisms such as *Toxoplasma gondii*.

Breakpoints:
According to the NCCLS (National Committee on Clinical Laboratory Standards) in 2001 the following breakpoints have been defined for azithromycin:
- 2 µg/ml susceptible; 4 µg/ml intermediate; ≥8 µg/ml resistant
- *Haemophilus* spp.: ≤4 µg/ml susceptible
- *Streptococcus pneumoniae* and *Streptococcus pyogenes*: ≤0.5 µg/ml susceptible;
- 1 µg/ml intermediate; ≥2 µg/ml resistant

There are currently no recommended NCCLS breakpoints for Enterobacteriaceae, *Neisseria gonorrhoeae*, *Moraxella catarrhalis* and *Mycobacterium avium complex*.

Susceptibility:
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Species	Range of acquired resistance (%)
Commonly susceptible species	
Aerobic Gram-positive	
Corynebacterium diphteriae	-
Listeria spp.	-
Staphylococcus aureus Methicillin-susceptible	0-19
Coagulase-neg. staphylococci Methicillin-susceptible	-
Streptococcus pneumoniae Erythromycin-sensitive Penicillin-sensitive	5-37 - 3-23
Streptococcus pyogenes Erythromycin-sensitive	0-43 21
Streptococci viridans group	20-32
Aerobic Gram-negative	
Bordetella pertussis	-
Escherichia coli – ETEC	-
Escherichia coli – EAEC	-
Haemophilus influenzae	0-2
Haemophilus ducreyi	-
Legionella spp.	-
Moraxella catarrhalis Erythromycin-sensitive Erythromycin-intermediate	0-2 - -
Neisseria gonorrhoeae	0
Pasteurella multocida	-
Anaerobic	
Clostridium perfringens	-
Fusobacterium spp.	-
Prevotella spp.	-
Porphyromonas spp.	-
Propionibacterium spp.	-

Other microorganisms	
Borrelia burgdorferi	-
Chlamydia pneumoniae	-
Chlamydia trachomatis	-
Helicobacter pylori	-
Mycobacterium avium complex	-
Mycoplasma pneumoniae	-
Ureaplasma urelyticum	-
Species for which acquired resistance may be a problem	
Aerobic Gram-positive	
Streptococcus pneumoniae Penicillin-intermediate Penicillin-resistant Erythromycin-intermediate	 20-62 23-78 -
Streptococcus pyogenes Erythromycin-intermediate	 -
Streptococci viridans group Penicillin-intermediate	 -
Aerobic Gram-negative	
Moraxella catarrhalis Erythromycin-resistant	
Anaerobic	
Peptostreptococcus spp.	-
Inherently resistant organisms	
Aerobic Gram-positive	
Corynebacterium spp.	-
Enterococcus spp.	-
Staphylococci MRSA, MRSE	Resistant
Streptococcus pneumoniae Erythromycin-resistant Penicillin & Erythromycin resistant	 - -
Streptococcus pyogenes Erythromycin-resistant	 -
Streptococci viridans group Penicillin-resistant Erythromycin-resistant	 - -

Aerobic Gram-negative	
Pseudomonas aeruginosa	-
Anaerobic	
Bacteroides fragilis group	-

Other information:
The diagnostic procedures available in vitro at this moment to determine the susceptibility of *Mycobacterium avium complex* (MAC) organisms are not generally accepted and validated.
Streptococci and staphylococci that are resistant to erythromycin are also resistant to azithromycin. Cross-resistance to *Mycobacterium avium* complex organisms occurs between clarithromycin and azithromycin.

Pharmacokinetics
After oral administration the bioavailability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours (C_{max} after a single dose of 500 mg orally was approximately 0.4 mg/l).

Kinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the active substance is heavily tissue bound (steady state distribution volume of approximately 31 l/kg). Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC_{90} for likely pathogens after a single dose of 500 mg.

In experimental *in vitro* and *in vivo* studies azithromycin accumulates in the phagocytes, freeing is stimulated by active phagocytosis. In animal studies this process appeared to contribute to the accumulation of azithromycin in the tissue.

