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

AZEE–500 INJECTION I.V (Azithromycin for Injection USP 500mg)

COMPOSITION
Each vial contains:
Azithromycin USP (as dihydrate) equivalent to
Azithromycin (anhydrous) USP……500 mg
as sterile, freeze-dried powder for reconstitution with sterilized water for injection BP

Each mL of reconstituted injection contains:
Azithromycin USP (as dihydrate) equivalent to
Azithromycin (anhydrous) USP…….100mg

DESCRIPTION
Dry Powder: White to off white powder / cake
Diluent: Clear and colourless liquid.

Description of reconstituted solution:
On reconstitution gives clear colourless solution.

PHARMACOLOGY

Pharmacodynamics
Azithromycin acts by binding to the 50s ribosomal subunit of susceptible microorganisms and thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.
Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was >30 after one hour incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.
Azithromycin has been shown to be active against most isolates of the following microorgamisms, both *in vitro* and in clinical infections.

Aerobic and facultative gram-positive microorganisms
Staphylococcus aureus
Streptococcus pneumoniae
NOTE: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains. Most strains of Enterococcus faecalis and methicillin-resistant staphylococci are resistant to azithromycin.

Aerobic and facultative gram-negative microorganisms
Haemophilus influenzae
Morazella catarrhalis
Neisseria honorrhoeae

"Other" microorganisms
Chlamydia pneumoniae
Chlamydia trachomatis

Legionella pneumophila
Mycolasma hominis
Mycolasma pneumoniae

Beta-lactamase production should have no effect on azithromycin activity.
The following *in vitro* data are available, but their clinical significance is unknown.
At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoints for azithromycin. However, the safety and effectiveness of azithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic and facultative gram-positive microorganisms
Streptococci (Groups C,F,G)
Viridans group streptococci

Aerobic and facultative gram-negative microorganisms
Bordetella pertussis

Anaerobic microorganisms
Peptostreptococcus species
Prevotella bivia

"Other" microorganism
Ureaplasma urealyticum

Pharmacokinetics
After single intravenous infusions of 500mg at a concentration of 2mg/ml for one hour, Cmax was found to be 3.63 micrograms/mL and AUC24 was found to be 9.60 micrograms.h/mL.
Azithromycin is widely distributed throughout the body and concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues. Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following three days.

INDICATIONS
Azithromycin is indicated for the treatment of patients with infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Legionella pneumophila, Moraxella catarrhalis, Mycoplasma pneumoniae, Staphylococcus aureus*, or *Streptococcus pneumoniae* in patients who require initial intravenous therapy.

Pelvic inflammatory disease due to *Chlamydia trachomatis, Neisseria gonorrhoeae*, or *Mycoplasma hominis* in patients who require initial intravenous therapy. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial agent with anaerobic activity should be administered in combination with azithromycin. Azithromycin injection should be followed by azithromycin by the oral route as required.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative microorganism and its susceptibility to azithromycin. Therapy with azithromycin may

be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of azithromycin and other antibacterial drugs, Azithromycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

DOSAGE AND METHOD OF ADMINISTRATION

The recommended dose of azithromycin for injection for the treatment of adult patients with community-acquired pneumonia due to the indicated organisms is:
500 mg as a single daily dose by the intravenous route for at least two days. Intravenous therapy should be followed by azithromycin by the oral route at a single, daily dose of 500 mg, administered as two 250 mg tablets to complete a 7- to 10-day course of therapy. The timing of the switch to oral therapy should be done at the discretion of the physician and in accordance with clinical response. The recommended dose of azithromycin for the treatment of adult patients with pelvic inflammatory disease due to the indicated organisms is: 500 mg as a single daily dose by the intravenous route for one or two days. Intravenous therapy should be followed by azithromycin by the oral route at a single, daily dose of 250 mg to complete a 7-day course of therapy. The timing of the switch to oral therapy should be done at the discretion of the physician and in accordance with clinical response. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial agent with anaerobic activity should be administered in combination with azithromycin.

Renal Insufficiency

No dosage adjustment is recommended for subjects with renal impairment (GFR≤80 mL/min). 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 have not been established. No dose adjustment recommendations can be made in patients with impaired hepatic function.

The infusate concentration and rate of infusion for azithromycin should be either 1 mg/mL over 3 hours or 2 mg/mL over 1 hour.

Note:

Azithromycin should not be given as a bolus or as an intramuscular injection. Other intravenous substances, additives, or medications should not be added to azithromycin or infused simultaneously through the same intravenous line.

Reconstitution

Prepare the initial solution of azithromycin for injection by adding 4.8 mL of Sterile Water for Injection to the 500 mg vial and shaking the vial until all of the drug is dissolved. Since azithromycin for injection is supplied under vacuum, it is recommended that a standard 5 mL (non-automated) syringe be used to ensure that the exact amount of 4.8 mL of Sterile Water is

dispensed. Each mL of reconstituted solution contains 100 mg azithromycin. Reconstituted solution is stable for 24 hours when stored below 30°C (86°F).

Parenteral drug products should be inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the drug solution should be discarded.

Dilute this solution further prior to administration as instructed below.

Dilution
To provide azithromycin over a concentration range of 1-2 mg/mL, transfer 5 mL of the 100 mg/mL azithromycin solution into the appropriate amount of any of the diluents listed below:

Normal Saline (0.9% sodium chloride)
1/2 Normal Saline (0.45% sodium chloride)

Final Infusion Solution Concentration (mg/mL)	Amount of Diluent (mL)
1 mg/mL	500 mL
2 mg/mL	250 mL

Other intravenous substances, additives, or medications should not be added to azithromycin for injection or infused simultaneously through the same intravenous line.

