PROFESSIONAL INFORMATION

CIPLA AZITHROMYCIN 500 INJ

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CIPLA AZITHROMYCIN 500 INJ, 500 mg powder for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CIPLA AZITHROMYCIN 500 INJ vial contains 500 mg of azithromycin (as the dihydrate), providing 100 mg/mL solution following reconstitution.

Other ingredients include citric acid monohydrate and 3N sodium hydroxide.

Sugar free.

For full list of excipients, **see section 6.1**

3. PHARMACEUTICAL FORM

CIPLA AZITHROMYCIN 500 INJ is a white to off-white powder or cake. The reconstituted solution is clear and colourless, visually free of undissolved matter and essentially free from particles of foreign matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CIPLA AZITHROMYCIN 500 INJ is indicated in the following:

Adults:

CIPLA AZITHROMYCIN 500 INJ is indicated for the treatment of community acquired pneumonia caused by susceptible organisms, including *Legionella pneumophila*, in patients who require initial intravenous therapy.

Children:

The safety and efficacy of CIPLA AZITHROMYCIN 500 INJ for the treatment of infections in children have not been established.

4.2 Posology and method of administration

Posology

The recommended dose of CIPLA AZITHROMYCIN 500 INJ for the treatment of adult patients with community acquired pneumonia requiring hospitalisation 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 as a single daily dose of 500 mg to complete a 7-day to 10-day course of therapy. The timing of the conversion to oral therapy should be done at the discretion of the physician and in accordance with clinical response.

Use in elderly:

No dosage adjustment is necessary in elderly patients requiring azithromycin

therapy.

Use in children:

The safety and effectiveness of CIPLA AZITHROMYCIN 500 INJ for the treatment of infections in children have not been established.

Method of administration

CIPLA AZITHROMYCIN 500 INJ after reconstitution and dilution is for administration by intravenous infusion. CIPLA AZITHROMYCIN 500 INJ should not be given as a bolus or as an intramuscular injection.

The infusate concentration and rate of infusion for CIPLA AZITHROMYCIN 500 INJ powder for solution for infusion should be either 1 mg/mL over 3 hours or 2 mg/mL over 1 hour.

Preparation of the solution for intravenous administration is as follows:

Reconstitution:

Prepare the initial solution of CIPLA AZITHROMYCIN 500 INJ powder for solution for infusion by adding 4,8 mL of sterilised Water for Injections to the 500 mg vial and shaking the vial until all of the agent is dissolved. It is recommended that a standard 5 mL (non-automated) syringe be used to ensure that the exact amount of 4,8 mL of sterilised Water for Injections is dispensed.

Each mL of reconstituted solution contains 100 mg azithromycin.

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

Dilute this solution further prior to administration as instructed below.

Dilution:

To provide azithromycin over a concentration range of 1,0 to 2,0 mg/mL, transfer 5 mL of the 100 mg/mL azithromycin solution into the appropriate amount of any of the diluents listed below.

Final Infusion Solution Concentration (mg/mL)	Amount of Diluent (mL)
1,0 mg/mL	500 mL
2,0 mg/mL	250 mL

The reconstituted solution can be diluted with:

0,9 % sodium chloride

0,45 % sodium chloride

5 % Dextrose in Water

Lactated Ringer's Solution

5 % Dextrose in 0,45 % sodium chloride with 20 mmol/l KCl

5 % Dextrose in Lactated Ringer's Solution

5 % Dextrose in 0,3 % sodium chloride

5 % Dextrose in 0,45 % sodium chloride

It is recommended that a 500 mg dose of CIPLA AZITHROMYCIN 500 INJ powder for solution for infusion, diluted as above, be infused over a period of not less than 60 minutes.

CIPLA AZITHROMYCIN 500 INJ reconstituted solution may be diluted using the instructions and compatible infusion solutions provided above. Other intravenous substances, additives or medications should not be added to CIPLA AZITHROMYCIN 500 INJ, or infused simultaneously through the same intravenous line.

4.3 Contraindications

CIPLA AZITHROMYCIN 500 INJ is contraindicated in the following:

- Patients with a known hypersensitivity to azithromycin, erythromycin or any of the macrolide or ketolide antibiotics.
- CIPLA AZITHROMYCIN 500 INJ and ergot derivatives should not be co-administered, due to the theoretical possibility of ergotism.
- **Use in hepatic impairment:**
    - As the liver is the principal route of excretion of CIPLA AZITHROMYCIN 500 INJ, it should not be prescribed in patients with hepatic disease.
- Children.

4.4 Special warnings and precautions for use

Less frequently serious allergic reactions, including angioneurotic oedema and anaphylaxis, dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), toxic epidermal necrolysis, Stevens Johnson syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with CIPLA AZITHROMYCIN 500 INJ 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.