In serum the protein binding of azithromycin is variable and depending on the serum concentration varies from 50% in 0.05 mg/l to 12% in 0.5 mg/l.

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. About 12% of an intravenously administered dose is excreted in the urine unchanged over a period of 3 days; the majority in the first 24 hours. Biliary excretion of azithromycin, predominantly in unchanged form, is a major route of elimination.

The identified metabolites (formed by N- and O- demethylation, by hydroxylation of the desosamine and aglycone rings, and by the splitting of the cladinose conjugate) are microbiologically inactive.

After a 5 day treatment slightly higher (29%) AUC values were seen in the elderly volunteers (>65 years of age) compared to the younger volunteers (< 45 years of age). However these differences are not regarded as clinically relevant; therefore a dose adjustment is not recommended.

Pharmacokinetics in special populations

Renal insufficiency
Following a single oral dose of azithromycin 1 g, mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renal function (GFR> 80 ml/min). In subjects with severe renal impairment, the mean C_{max} and AUC_{0-120} increased 61% and 35% respectively compared to normal.

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. In these patients, urinary recovery of azithromycin appears to increase perhaps to compensate for reduced hepatic clearance.

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.

Infants, toddlers, children and adolescents
Pharmacokinetics have been studied 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 C_{max} achieved is slightly lower than adults with 224 ug/l in children aged 0.6-5 years and after 3 days dosing and 383 ug/l in those aged 6-15 years. The $t_{1/2}$ of 36 h in the older children was within the expected range for adults.

Indications
Azithromycin tablets can be applied in situations where micro-organisms sensitive to azithromycin have caused:
- Upper respiratory tract infections: sinusitis, pharyngitis, tonsillitis
- Acute otitis media
- Lower respiratory tract infections: acute bronchitis and mild to moderately severe community acquired pneumonia
- Skin and soft tissue infections
- Uncomplicated *Chlamydia trachomatis* urethritis and cervicitis

Considerations should be given to official guidance on the appropriate use of antibacterial agents.

Dosage and Method of Administration
Azithromycin tablets should be given as a single daily dose. The tablets may be taken with food.

Adults
In uncomplicated *Chlamydia trachomatis* urethritis and cervicitis the dosage is 1000 mg as a single oral dose.
For all other indications the dose is 1500 mg, to be administered as 500 mg per day for three consecutive days.
As an alternative the same total dose (1500 mg) can also be administered over a period of five days with 500 mg on the first day and 250 mg on the second to the fifth day.

Elderly patients
The same dose range as in younger patients may be used in the elderly.

Children
Azithromycin tablets should only be administered to children weighing more than 45 kg when normal adult dose should be used. For children under 45 kg other pharmaceutical forms of azithromycin, e.g. suspensions, may be used.

In patients with renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min) .

In patients with hepatic impairment
A dose adjustment is not necessary for patients with mild to moderately impaired liver function.

Contraindications
The use of azithromycin is contraindicated in patients with hypersensitivity to azithromycin, to other macrolide antibiotics, or to any of the excipients.

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SPECIAL INSTRUCTION: (FOR PACK INSERT)	1) THICKNESS OF FOLDED LEAFLET SHOULD BE 3 to 4 MM 2) PROOFLESS ARTWORK 3) Red colour will be given to Outline box of artwork (This is only for illustration and DON'T PRINT)

Warnings and precautions

Hypersensitivity
Rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.
In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARS) [e.g Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP)], AZEE-500 (Azithromycin Tablets 500mg) should be discontinued immediately and appropriate treatment should be urgently initiated.

Infections
Observations for signs of superinfection with non-susceptible organisms, including fungi is recommended.

Pseudomembranous colitis has been reported with the use of macrolide antibiotics. This diagnosis should therefore be considered in patients who get diarrhoea after starting the treatment with azithromycin. Should pseudomembranous colitis be induced by azithromycin, then anti-peristaltics should be contraindicated.

