APPROVED PROFESSIONAL INFORMATION FOR

CIPLA AZITHROMYCIN 500 TABLETS

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

CIPLA AZITHROMYCIN 500 (Tablets)

COMPOSITION:

CIPLA AZITHROMYCIN 500 (Tablets): Each tablet contains azithromycin dihydrate equivalent to 500 mg azithromycin.

Other ingredients are croscarmellose sodium, dicalcium phosphate, magnesium stearate, povidone, sodium lauryl sulphate, starch and Opadry white (containing, Hypromellose 15cP, polyethylene glycol 6000 and titanium dioxide)

PHARMACOLOGICAL CLASSIFICATION:

A.20.1.1 Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Azithromycin is a macrolide antibiotic. It exerts its antibacterial action by binding reversibly to the 50S ribosomal subunit of the 70S ribosome of sensitive micro-organisms, thereby

inhibiting bacterial RNA-dependent protein synthesis.

Azithromycin demonstrates activity *in vitro* against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus*; *Streptococcus pneumoniae*, *Streptococcus pyogenes* (Group A); *Haemophilus influenzae*; *Moraxella catarrhalis*; *Legionella pneumophila*, *Bordetella pertussis*; *Borrelia burgdorferi*; *Haemophilus ducreyi*; and *Chlamydia trachomatis*.

Azithromycin also demonstrates *in vitro* activity against *Mycoplasma pneumoniae* and *Treponema pallidum*.

In vitro sensitivity does not necessarily imply *in vivo* efficacy.

Pharmacokinetics:

Azithromycin is widely distributed throughout the body, following oral administration in humans; bioavailability is approximately 37 %. No significant decrease in bioavailability has been observed when azithromycin tablets were administered with a meal. The time taken to peak plasma levels is 2 – 3 hours. Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days.

INDICATIONS:

CIPLA AZITHROMYCIN 500 is indicated in the following:

Adults:

- **CIPLA AZITHROMYCIN 500** tablets are indicated for mild to moderate infections

caused by susceptible organisms: in lower respiratory tract infections including bronchitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* or *Staphylococcus aureus* and pneumonia due to *Streptococcus pneumoniae* or *Haemophilus influenzae*; uncomplicated skin and soft tissue infections due to *Staphylococcus aureus*; sinusitis due to *Haemophilus influenzae*, *Streptococcus pneumoniae* or *Staphylococcus aureus* and as an alternative to first line therapy of pharyngitis/tonsillitis.

- **CIPLA AZITHROMYCIN 500** tablets are indicated in the treatment of uncomplicated genital infections due to *Chlamydia trachomatis* and/or non-multiresistant *Neisseria gonorrhoea.* It is also indicated in the treatment of chancroid due to *Haemophilus ducreyi.*

Children: ≥ 45 kg

- **CIPLA AZITHROMYCIN 500** tablets are indicated for pharyngitis/tonsillitis and otitis media caused by susceptible organisms in children over 45 kg (see **"DOSAGE AND DIRECTIONS FOR USE"**).

This formulation is not suitable for children below 45 kg.

CONTRAINDICATIONS:

CIPLA AZITHROMYCIN 500 is contraindicated in the following:

- Patients with a known hypersensitivity to azithromycin, erythromycin or any of the macrolide antibiotics, and to any of the other ingredients in this formulation.
- **CIPLA AZITHROMYCIN 500** and ergot derivatives should not be co-administered,

due to the possibility of ergotism (see **WARNINGS and SPECIAL PRECAUTIONS** and **INTERACTIONS**)

- The treatment of infected burn wounds.

Use in hepatic impairment:

- As the liver is the principal route of excretion of **CIPLA AZITHROMYCIN 500**, it should not be prescribed in patients with hepatic disease (see **WARNINGS and SPECIAL PRECAUTIONS)**.

WARNINGS and SPECIAL PRECAUTIONS:

Rare serious allergic reactions, including angioneurotic oedema and anaphylaxis, dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), toxic epidermal necrolysis (TEN), Stevens Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with **CIPLA AZITHROMYCIN 500** have resulted in recurrent symptoms and required a longer period of observation and treatment.

If an allergic reaction occurs, treatment should be discontinued, and appropriate symptomatic therapy initiated. The allergic symptoms may reappear when the symptomatic therapy is stopped.

Since the liver is the principal route of elimination of **CIPLA AZITHROMYCIN 500**, the use in patients with hepatic disease is not advised (see **CONTRAINDICATIONS)**. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported

(see **SIDE EFFECTS**). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

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. Treatment should be stopped if liver dysfunction has emerged.

In patients receiving ergot derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergotamine derivatives and **CIPLA AZITHROMYCIN 500**. However, because of the theoretical possibility of ergotism, **CIPLA AZITHROMYCIN 500** and ergot derivatives should not be administered concurrently (see **INTERACTIONS**).

