SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE:

CEPTOMAX 200 mg/5 mL powder for oral suspension.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 5 ml contains:

Azithromycin dihydrate 209.6 mg equivalent to 200.00 mg azithromycin

Contains sugar: sucrose 3,69 g

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

3. PHARMACEUTICAL FORM:

Powder for oral suspension.

White coloured, cherry scented, fluid, homogeneous granules free from particles which constitutes white or off-white suspension after reconstitution with water.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

Adults and children over 45 kg:

CEPTOMAX is indicated for mild to moderate infections caused by susceptible organisms.

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

Paediatric population

Children: 1 year and over (under 45 kg)

CEPTOMAX is indicated for:

- pharyngitis/tonsillitis and
- otitis media caused by susceptible organisms.

4.2 Posology and method of administration

Usual dose:

Paediatric population

Use in children: 1 year and older

The total dose in children is 30 mg/kg which should be given as a single daily dose of 10 mg/kg for 3 days according to the following guidance:

Weight	**Dose and duration**
< 15 kg	10 mg/kg once daily on days 1 - 3
15 – 25 kg	200 mg (5 mL) once daily on days 1 - 3
26 – 35 kg	300 mg (7,5 mL) once daily on days 1 - 3
36 – 45 kg	400 mg (10 mL) once daily on days 1 - 3
> 45 kg	500 mg once daily (12,5 mL) only if patient is unable to swallow tablets.

Reconstituting instructions for CEPTOMAX 200 mg/5 mL powder for oral suspension for 15 mL and 30 mL bottles:

The table below indicates the volume of water to be used for constitution:

Total deliverable volume (azithromycin content)	**Amount of water to be added**	**Azithromycin concentration after reconstitution**
15 mL (600 mg)	7,5 mL	200 mg/5 mL
30 mL (1200 mg)	15 mL	200 mg/5 mL

Method of administration

Shake well before each use, the oversized bottle provides shake space**.**

CEPTOMAX suspension should be administered to children using the 5 ml oral

dosing syringe or the spoon provided. **CEPTOMAX** suspension can be taken with food.

4.3 Contraindications

CEPTOMAX is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients listed in section 6.1 (see also section 4.4)

Because of the theoretical possibility of ergotism, **CEPTOMAX** and ergot derivatives should not be co-administered.

4.4 Special warnings and precautions for use

Hypersensitivity

Azithromycin as contained in **CEPTOMAX** may cause serious allergic reactions, including angioedema and anaphylaxis, dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). Some of these reactions with azithromycin as contained in **CEPTOMAX** have resulted in recurrent symptoms and required a longer period of observation and treatment.

If an allergic reaction occurs, **CEPTOMAX** should be discontinued, and appropriate therapy should be instituted. Medical practitioner should be

aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Hepatic function

Since liver is the principal route of elimination for azithromycin, the use of **CEPTOMAX** should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (see section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicines.

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. **CEPTOMAX** administration should be stopped if liver dysfunction has emerged.

Ergot derivatives

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 ergot and azithromycin. However, because of the theoretical possibility of ergotism, **CEPTOMAX** and ergot derivatives should not be coadministered (see section 4.3).

Superinfection

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

Pseudomembranous colitis

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 **CEPTOMAX**.

Clostridium difficile associated diarrhoea (CDAD)

Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial medicines alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial medicines.

Renal impairment

In patients with severe renal impairment (GFR <10 mL/min) a 33 % increase in systemic exposure to azithromycin was observed (see Section 5.2).

