**SCHEDULING STATUS:**

S4

## 1. NAME OF THE MEDICINE

**ZINOXIME 250 mg,** film-coated tablets

**ZINOXIME 500 mg,** film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZINOXIME 250 mg: Each film-coated tablet contains cefuroxime axetil (amorphous) equivalent to cefuroxime 250 mg.

ZINOXIME 500 mg: Each film-coated tablet contains cefuroxime axetil (amorphous) equivalent to cefuroxime 500 mg.

Sugar free.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

ZINOXIME 250 mg: White to off-white, film-coated, capsule shaped tablets with ‘A33’ debossed on one side and plain on the other side.

ZINOXIME 500 mg: White to off-white, film-coated, capsule shaped tablets with ‘A34’ debossed on one side and plain on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ZINOXIME is indicated for the treatment of infections caused by susceptible strains of the following organisms in the following infections:

- Pharyngitis and tonsillitis caused by *Streptococcus pyogenes*. Penicillin is the usual medicine of choice in the treatment and prevention of streptococcal infections including the prophylaxis of rheumatic fever. ZINOXIME is generally effective in the eradication of streptococci from the oral pharynx. ZINOXIME is not indicated for the prophylaxis of subsequent rheumatic fever due to insufficient data available to support such use.
- Otitis media caused by *Streptococcus pneumoniae, Haemophilus influenzae* (methicillin-sensitive strains), *Moraxella* (*Branhamella*) *catarrhalis* and *Streptococcus pyogenes*.
- Sinusitis caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*.
- Bronchitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (methicillin-sensitive strains) and *Haemophilus parainfluenzae* (ampicillin-sensitive strains).
- Acute uncomplicated cystitis caused by *Escherichia coli* and *Klebsiella pneumoniae*.
- Lyme disease caused by *Borrelia burgdorferi*. ZINOXIME is indicated for the treatment of early Lyme disease and subsequent prevention of late Lyme disease in adults and children over the age of 12 years.

## 4.2 Posology and method of administration

**Posology**

**Adults**

***Pharyngitis and tonsillitis***

250 mg twice daily for seven days (range 5 –10 days).

***Otitis media***

500 mg twice daily for seven days (range 5 –10 days).

***Sinusitis and bronchitis***

250 mg twice daily for seven days (range 5 –10 days).

***Acute, uncomplicated cystitis***

250 mg twice daily for seven days (range 5 –10 days).

***Lyme disease***

Adults and children over 12 years of age: 500 mg twice daily for 14 days (range 10 – 21 days).

**Children**

The usual dose is 125 mg twice daily for 7 days (range 5 – 10 days). A cefuroxime suspension available on the market should be prescribed for this age group.

There is no experience with ZINOXIME in children under 3 months of age.

***Pharyngitis and tonsillitis***

10 mg/kg twice daily to a maximum of 125 mg twice daily for seven days (range 5 –10 days).

***Otitis media***

In children 3 months to 2 years of age the usual dose is: 10 mg/kg twice daily to a maximum of 125 mg twice daily (range 5 –10 days).

In children over 2 years of age the usual dose is: 15 mg/kg twice daily to a maximum of 250 mg twice daily for seven days (range 5 – 10 days).

***Sinusitis and bronchitis***

The dose is 10 mg/kg twice daily to a maximum of 125 mg twice daily for seven days (range 5 –10 days).

***Acute, uncomplicated cystitis***

The dose is 15 mg/kg twice daily to a maximum of 250 mg twice daily for seven days (range 5 –10 days).

**Method of administration**

Oral use.

Due to the bitter taste of cefuroxime, the tablets should not be crushed.

ZINOXIME should be taken half an hour after food for optimum absorption.

## 4.3 Contraindications

- Hypersensitivity to cephalosporin antibiotics, cefuroxime or to any of the excipients listed in section 6.1.
- Hypersensitivity to penicillin and other beta-lactam antibiotics.

## 4.4 Special warnings and precautions for use

ZINOXIME should be used with caution in patients with:

- A history of gastrointestinal disease, especially ulcerative colitis, regional enteritis or pseudomembranous colitis.
- Renal function impairment – a reduced dose may be required.
- Porphyria – as safety has not been established.

**Hypersensitivity reactions**

Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta lactam antibiotics because there is a risk of cross-sensitivity. As with all beta-lactam antibacterial medicines, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefuroxime (as in ZINOXIME) must be discontinued immediately and adequate emergency measures must be initiated.

Before commencing treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to cefuroxime, to other cephalosporins or to any other type of beta-lactam medicine. Caution should be used if cefuroxime is given to patients with a history of non-severe hypersensitivity to other beta-lactam medicines.

**Jarisch-Herxheimer reaction**

The Jarisch-Herxheimer reaction has been seen following cefuroxime (as in ZINOXIME) treatment of Lyme disease. It results directly from the bactericidal activity of cefuroxime (as in ZINOXIME) on the causative bacteria of Lyme disease, the spirochaete *Borrelia burgdorferi*. Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease (see section 4.8).