There is no experience regarding the safety and efficacy of the long-term application of azithromycin for the above mentioned indications. In case of quickly recurring infections, treatment with an other antibacterial agent should be considered.

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

Azithromycin is not the substance of first choice for the treatment of pharyngitis and tonsillitis caused by *Streptococcus pyogenes*. For this and for the prophylaxis of acute rheumatic fever penicillin is the treatment of first choice.

Use in renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10–80 ml/min). Caution is advised in patients with severe renal impairment (GFR < 10 ml/min) as systemic exposure may be increased.

Use in hepatic impairment
Since azithromycin is metabolised in the liver and excreted in the bile, the medicinal product should not be given to patients suffering from severe liver disease. No studies have been conducted regarding the treatment of such patients with azithromycin. When severe liver impairment occurs, the treatment with azithromycin should be ceased.

Neurological or Psychiatric Disorders
Azithromycin should be administered with caution to patients with neurological or psychiatric disorders.

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

Prolongation of the QT interval
Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including azithromycin. Prescribers 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 congenital or documented QT prolongation.
- Patients currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA and III, antipsychotic agents, antidepressants, and fluoroquinolones.
- Patients with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency.
- Elderly patients: Elderly patients may be more susceptible to drug-associated effects on the QT interval.

Infantile Hypertrophic Pyloric Stenosis (IHPS)
Infantile hypertrophic pyloric stenosis (IHPS) has been reported following the use of azithromycin in infants (treatment up to 42 days of life). Parents and caregivers should be informed to contact their physician if vomiting and / or irritability with feeding occurs.

Interaction with other Medicaments

Theophylline
Pharmacokinetic studies in healthy volunteers revealed no interaction between azithromycin and theophylline with concomitant administration. Since interactions of other macrolides with theophylline were reported, care should be taken of signs of increased theophylline levels.

Coumarin-type oral anticoagulants
An increased tendency towards haemorrhaging has been reported in connection with the concurrent use of azithromycin and warfarin or coumarin-like oral anticoagulants. Attention should be paid to the frequency of prothrombin time monitoring.

Carbamazepine
In a pharmacokinetic interaction study in healthy volunteers, no significant effect was seen in the pharmacokinetics of carbamazepine or its active metabolite.

Ergotamine derivatives
In patients treated with ergotamine derivatives ergotism can be induced by the concomitant administration of some macrolide antibiotics. There is no known data about the possibility of an interaction between ergotamine derivatives and azithromycin. Because of the theoretical possibility of ergotism azithromycin and ergotamine derivatives should not be combined.

Ciclosporin
Since pharmacokinetic and clinical studies on the possible combined effects of azithromycin and ciclosporin have not been carried out, the therapeutic situation should be carefully considered before these active substances are administered simultaneously. If combination treatment is considered justifiable, the ciclosporin levels should be carefully monitored and the dosage should be adjusted accordingly.

Digoxin
It is known that some macrolide antibiotics limit the metabolism of digoxin (in the gut). In patients treated concomitantly with azithromycin and digoxin the possibility of increased digoxin levels should be borne in mind, and digoxin levels monitored.

Antacids
In a pharmacokinetic study on the effect of concomitant administration of antacids and azithromycin, no effect on the total bio-availability was seen, although the peak serum levels were reduced by 30%. Azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

Trimethoprim/sulfamethoxazole
Coadministration of trimethoprim/sulfamethoxazole (160 mg/800 mg) for 7 days with azithromycin 1200 mg on day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.

Fluconazole
Coadministration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg Fluconazole. Total exposure and half-life of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed.

Zidovudine
Single administrations of 1000 mg of azithromycin and multiple administrations of 600 mg or 1200 mg azithromycin had no effect on the plasma pharmacokinetics or the renal excretion of zidovudine or its glucuronide metabolite. However, 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.

Terfenadine
Azithromycin has no effect on the pharmacokinetics of terfenadine administered every 12 hours in the recommended dosage of 60 mg. Measured in a steady state dosing of terfenadine, adding azithromycin did not result in a significant change in the cardiac repolarisation (QT interval).

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.