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**. Observation for signs of superinfection with non-susceptible organisms, including fungi, is recommended.

Use in renal impairment:

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

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsade de pointes, have been observed in treatment with other macrolides, including that of azithromycin. Caution should be taken in patients who:

- have congenital or documented acquired QT prolongation
- is currently receiving treatment with other active substances known to prolong QT interval
- exhibit electrolyte disturbances especially in cases of hypokaleamia and hypomagnesaemia
- have clinically relevant bradycardia, cardiac arrythmia or severe cardiac insufficiency

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving **CIPLA AZITHROMYCIN 500** (see **SIDE EFFECTS**).

Use in children under 1 year of age:

The safety and efficacy of oral **CIPLA AZITHROMYCIN 500** preparations in children less than 1 year have not been established.

The following should be considered before prescribing azithromycin:

The off-label use of **CIPLA AZITHROMYCIN 500** for the prevention of bronchiolitis obliterans syndrome in patients who received haematopoietic stem cell transplantation for a prolonged period is not recommended. An increased rate of relapses in haematological malignancies were observed. Therefore, prescribers are advised to

prescribe **CIPLA AZITHROMYCIN 500** at the recommended doses, and use the medicine as directed and only for its registered indications.

CIPLA AZITHROMYCIN 500 is not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.

As for other macrolides, high resistance rates of *Streptococcus pneumoniae* have been reported. This should be considered when treating infections caused by *Streptococcus pneumoniae*.

In bacterial pharyngitis the use of **CIPLA AZITHROMYCIN 500** is recommended only in cases where first line therapy with beta-lactams is not possible.

Susceptibility testing is recommended when **CIPLA AZITHROMYCIN 500** is used for the treatment of skin and soft tissue infections caused by *Staphylococcus aureus*.

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

CIPLA AZITHROMYCIN 500 should be used with caution in patients with neurological or psychiatric disorders.

Use of **CIPLA AZITHROMYCIN 500** may cause an overgrowth of non-susceptible

organisms. Appropriate measures should be taken to prevent or treat such superinfection.

Effects on ability to drive and use machines:

No data are available regarding the influence of **CIPLA AZITHROMYCIN 500** 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.

INTERACTIONS:

Ergot derivatives:

Because of the possibility of ergotism, characterised by severe peripheral vasospasm and dysaesthesia, **CIPLA AZITHROMYCIN 500** and ergot derivatives should not be co-administered.

Antacids:

In patients receiving **CIPLA AZITHROMYCIN 500** tablets and antacids, **CIPLA AZITHROMYCIN 500** tablets should be taken at least 1 hour before or 2 hours after the antacid.

It was observed that the pharmacokinetics of **CIPLA AZITHROMYCIN 500** is not affected by the administration of a single dose of cimetidine administered 2 hours prior to **CIPLA AZITHROMYCIN 500**.

CIPLA AZITHROMYCIN 500 may increase serum levels of the following: alfentanil, alprazolam, astemizole, cyclosporine, disopyramide, midazolam, omeprazole, quinidine, sildenafil, simvastatin, tacrolimus, triazolam, vinblastine, phenytoin and valproate: **CIPLA AZITHROMYCIN 500** may increase serum levels of these medicines. Serum concentrations of these medicines may require monitoring.

Atorvastatin:

Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on an HMG CoA-reductase-inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

Carbamazepine:

In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

Cetirizine:

In healthy volunteers, coadministration of a 5-day regimen of azithromycin with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the 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.

Didanosins (Dideoxyinosine):

Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

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.

Coadministration of azithromycin and the following medicines yielded no clinically significant pharmacokinetic interactions:
Efavirenz, indinavir and methylprednisolone.

Nelfinavir:

Coadministration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant

adverse effects were observed, and no dose adjustment is required.

Rifabutin:

Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either drug. 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.

Terfenadine:

Pharmacokinetic studies have reported no evidence of an interaction between azithromycin and terfenadine. There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however, there was no specific evidence that such an interaction had occurred.

Trimethoprim/sulfamethoxazole:

Coadministration of trimethoprim/sulfamethoxazole DS (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.

Zidovudine:

Single 1000 mg doses and multiple doses of 600 mg or 1200 mg azithromycin had little effect on the plasma pharmacokinetics or urinary 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.

Theophylline:

The area under the plasma concentration-time curve may be increased. Monitoring of theophylline serum concentration is recommended.

Digoxin:

Serum digoxin concentrations may be increased. Monitoring of digoxin serum concentrations is recommended.

Warfarin:

Prothrombin time should be monitored.

HUMAN REPRODUCTION:

Use during pregnancy and lactation:

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

DOSAGE AND DIRECTIONS FOR USE:

CIPLA AZITHROMYCIN 500 should be administered orally as a single daily dose with or

without food.