Since the liver is the principal route of elimination for CIPLA AZITHROMYCIN 500 INJ, it should be used with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with CIPLA AZITHROMYCIN 500 INJ. In cases 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 should be performed immediately. CIPLA AZITHROMYCIN 500 INJ should be stopped if liver dysfunction has emerged.

In patients receiving ergotamine derivatives, ergotism has been precipitated by co-administration of some macrolide antibiotics. There are data concerning the possibility of an interaction between ergot and azithromycin. However, because of the theoretical possibility of ergotism, CIPLA AZITHROMYCIN 500 INJ and ergot derivatives should not be co-administered.

Pseudomembranous colitis has been reported and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients with diarrhoea subsequent to administration of CIPLA AZITHROMYCIN 500 INJ.

Observation for signs of super-infection with non-susceptible organisms, including fungi, is recommended. Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrythmia and torsade de pointes, have been seen in treatment with other macrolides. A similar effect cannot be completely ruled out in patients at risk for prolonged repolarisation.

Use in renal impairment:

A 33 % increase in systemic exposure to azithromycin was observed in patients with severe renal impairment (GFR < 10 mL/min).

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

AZITHROMYCIN 500 INJ.

Use in children:

The safety and efficacy of CIPLA AZITHROMYCIN 500 INJ for the treatment of infections in children has not been established.

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

CIPLA AZITHROMYCIN 500 INJ is only to be prescribed at the recommended dose and the medicine is to be used as directed only for registered indications.

4.5 Interaction with other medicines and other forms of interaction

Ergot derivatives:

Because of the theoretical possibility of ergotism, CIPLA AZITHROMYCIN 500 INJ and ergot derivatives should not be co-administered.

Special administration advised with the following:

Cimetidine:

A single dose of cimetidine administered 2 hours before CIPLA AZITHROMYCIN 500 INJ had no effect on the pharmacokinetics of azithromycin.

No significant interactions reported with the following:

Carbamazepine:

CIPLA AZITHROMYCIN 500 INJ has no significant effect on the plasma levels of carbamazepine or its active metabolite.

Methylprednisolone:

CIPLA AZITHROMYCIN 500 INJ has no significant effect on the pharmacokinetics of methylprednisolone.

Theophylline:

There is no evidence of any pharmacokinetic interaction when CIPLA AZITHROMYCIN 500 INJ and theophylline are co-administered to healthy volunteers.

Zidovudine:

No significant effect on the pharmacokinetic parameters of zidovudine and its glucuronide metabolite was found.

Special precautionary monitoring is advised with the following:

Cyclosporin:

Some of the related macrolide antibiotics interfere with the metabolism of cyclosporin. In the absence of pharmacokinetic studies or clinical data

investigating potential interaction between CIPLA AZITHROMYCIN 500 INJ and cyclosporin, caution should be exercised before co-administration of these two medicines. If co-administration is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Digoxin:

Some of the macrolide antibiotics have been reported to impair the metabolism of digoxin (in the gut) in some patients. Therefore, in patients receiving concomitant CIPLA AZITHROMYCIN 500 INJ, a related azalide antibiotic, and digoxin the possibility of raised digoxin levels should be borne in mind.

Warfarin:

CIPLA AZITHROMYCIN 500 INJ does not alter the anticoagulant effect of a single 15 mg dose of warfarin administered to healthy volunteers. CIPLA AZITHROMYCIN 500 INJ and warfarin may be co-administered but monitoring of the prothrombin time should be continued as routinely performed.

Terfenadine:

There are less frequent reports of an interaction in patients receiving CIPLA AZITHROMYCIN 500 INJ and terfenadine.

Medicines metabolised by the cytochrome P450 enzyme system (e.g. alprazolam, quinidine, sildenafil, simvastatin, tacrolimus, triazolam,

vinblastine, phenytoin and valproate):

CIPLA-AZITHROMYCIN 500 INJ may increase serum levels of these medicines. Serum concentrations of these medicines may require monitoring.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety and efficacy of CIPLA AZITHROMYCIN 500 INJ in pregnancy have not been established.

Breastfeeding

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 CIPLA AZITHROMYCIN 500 INJ. 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.

Fertility

Effect on fertility has not been established.

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that CIPLA AZITHROMYCIN 500 INJ may

have an effect on a patient's ability to drive or operate machines.

4.8 Undesirable effects

The following undesirable effects may occur with the use of CIPLA AZITHROMYCIN 500 INJ:

Infections and infestations:

Less frequent: Vaginitis, moniliasis, candidiasis.

Frequency unknown: Pseudomembranous colitis.

Blood and lymphatic system disorders:

Less frequent: Neutropenia, thrombocytopenia, leukopenia.

Frequency unknown: Haemolytic anaemia.