Didanosine
In comparison to placebo daily doses of 1200 mg azithromycin and didanosine did not seem to have an effect on the pharmacokinetics of didanosine in the 6 test subjects.

Rifabutin
Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either active substance. Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established.

Astemizol, triazolam, midazolam, alfentanil
There is no known data regarding interaction with astemizol, triazolam, midazolam or alfentanil. Caution is needed in the concomitant use of these medicinal products and azithromycin, as an increase of action with the concomitant use of the macrolide antibiotic erythromycin has been described.

Protease Inhibitors
Coadministration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Pregnancy and Lactation

Pregnancy
There are no adequate and well controlled studies in pregnant women. Animal reproduction studies show passage across the placenta. No teratogenic effects were observed in rat reproduction studies. 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 in life threatening cases during pregnancy.

Lactation
Azithromycin passes into breast milk. Because it is not known whether azithromycin may have adverse effects on the breast-fed infant, 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.

Side Effects

Infections and infestations:
Uncommon: Vaginitis
Rare: Candidiasis

Blood and the lymphatic system disorders:
Rare: Thrombocytopenia, haemolytic anaemia. Transient mild reductions in neutrophil counts have occasionally been observed in clinical trials for which a causal relationship with azithromycin treatment has not been confirmed.

Immune system disorders:
Rare: Anaphylaxis, including oedema (rarely fatal)

Metabolism and nutrition disorders:
Uncommon: Anorexia

Psychiatric disorders:
Rare: Aggressive reaction, agitation, anxiety, nervousness, depersonalisation, in elderly patients delirium may occur.

Nervous system disorders:
Uncommon: Dizziness/vertigo, convulsions, headache, somnolence, disturbances of smell and/or taste.
Rare: Paraesthesia, syncope, insomnia, hyperactivity.

Ear and labyrinth disorders:
Rare: Impaired hearing.
Impaired hearing including deafness and/or tinnitus has been reported after prolonged treatment at high doses in clinical trials. A majority of these cases has been reversible, of those that were possible to follow up.
Cardiac disorders:
Rare: Palpitations, arrhythmia (including ventricular tachycardia). There is a potential risk of QT prolongation and torsades de pointes, particularly in patients who are susceptible to these conditions.

Gastrointestinal disorders:
Common: Nausea, diarrhoea, abdominal discomfort (pain/cramps), vomiting.
Uncommon: Loose stools (as a result of infrequent dehydration), flatulence, dyspepsia.
Rare: Constipation, pseudomembranous colitis, pancreatitis, discolouration of the teeth, tongue discolouration.

Post-marketing Experience: Infantile hypertrophic pyloric stenosis

Hepato-biliary disorders:
Rare: Abnormal liver function test values, hepatitis, cholestatic jaundice, rare cases of hepatic necrosis and hepatic failure which have rarely resulted in death.

Skin and subcutaneous tissue disorders:
Uncommon: Rash, pruritus.
Rare: Angioneurotic oedema, urticaria, photosensitivity, erythema multiforme, Stevens-Johnson's syndrome, toxic epidermal necrolysis.
Frequency not known: severe cutaneous adverse reactions (SCARS) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP).

Musculoskeletal, connective tissue and bone disorders:
Uncommon: Arthralgia

Renal and urinary disorders:
Rare: Interstitial nephritis, acute renal failure.

General disorders:
Rare: Asthenia, fatigue, malaise.

Overdose
Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. Characteristic symptoms of an overdose of macrolide antibiotics were reversible hearing loss, severe nausea, vomiting and diarrhoea. In case of an overdose, lavage and general supporting measures are indicated.

Storage Conditions
Store below 30°C

Shelf life
36 months

Pack size
5 x Blister pack of 3 tablets each

Product Registration Holder in Malaysia
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Manufactured by
CIPLA LTD.
Plot No. S-103 to S-105, S-107 to S-112, L-138,
L-147, L-147/1 to L-147/3 & L-147/A
Verna Industrial Estate,
Verna, Goa, India

Date of Revision
May 2026

Cipla

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