Adults: For all indications other than sexually transmitted diseases, the total dose is 1,5 g which should be given as 500 mg daily for 3 days or 500 mg on day 1 and then 250 mg daily on days 2 – 5. For sexually transmitted diseases caused by *Chlamydia trachomatis* or *Haemophilus ducreyi* the dose is 1 g given as a single dose.

For uncomplicated genital infections caused by non-multiresistant *N.gonorrhoea*, the dose is 1 g given as a single oral dose.

Use in the elderly:

Normal adult dosage is recommended.

Use in children:

Children over 45 kg – dose as per adults.

This formulation is not suitable for children under 45 kg.

SIDE EFFECTS:

The following side effects may occur with the use of **CIPLA AZITHROMYCIN 500:**

Infections and infestations:

Less frequent: Vaginitis, moniliasis, candidiasis, oral candidiasis, vaginal infection, pneumonia, fungal infection, bacterial infection,

pharyngitis, gastroenteritis, respiratory disorder, rhinitis.

Frequency unknown: Pseudomembranous colitis.

Blood and lymphatic system disorders:

Less frequent: Reductions in neutrophil counts have occasionally been observed, thrombocytopenia, leukopenia, eosinophilia.

Frequency unknown: Haemolytic anaemia.

Immune system disorders:

Less frequent: Angioedema and hypersensitivity.

Frequency unknown: Anaphylactic reaction.

Psychiatric disorders:

Less frequent: Agitation, depersonalisation, nervousness, insomnia.

Frequency unknown: Aggression, anxiety, delirium, hallucination.

Nervous system disorders:

Less frequent: Headache, vertigo, dizziness, convulsions, somnolence and fatigue, asthenia, taste perversion, hyperactivity, syncope and paraesthesia.

Frequency unknown: Parosmia, anosmia, myasthenia gravis.

Eye disorders:

Frequent: Visual impairment.

Ear and labyrinth disorders:

Frequent: Deafness.

Less frequent: There have been reports of hearing impairment including hearing loss, vertigo, and tinnitus in some patients receiving **CIPLA AZITHROMYCIN 500**.

Cardiac disorders:

Less frequent: Chest pain, palpitations.

Frequency unknown: Torsades de pointes, arrhythmia including ventricular tachycardia, electrodiogram QT prolongation.

Vascular disorders:

Less frequent: Hot flush

Frequency unknown: Hypotension.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Dyspnoea, epistaxis.

Gastrointestinal disorders:

Frequent: Anorexia, nausea, abdominal discomfort (pain /cramps), flatulence, vomiting and diarrhoea.

Less frequent: Dehydration, dyspepsia, constipation and loose stools, taste disturbances, melaena, pseudomembranous colitis (abdominal cramps or pain, tenderness, severe, watery diarrhoea which may also be bloody, and fever), gastritis, dysphagia, dry mouth, eructation, mouth ulceration, salivary hypersecretion.

Frequency unknown: Tongue and teeth discoloration, pancreatitis.

Hepatobiliary disorders:

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

Frequency unknown: Hepatic failure (which has rarely resulted in death), hepatitis fulminant, hepatic necrosis.

Skin and subcutaneous tissue disorders:

Frequent: Rash, pruritus.

Less frequent: Stevens-Johnson syndrome, photosensitivity reaction, allergic reactions including angioneurotic oedema, urticaria, dermatitis, dry skin, hyperhidrosis, acute generalised exanthematous pustulosis (AGEP).

Frequency unknown: Drug reaction with eosinophilia and systemic symptoms (DRESS), serious skin reactions including erythema multiforme, and toxic epidermal necrolysis have occurred.

Musculoskeletal and connective tissue disorders:

Frequent: Arthralgia.

Less frequent: Osteoarthritis, myalgia, back pain, neck pain.

Renal and urinary disorders:

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

Reproductive system and breast disorders:

Less frequent: Metrorrhagia, testicular disorder.

General disorders and administrative site conditions:

Frequent: Fatigue.

Less frequent: Allergic reactions including arthralgia, face oedema, pyrexia, peripheral pain, malaise, asthenia-oedema, urticaria, rash, photosensitivity, angioedema and anaphylaxis have occurred.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Typical symptoms of overdosage with macrolide antibiotics include hearing loss, severe nausea, vomiting and diarrhoea. Gastric lavage and general supportive measures are

indicated.

IDENTIFICATION:

CIPLA AZITHROMYCIN 500: White to off-white, film-coated, capsule-shaped, biconvex tablets plain on one side and central breakline on the other.

PRESENTATION:

CIPLA AZITHROMYCIN 500: Aluminium foil blister strip containing 3 tablets packed in a carton.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

Keep the blister in the outer container until required for use.

STORE THIS MEDICINE OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

42/20.1.1/0506

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

CIPLA MEDPRO (PTY) LTD

Building 9

Parc du Cap

Mispel Street

Bellville

7530

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION:

First published: 05 August 2011

Reviewed: 14 February 2020