**Overgrowth of non-susceptible microorganisms**

Use of cefuroxime (as in ZINOXIME) may result in the overgrowth of Candida. Prolonged use may also result in the overgrowth of other non-susceptible microorganisms (e.g. Candida, enterococci and *Clostridium difficile*), which may require interruption of treatment (see section 4.8).

Pseudomembranous colitis may occur, which may range in severity from mild to life threatening. Patients who develop abdominal or stomach cramps, abdominal tenderness, severe and watery diarrhoea (which may be bloody) and fever subsequent to the administration of cefuroxime (as in ZINOXIME), should be investigated for this diagnosis.

Discontinuation of therapy with ZINOXIME and the administration of specific treatment for *Clostridium difficile* should be considered. Medicines that inhibit peristalsis should not be given (see section 4.8).

**Interactions with laboratory tests**

It is recommended that either glucose oxidase or hexokinase methods be used to determine blood/plasma glucose levels in patients receiving ZINOXIME. This medicine may give false-negative test results with ferricyanide blood glucose test. ZINOXIME does not interfere in the alkaline picrate assay for creatinine.

A false-positive Coombs reaction may appear in patients who receive large doses of ZINOXIME.

**ZINOXIME contains sodium**

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially

sodium free.

## 4.5 Interaction with other medicines and other forms of interaction

- Concurrent administration of probenecid increases the area under the mean serum concentration time-curve by 50 %.
- Medicines which reduce gastric acidity may result in a lower bioavailability of cefuroxime (as in ZINOXIME) compared with that of the fasting state and tend to cancel the effect of enhanced absorption after food.
- ZINOXIME may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.
- Concomitant use of ZINOXIME with oral anticoagulants may result in an increased INR.
- The combined use of ZINOXIME with furosemide should be avoided due to enhanced nephrotoxicity.
- Concomitant use of ZINOXIME with aminoglycosides should be undertaken with caution due to nephrotoxicity.

## 4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation have not been established.

Cefuroxime (as in ZINOXIME) is excreted in breast milk in small quantities. Adverse effects at therapeutic doses are not expected, although a risk of diarrhoea and fungus infection of the mucous membranes cannot be excluded. The possibility of sensitisation should be considered.

There are no data on the effects of cefuroxime (as in ZINOXIME) on fertility.

## 4.7 Effects on ability to drive and use machines

ZINOXIME may cause headache and dizziness which may impair the ability to drive a vehicle or operate machinery (see section 4.8). Patients should be advised to exercise caution after taking ZINOXIME until the effects are known.

## 4.8 Undesirable effects

**Infections and infestations**

*Frequent:* Candida overgrowth, oral thrush, vaginitis.

*Frequency unknown:* *Clostridium difficile* overgrowth.

**Blood and lymphatic system disorders**

*Frequent:* Eosinophilia.

*Less frequent:* Thrombocytopenia, leukopenia (sometimes profound), neutropenia.

*Frequency unknown:* Haemolytic anaemia.

**Immune system disorders**

*Less frequent:* Hypersensitivity reactions including skin rashes, urticaria, pruritus, bronchospasm, drug fever, serum sickness, anaphylaxis, cutaneous vasculitis, Jarisch-Hexheimer reaction.

**Nervous system disorders**

*Frequent:* Headache, dizziness.

*Frequency unknown:* Convulsions.

**Ear and labyrinth disorders**

*Less frequent:* Hearing loss in children with meningitis.

**Gastrointestinal disorders**

*Frequent:* Nausea, diarrhoea, abdominal pain.

*Less frequent:* Vomiting, diarrhoea, in some cases accompanied by blood in stools, which may be a symptom of enterocolitis. A particular form of enterocolitis, is pseudomembranous colitis (see section 4.4).

**Hepatobiliary disorders**

Frequency unknown: Transient increases in hepatic enzyme levels, alanine aminotransferase

(serum glutamic pyruvic acid transaminase), aspartate aminotransferase (serum glutamic oxaloacetic transaminase), LDH (lactate dehydrogenase) levels, cholestatic jaundice, hepatitis, rise in bilirubin.

**Skin and subcutaneous tissue disorders**

*Less frequent:* Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, porphyria, skin rashes.

*Frequency unknown*: Angioneurotic oedema.

**Renal and urinary disorders**

*Less frequent:* Acute interstitial nephritis, nephrotoxicity when ZINOXIME is used in combination with aminoglycosides or furosemide (see section 4.5).

**Reproductive system and breast disorders**

*Frequency unknown:* Vaginal candidiasis.

**Investigations**

*Frequency unknown:* Positive antiglobulin (Coomb's) test.

**Description of selected adverse reactions**

Cephalosporins as a class tend to be absorbed onto the surface of red cells membranes and react with antibodies directed against the medicine to produce a positive Coombs' test (which can interfere with crossmatching of blood) and very rarely haemolytic anaemia. Transient rises in serum liver enzymes have been observed which are usually reversible.

**Paediatric population**

The safety profile for ZINOXIME in children is consistent with the profile in adults.

**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 “Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

## 4.9 Overdose

See section 4.8.