Cardiovascular Events

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac dysrhythmia and torsades de pointes, in treatment with macrolides including azithromycin (see section 4.8) has been reported. Therefore as the following situations may lead to an increased risk for ventricular dysrhythmia (including torsade de pointes) which can lead to cardiac arrest, **CEPTOMAX** should be used with caution in patients with ongoing pro dysrhythmic conditions (especially women and elderly patients) such as patients:

• With congenital or documented QT prolongation

• Currently receiving treatment with other active substances known to prolong QT interval such as anti-dysrhythmics of class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), cisapride and terfenadine; antipsychotic medicines such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin

• With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia

• With clinically relevant bradycardia, cardiac dysrhythmia or severe cardiac insufficiency

A short-term risk of dysrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including azithromycin has been identified therefore, consideration of these findings should be balanced with treatment benefits when prescribing **CEPTOMAX**.

Myasthenia gravis

There has been exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome in patients receiving azithromycin therapy (see section 4.8).

Safety and efficacy for the prevention or treatment of *Mycobacterium avium* complex in children have not been established.

Paediatric population

The safety and efficacy of **CEPTOMAX** in children less than 1 year have not been established.

CEPTOMAX contains sucrose

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take **CEPTOMAX.**

4.5 Interaction with other medicines and other forms of interaction

Antacids

In patients receiving both **CEPTOMAX** and antacids, the medicines should not be taken simultaneously, as it may cause a decrease in concentration of **CEPTOMAX**. **CEPTOMAX** should be taken at least 1 hour before or 2 hours after the antacid.

Digoxin and colchicine (P-gp substrates)

Concomitant administration of macrolide antibiotics, including **CEPTOMAX**, with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if **CEPTOMAX** and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.

Ergot

Due to the theoretical possibility of ergotism, the concurrent use of **CEPTOMAX** with ergot derivatives is not recommended (see Section 4.3 and 4.4).

*Pharmacokinetic studies have been conducted between **CEPTOMAX** and the following* medicines *known to undergo significant cytochrome P450 mediated metabolism.*

Atorvastatin

Co-administration of atorvastatin (10 mg daily) and **CEPTOMAX** (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-

reductase inhibition assay). However, there has been cases of rhabdomyolysis in patients receiving **CEPTOMAX**.

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 dysrhythmias and torsades de pointes.

Coumarin-Type Oral Anticoagulants (Warfarin)

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15 mg dose of warfarin administered to healthy patients. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to co-administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when **CEPTOMAX** is used in patients receiving coumarin-type oral anticoagulants.

Ciclosporin

In a pharmacokinetic study with healthy patients that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of ciclosporin, the resulting ciclosporin C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these medicines. If co-

administration of these medicines is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

Fluconazole

Co-administration 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 co-administration of fluconazole, however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed.

Zidovudine

Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin, as contained in **CEPTOMAX** 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.

Substances that prolong the QT interval

CEPTOMAX should not be used concomitantly with other active substances that prolong the QT interval (see section 4.4).

4.6 Fertility, pregnancy, and lactation

The safety and efficacy of CEPTOMAX in pregnancy and lactation have not been established.

Pregnancy

In reproduction toxicity studies in animals, azithromycin was shown to pass the placenta, but no teratogenic effects were observed. **CEPTOMAX** should only be used during pregnancy if clearly needed.

Breastfeeding

Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in breastfeeding women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk.

CEPTOMAX should only be used in lactating women where adequate alternatives are not available.

Fertility

In fertility studies conducted in rat, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

4.7 Effects on the ability to drive and use machines

CEPTOMAX may cause dizziness which may influence the ability to drive and use machines. Patients should not drive or operate machines until they know how **CEPTOMAX** affects them. Visual impairment and blurred vision may have an effect on a patient's ability to drive or operate machinery (section 4.8)

4.8 Undesirable effects

	Frequent	**Less frequent**	**Frequency unknown**
Infections and Infestations		Candidiasis, vaginal infection, pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, respiratory disorder, rhinitis, oral candidiasis	Pseudomembranous colitis (see section 4.4)
Blood and Lymphatic System Disorders		Leukopenia, neutropenia, eosinophilia	Thrombocytopenia, haemolytic anaemia