CONTRAINDICATIONS
Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, or any macrolide antibiotics.

INCOMPATIBILITIES
Not applicable

WARNINGS AND PRECAUTIONS
Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy. Although rare, fatalities have been reported. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

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) & acute generalized exanthematous pustulosis (AGEP)], Azithromycin should be discontinued immediately and appropriate treatment should be urgently initiated. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

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.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of 'antibiotic-associated colitis.'

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. 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.

Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. Due to the limited data in subjects with GFR <10 mL/min, caution should be exercised when prescribing azithromycin in these patients.

Azithromycin should be reconstituted and diluted as directed and administered as an intravenous infusion over not less than 60 minutes.

Local I.V. site reactions have been reported with the intravenous administration of azithromycin. The incidence and severity of these reactions were the same when 500 mg azithromycin were given over 1 hour (2 mg/mL as 250 mL infusion) or over 3 hours (1 mg/mL as 500 mL infusion). All volunteers who received infusate concentrations above 2 mg/mL experienced local I.V. site reactions and, therefore, higher concentrations should be avoided.

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, 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 hypokalemia and hypomagnesemia
- Patients with clinically relevant bradycardia, cardiac arrhythmia or cardia insufficiency.
- Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval.

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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.

Prescribing azithromycin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

INTERACTIONS WITH OTHER MEDICAMENTS

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 side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted.

Azithromycin given by the oral route did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

Drug interaction studies were performed with azithromycin and other drugs likely to be co-administered. When used in therapeutic doses, azithromycin had a modest effect on the pharmacokinetics of atorvastatin, carbamazepine, cetirizine, didanosine, efavirenz, fluconazole, indinavir, midazolam, rifabutin, sildenafil, theophylline (intravenous and oral), triazolam, trimethoprim/sulfamethoxazole or zidovudine. Co-administration with efavirenz or fluconazole had a modest effect on the pharmacokinetics of azithromycin. No dosage adjustment of either drug is recommended when azithromycin is co-administered with any of these agents.

Interactions with the drugs listed below have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products. Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised:
Digoxin - elevated digoxin concentrations.
Ergotamine or dihydroergotamine - acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.
Terfenadine, cyclosporine, hexobarbital and phenytoin - elevated concentrations.

PREGNANCY AND LACTATION

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.
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 women.

SIDE EFFECTS

The majority of side-effects are gastrointestinal in origin with anorexia, nausea, abdominal discomfort (pain/cramps), flatulence, vomiting and diarrhoea less frequently resulting in dehydration, dyspepsia, constipation and loose stools.

Local inflammation/pain at the infusion site has been reported with intravenous administration of azithromycin.

There have been reports of hearing impairment including hearing loss, deafness and or tinnitus in some patients receiving azithromycin.
Interstitial nephritis and acute renal failure have been reported.
Cases of abnormal liver function including hepatitis and cholestatic jaundice have been reported.
Reductions in neutrophil counts have occasionally been observed.

The following side-effects have occurred: Chest pain, malaena, nephritis, vaginitis, headache, vertigo, dizziness, convulsions, somnolence and fatigue.
There have been rare reports of taste disturbances.

Asthenia and paraesthesiae have been reported although a causal relationship may not have been established.

Skin and Subcutaneous Tissue Disorders:
Allergic reactions including arthralgia, oedema, urticaria, rash, photosensitivity, angioedema and anaphylaxis (less frequently fatal) have occurred.

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) & acute generalized exanthematous pustulosis (AGEP).

Postmarketing Experience:
Cardiac Disorders: Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongation and torsades de pointes (see Warnings and Precautions).

Gastrointestinal Disorders: Infantile hypertrophic pyloric stenosis.

OVERDOSE

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. The typical symptoms of an overdose of macrolide antibiotics include reversible hearing loss, severe nausea, vomiting and diarrhoea. In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and supporting measures are indicated as required.

STORAGE CONDITIONS

Dry Powder: Store below 30°C in dry form.
Reconstituted solution: Store below 30°C

SHELF LIFE

Shelf Life for Dry Powder: 36 months
Shelf Life after Reconstitution: Use within 24 hours after reconstitution.

Shelf Life and Storage After Dilution:

When diluted according to the instructions (1 mg/mL to 2 mg/mL), azithromycin for injection is stable for 24 hours at or below room temperature 30ºC (86ºF) or for 7 days if stored under refrigeration 5ºC (41ºF)

PRESENTATION
Unit pack having 10 mL glass vial of azithromycin for injection USP 500mg and FFS vial of sterilized water for injection of fill values 5 mL each.

REGISTRATION HOLDER IN MALAYSIA
Cipla Malaysia Sdn Bhd
Suite 1101, Amcorp Tower,
Amcorp Trade Centre,
18 Persiaran Barat, 46050
Petaling Jaya, Selangor,
Malaysia.

AZEE-500 INJECTION
Mfd. By
Cipla Ltd.
Verna Industrial Estate,
Goa 403722 India.

Sterilised Water For Injection
Mfd. By
Aculife Healthcare Pvt. Ltd,
Village-Sachana
Tal. Viramgam,
Dist. Ahmedabad-382150

DATE OF REVISION
May 2021