**Symptoms of overdose**

Seizures have been reported. Overdose can lead to neurological sequelae including encephalopathy, convulsions and coma. Symptoms of overdose can occur if the dose is not reduced appropriately in patients with renal impairment (see section 4.4).

**Treatment of overdose**

Treatment is symptomatic and supportive. Serum levels of ZINOXIME can be reduced by haemodialysis or peritoneal dialysis.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Category and class: A 20.1.1: Broad and medium spectrum antibiotics.

Pharmacotherapeutic groups: Antibacterials for systemic use, second-generation cephalosporins.

ATC code: J01DC02.

Cefuroxime is a bacterial second-generation cephalosporin. The antibacterial action of cefuroxime results from inhibition of bacterial cell wall synthesis by binding to essential target proteins in bacterial cytoplasmic membranes. Cefuroxime has bacterial activity against a wide range of bacterial organisms, including beta-lactamase producing strains.

**Mechanism of resistance**

Bacterial resistance to cefuroxime may be due to one or more of the following mechanisms:

- Hydrolysis by beta-lactamases; including (but not limited to) by extended-spectrum beta-lactamases (ESBLs), and AmpC enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacteria species.
- Reduced affinity of penicillin-binding proteins for cefuroxime.
- Outer membrane impermeability, which restricts access of cefuroxime to penicillin binding proteins in Gram-negative bacteria.
- Bacterial efflux pumps.

Organisms that have acquired resistance to other injectable cephalosporins are expected to be resistant to cefuroxime.

Depending on the mechanism of resistance, organisms with acquired resistance to penicillins may demonstrate reduced susceptibility or resistance to cefuroxime.

**Microbiological 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 cefuroxime in at least some types of infections is questionable.

## 5.2 Pharmacokinetic properties

**Absorption**

Cefuroxime axetil is an oral prodrug of cefuroxime. After oral absorption, cefuroxime axetil is hydrolysed in the intestinal mucosa and blood to release cefuroxime into the plasma. Oral absorption is optimal when administered with food. Peak serum levels of cefuroxime occur approximately 2 to 3 hours after oral dosing, when taken with food. The pharmacokinetics of

cefuroxime is linear over the oral dosage range of 125 – 1 000 mg. No accumulation of cefuroxime occurred following repeat oral doses of 250 – 500 mg.

**Distribution**

Protein binding is approximately 33 % to 50 %. Concentrations of cefuroxime more than the minimum inhibitory levels for common pathogens can be achieved in the tonsilla, sinus tissues, bronchial mucosa, bone, pleural fluid, joint fluid, synovial fluid, interstitial fluid, bile, sputum and aqueous humor. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.

**Biotransformation**

Cefuroxime is not metabolised.

**Elimination**

The elimination half-life is between 1 and 1,5 hours after oral dosing. Cefuroxime is excreted by glomerular filtration and tubular secretion. The renal clearance is in the region of 125 to 148 mL/min/1,73 $m^2$. The elimination half-life is prolonged with renal impairment and in neonates. Serum levels of cefuroxime are reduced by dialysis.

**Special populations**

*Gender*

No differences in the pharmacokinetics of cefuroxime were observed between males and females.

*Elderly*

No special precaution is necessary in the elderly patients with normal renal function at dosages up to the normal maximum of 1 g per day. Elderly patients are more likely to have decreased renal function; therefore, a reduced dose may be required.

*Paediatrics*

In older infants (aged >3 months) and in children, the pharmacokinetics of cefuroxime are similar to

that observed in adults. There is no clinical trial data available on the use of cefuroxime axetil in children under the age of 3 months.

*Renal impairment*

The safety and efficacy of cefuroxime axetil in patients with renal failure have not been established. Cefuroxime is primarily excreted by the kidneys. Therefore, in patients with markedly impaired renal function (i.e. creatinine clearance <30 mL/minute) it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion (see section 4.4). Cefuroxime is effectively removed by dialysis.

*Hepatic impairment*

There are no data available for patients with hepatic impairment. Since cefuroxime is primarily eliminated by the kidney, the presence of hepatic dysfunction is expected to have no effect on the pharmacokinetics of cefuroxime.

**Pharmacokinetic/pharmacodynamic relationship**

For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with *in vivo* efficacy has been shown to be the percentage of the dosing interval (% T) that the unbound concentration remains above the MIC of cefuroxime for individual target species (i.e. % T>MIC).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Core*

Microcrystalline cellulose

Croscarmellose sodium

Hydrogenated vegetable oil

Colloidal silica, anhydrous

Sodium laurilsulfate.

*Coating*

Hypromellose

Macrogol 400

Titanium dioxide (E171).

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

36 months.

### 6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blister strip in the outer carton until required for use.

### 6.5 Nature and contents of container

Tablets are packed in cold form laminate: 25-micron polyamide / 45-micron aluminium foil / 60-micron PVC film as the forming material and aluminium foil as the lidding material.

Each blister contains 10 tablets.

Pack size: 10 tablets.

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 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 NUMBERS

ZINOXIME 250 mg: 41/20.1.1/0752

ZINOXIME 500 mg: 41/20.1.1/0753

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 April 2008

## 10. DATE OF REVISION OF THE TEXT

18 March 2024