Immune System Disorders		Angioedema, hypersensitivity	Anaphylactic reaction (see section 4.4)
Metabolism and Nutrition Disorders		Anorexia	
Psychiatric Disorders		Nervousness, insomnia, agitation	Aggression, anxiety, delirium, hallucination
Nervous System Disorders	Headache	Dizziness, somnolence dysgeusia, paraesthesia	Syncope, convulsion, hypoesthesia, psychomotor hyperactivity anosmia, ageusia, parosmia, myasthenia gravis (see section 4.4)
Eye Disorders			Visual impairment, blurred vision

Ear and Labyrinth Disorders		Ear disorder, vertigo	Hearing impairment including deafness and/or tinnitus
Cardiac Disorders		Palpitations	Torsades de pointes, (see section 4.4) dysrhythmia (see section 4.4) including ventricular tachycardia, electrocardiogram QT prolonged (see section 4.4)
Vascular Disorders		Hot flush	Hypotension
Respiratory, thoracic and mediastinal disorders		Dyspnoea, epistaxis	
Gastrointestinal Disorders	Diarrhoea, vomiting, abdominal pain, nausea	Constipation, flatulence, dyspepsia, gastritis	Pancreatitis, tongue discolouration

		dysphagia abdominal distension, dry mouth, eructation, mouth ulceration salivary hypersecretion	
Hepatobiliary Disorders		Hepatic function abnormal, jaundice cholestatic	Hepatic failure (see section 4.4), hepatitis fulminant, hepatic necrosis,
Skin and Subcutaneous Tissue Disorders		Rash, pruritus, urticaria, dermatitis, dry skin, hyperhidrosis, photosensitivity reaction, Acute Generalised Exanthematous Pustulosis (AGEP)	Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme

Musculoskeletal and Connective Tissue Disorders		Osteoarthritis, myalgia, back pain, neck pain	Arthralgia
Renal and Urinary Disorders		Dysuria, renal pain	Renal failure acute, nephritis interstitial
Reproductive system and breast disorders		Metrorrhagia, testicular disorder	
General Disorders and Administration Site Conditions	*Injection site pain, injection site inflammation	Oedema, asthenia, malaise, fatigue, face oedema, chest pain, pyrexia, pain, peripheral oedema,	
Investigations	Lymphocyte count decreased,	Aspartate aminotransferase increased,	

	eosinophil count increased, blood bicarbonate decreased, basophils increased, monocytes increased, neutrophils 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	

Injury and poisoning		Post procedural complication	

Reporting side effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of 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://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use. ATC code: J01FA10

Mode of action

Azithromycin is an azalide, a subclass of the macrolide antibiotics. Chemically it is derived by insertion of a nitrogen atom into the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza9a-methyl-9a-homoerythromycin A. The molecular weight is 749,0. Azithromycin binds to the 23S rRNA of the 50S ribosomal subunit. It blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

Cardiac electrophysiology

QTc interval-prolongation was studied in a randomised, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1 000 mg) alone or in combination with azithromycin (500 mg, 1 000 mg, and 1 500 mg once daily). Co-administration of azithromycin significantly increased the QTc interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95 % upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1 000 mg and 1 500 mg azithromycin, respectively.

Efflux pumps occur in a number of bacteria, including Gram-negatives, such as Haemophilus influenzae (where they may determine intrinsically higher MICs) and staphylococci. In streptococci and enterococci, an efflux pump that recognises 14- and 15-membered macrolides (which include, respectively, erythromycin and azithromycin) is encoded by mef(A) genes.

Mechanism of resistance

Azithromycin demonstrates cross-resistance with erythromycin-resistant Gram-positive organisms. Ribosomal modifications determine cross-resistance with other classes of antibiotics whose ribosomal binding sites overlap that of the macrolides: the lincosamides (including clindamycin), and the streptogramins B (which include, for example, the quinupristin component of quinupristin/dalfopristin). A decrease in macrolide susceptibility over time has been noted in particular in Streptococcus pneumoniae and Staphylococcus aureus, and has also been observed in Viridans streptococci and in Streptococcus agalactiae.