Immune system disorders:

Less frequent: Anaphylaxis, angiodema, hypersensitivity.

Metabolism and nutrition disorders:

Frequent: Anorexia.

Psychiatric disorders:

Less frequent: Nervousness, aggressive reaction, agitation, anxiety.

Nervous system disorders:

Frequent:	Dizziness, headache, paraesthesia, dysgeusia.
Less frequent:	Somnolence, taste perversion, hyperactivity, syncope.
Frequency unknown:	Convulsion, psychomotor hyperactivity, ageusia, parosmia, myasthenia gravis.

Eye disorders:

Frequent:	Visual impairment.

Ear and labyrinth disorders:

Less frequent:	There have been reports of hearing impairment including hearing loss, deafness and/or tinnitus, vertigo.

Cardiac disorders:

Less frequent:	Chest pain, palpitations, arrhythmias, including ventricular tachycardia, QT prolongation, torsade de pointes.

Vascular disorders:

Less frequent:	Hypotension.

Gastrointestinal disorders:

Frequent: Abdominal discomfort, diarrhoea, nausea, dyspepsia, vomiting, flatulence.

Less frequent: Constipation, loose stools, pseudomembranous colitis, tongue discolouration, melaena, pancreatitis.

Hepatobiliary disorders:

Frequent: Cases of abnormal liver function. including hepatitis and cholestatic jaundice have been reported.

Less frequent: Hepatitis, cholestatic jaundice, hepatic necrosis and hepatic failure which have rarely resulted in death.

Skin and subcutaneous tissue disorders:

Less frequent: Pruritis, rash, oedema, urticaria, allergic reactions, angiodema, photosensitivity, serious skin reactions including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis, acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) have occurred.

Musculoskeletal and connective tissue disorders:

Less frequent: Arthralgia.

Renal and urinary disorders:

Less frequent: Interstitial nephritis and acute renal failure have been reported.

General disorders and administrative site conditions:

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

Less frequent: Asthenia, fatigue, malaise, chest pain.

Investigations:

Frequent: Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased.

Less frequent: Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal.

Frequency unknown: Electrocardiogram QT prolonged.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is

important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. Side effects may also be reported directly to Cipla Medpro (Pty) Ltd: drugsafetysa@cipla.com.

4.9 Overdose

There are no data on overdosage. Typical symptoms of overdosage with macrolide antibiotics include hearing loss, severe nausea, vomiting and diarrhoea. General supportive measures are indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.20.1.1 Broad and medium spectrum antibiotics.

Azithromycin is a macrolide antibiotic belonging to the azalide group. The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50s sub-unit and inhibition of peptide translocation.

Azithromycin demonstrates activity *in vitro* against a wide range of Gram-positive and Gram-negative bacteria.

Azithromycin also demonstrates *in vitro* activity against *Mycoplasma pneumoniae* and *Treponema pallidum*. *In vitro* sensitivity does not necessarily imply *in vivo* efficacy.

Inherently resistant organs include aerobic Gram-positive micro-organisms, such as *Enterococcus faecalis* and staphylococci (MRSA, MRSE), as well as anaerobic micro-organisms belonging to the *Bacteroides fragilis* group.

5.2 Pharmacokinetic properties

Azithromycin is widely distributed throughout the body, following administration in humans; bioavailability is approximately 37 %. The time taken to peak plasma levels is 2 to 3 hours. Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days.

Kinetic studies of variable times ranging from hours to days following administration, may show markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma), indicating that the medicine is highly tissue bound. Concentrations in target tissues such as lung, tonsil and prostate exceed the MIC90 for likely pathogens after a single dose of 500 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Citric acid monohydrate
- 3N Sodium hydroxide.

6.2 Incompatibilities

CIPLA AZITHROMYCIN 500 INJ must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3 Shelf life

24 months.

The reconstituted solution is stable for 24 hours when stored below 30 °C.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep vial in original packaging until use.

Discard any unused portion thereafter.

6.5 Nature and contents of container

CIPLA AZITHROMYCIN 500 INJ: CIPLA AZITHROMYCIN 500 INJ is packaged in a single use 10 mL tubular transparent flint glass vial and closed with a bromobutyl grey colour rubber stopper and aluminium flip-off tear-off

seal. The 10 mL vial is packed into a white back board carton.

6.6 Special precautions for disposal and other handling

For instructions on preparation and mixing of the powder for solution for infusion, see section 4.2.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9,

Parc du Cap

Mispel Street,

Bellville

7530

Customer care: 080 222 6662

8. REGISTRATION NUMBER

43/20.1.1/0612

9. DATE OF FIRST AUTHORISATION

05 August 2011

10. DATE OF REVISION OF THE TEXT

12 March 2021

Zitro 500 Injection:

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