Azithromycin has in vitro activity against:

• Aerobic and facultative Gram-positive bacteria (erythromycin-susceptible organisms)

• Aerobic and facultative Gram-negative bacteria

In vitro resistance to azithromycin:

Azithromycin-resistant organisms are encountered relatively frequently among aerobic and facultative gram-positive bacteria, in particular among methicillin-resistant Staphylococcus aureus (MRSA) and penicillin-resistant Streptococcus pneumoniae (PRSP). Pseudomonas spp. and most Enterobacteriaceae are inherently resistant to azithromycin, although azithromycin has been used to treat Salmonella enterica, Pneumocystis

jirovecii and Toxoplasma gondii infections. In vitro sensitivity does not necessarily imply in vivo efficacy.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration in humans, azithromycin is widely distributed throughout the body; bioavailability is approximately 37 %. No significant decrease in bioavailability was observed when azithromycin was administered with a meal. The time taken to peak plasma levels is 2 to 3 hours.

Distribution:

Kinetic studies of variable times ranging from hours to days after oral intake have shown 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.

Elimination:

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. Biliary excretion of azithromycin is a major route of elimination for unchanged medicine following oral administration. Very high concentrations of unchanged medicine have been found in human bile, together with 10 metabolites, formed by N- and O-demethylation, by

hydroxylation of the desosamine and aglycone rings, and by cleavage of the cladinose conjugate. Comparison of HPLC and microbiological assays in tissues suggests that metabolites play no part in the microbiological activity of azithromycin.

Pharmacokinetics in special patient groups:

Renal impairment:

The pharmacokinetics of azithromycin in adult patients with mild-to-moderate renal impairment (GFR 10 – 80 ml/min) were not affected following a single 1 g dose of immediate release azithromycin. Statistically significant differences in AUC0-120 (8,8 mg x hr/ml vs. 11,7 mg x hr/ml), Cmax (1,0 mg/ml vs. 1,6 mg/ml) and CLr (2,3 mL/min/kg vs. 0,2 ml/min/kg) were observed between the group with severe renal impairment (GFR < 10 ml/min) and the group with normal renal function.

Hepatic impairment:

In patients with mild (Class A) to moderate (Class B) hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. The urinary clearance of azithromycin appears to increase in these patients, perhaps to compensate for reduced hepatic clearance. Azithromycin has not been studied and should not be used in patients with severe hepatic impairment.

Elderly:

Elderly volunteers (> 65 years) had slightly higher AUC values than in young volunteers (< 40 years) after a 5-day regimen, but these are not considered clinically significant, and hence no dose adjustment is recommended

6. Pharmaceutical particulars

6.1 List of excipients

Banana flavor, cherry flavor, hydroxypropyl cellulose, sodium benzoate, sodium phosphate tribasic- anhydrous, sucrose, xanthan gum.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Before reconstitution: 24 months

After reconstitution: 5 days

6.4 Special precautions for storage

Before reconstitution: Store at or below 30°C in its original container.

After reconstitution: Store at or below 30°C in its original container.

6.5 Nature and contents of container

Dry powder mixture is filled in a natural HDPE bottle closed with a polypropylene cap and a white coloured induction foil, enclosed in a cardboard box containing a patient information leaflet, a dose graduated syringe (5 mL), a two-sided plastic spoon (2.5 – 5 mL), and a 15 mL polypropylene measuring cup.

6.6 Special precautions for disposal and other handling

No special requirements

7. Holder of certificate of registration

Innovata Pharmaceuticals

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Johannesburg

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South Africa

8. Registration numbers

A 55/20.1.1/0733

9. Date of first authorization/Renewal of the authorization

01/11/2022

10. Date of revision of the text

14/07/2025