PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

ZINUROZ 250 (film-coated tablets)

ZINUROZ 500 (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ZINUROZ 250 film-coated tablet contains cefuroxime axetil equivalent to 250 mg cefuroxime.

Each ZINUROZ 500 film-coated tablet contains cefuroxime axetil equivalent to 500 mg cefuroxime.

Excipient(s) with known effect:

ZINUROZ 250 contains mannitol (50 mg per tablet).

ZINUROZ 500 contains mannitol (100 mg per tablet).

3. PHARMACEUTICAL FORM

ZINUROZ 250: white to slightly yellowish, biconvex, scored on both sides, oblong film-coated tablets.

ZINUROZ 500: white to slightly yellowish, biconvex, oblong film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZINUROZ 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.*
- Otitis media caused by *Streptococcus pneumoniae, Haemophilus influenzae* (ampicillin-sensitive and resistant strains), *Moraxella (Branhamella) catarrhalis* and *Streptococcus pyogenes.*
- Sinusitis caused by *Streptococcus pneumoniae* and *Haemophilus influenzae.*
- Acute and chronic bronchitis caused by *Streptococcus pneumoniae, Haemophilus influenzae* (ampicillin-sensitive strains) and *Haemophilus parainfluenzae* (ampicillin-sensitive strains).
- Acute uncomplicated cystitis caused by *Escherichia coli* and *Klebsiella pneumoniae.*
- Lyme disease caused by *Borrelia burgdorferi.*

4.2 Posology and method of administration

Adults:

Sinusitis & acute or chronic bronchitis:

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

Acute, uncomplicated cystitis:

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

Lyme disease:

Adults and children over 12 years of age: 500 mg twice daily for 20 days.

Method of administration

Oral use.

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

4.3 Contraindications

Hypersensitivity to cefuroxime or to any of the excipients listed in section 6.1.

Patients with known hypersensitivity to cephalosporin antibiotics.

History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).

4.4 Special warnings and precautions for use

ZINUROZ 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: Safety has not been established.

Pseudomembranous colitis may occur. Patients who develop abdominal or stomach cramps, abdominal tenderness, severe and watery diarrhoea (which may be bloody) and fever, should be investigated for this diagnosis. If the diagnosis of pseudomembranous colitis is suspected, ZINUROZ should be stopped immediately and appropriate therapy initiated.

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 agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefuroxime must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning 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 medicines. Caution should be used if cefuroxime is given to patients with a history of non-severe hypersensitivity to other beta-lactam medicines.

Severe Cutaneous Adverse Reactions (SCAR), such as Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Erythema Multiforme (EM) and Acute Generalised Exanthematous Pustulosis (AGEP) have been reported in patients receiving cefuroxime (see section 4.8). If signs and symptoms suggestive of these reactions appear, cefuroxime should be withdrawn immediately and an alternative treatment should be considered.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following ZINUROZ treatment of Lyme disease. It results directly from the bactericidal activity of cefuroxime axetil 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

As with other antibiotics, use of cefuroxime axetil 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).

Antibacterial medicine-associated pseudomembranous colitis have been reported with nearly all antibacterial agents, including cefuroxime axetil and may range in severity from mild to life threatening. This diagnosis should be considered in patients with diarrhoea during or subsequent to the administration of cefuroxime axetil (see section 4.8). Discontinuation of therapy with cefuroxime axetil and the administration of specific treatment for *Clostridium difficile* should be considered. Medicines that inhibit peristalsis should not be given (see section 4.8).

Interference with diagnostic tests

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

The development of a positive Coomb's Test associated with the use of cefuroxime axetil may interfere with cross matching of blood (see section 4.8).

A false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving ZINUROZ.

ZINUROZ does not interfere in the alkaline picrate assay for creatinine.

4.5 Interaction with other medicines and other forms of interaction

Medicines which reduce gastric acidity may result in a lower bioavailability of cefuroxime axetil compared with that of the fasting state and tend to cancel the effect of enhanced absorption after food.

Cefuroxime axetil may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Cefuroxime axetil is excreted by glomerular filtration and tubular secretion. Concomitant use of probenecid is not recommended. Concurrent administration of probenecid significantly increases the peak concentration, area under the serum concentration time curve and elimination half-life of cefuroxime axetil.

Concurrent administration of probenecid increases the area under the mean serum concentration-time curve by 50 %.

Concomitant use with oral anticoagulants may give rise to increased International Normalised Ratio (INR).

4.6 Fertility, pregnancy and lactation

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

Pregnancy

There are limited data from the use of ZINUROZ in pregnant women. Studies in animals have shown no harmful effects on pregnancy, embryonal or foetal development, parturition or postnatal development.

Breastfeeding

ZINUROZ is excreted in human 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. Breastfeeding might have to be discontinued due to these effects.

Fertility

There are no data on the effects of ZINUROZ on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, as this medicine may cause dizziness, patients should be warned to be cautious when driving or operating machinery.

4.8 Undesirable effects

The most common adverse reactions are *Candida* overgrowth, eosinophilia, headache, dizziness, gastrointestinal disturbances and transient rise in liver enzymes.

Infections and infestations:

Frequent: *Candida* overgrowth, vaginal candidiasis.

Frequency not known: *Clostridium difficile* overgrowth.

Blood and lymphatic system disorders:

Frequent: Eosinophilia.

Less frequent: Positive Coomb's test, thrombocytopenia, leukopenia (sometimes profound).

Frequency not known: Haemolytic anaemia.

Immune system disorders:

Frequency not known: Drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction.

Nervous system disorders:

Frequent: Headache, dizziness.

Respiratory, thoracic and mediastinal disorders:

Frequency not known: Bronchospasm.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, abdominal pain.

Less frequent: Vomiting.

Frequency not known: Pseudomembranous colitis (see section 4.4).

Hepatobiliary disorders:

Frequent: Transient increases of hepatic enzyme levels.

Frequency not known: Jaundice (predominantly cholestatic), hepatitis.

Skin and subcutaneous tissue disorders:

Less frequent: Skin rashes.

Frequency not known: Urticaria, pruritus, Severe Cutaneous Adverse Reactions (SCARs), including Erythema Multiforme (EM), Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (exanthematic necrolysis) (see Immune system disorders), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Acute Generalised Exanthematous Pustulosis (AGEP), angioneurotic oedema.

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 drug to produce a positive Coombs' test (which can interfere with cross-matching of blood) and very rarely haemolytic anaemia.

Transient rises in serum liver enzymes have been observed which are usually reversible.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare 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

Suspected adverse reactions can also be reported directly to the HCR via https://pvi1j.solutions.iqvia.com or adverse.event.sac@sandoz.com

4.9 Overdose

Symptoms of overdose:

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 sections 4.2 and 4.4).

Treatment of overdose:

Treatment is symptomatic and supportive.

Serum levels of ZINUROZ can be reduced by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Antibacterials for systemic use, second-generation cephalosporins, ATC code: J01DC02

5.1 Pharmacodynamic properties

Mechanism of action

Cefuroxime is a bactericidal second-generation cephalosporin. Cefuroxime undergoes hydrolysis by esterase enzymes to the active antibiotic, cefuroxime. Cefuroxime inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death. Cefuroxime has bactericidal 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 de-repressed 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 ZINUROZ in at least some types of infections is questionable.

Cefuroxime is usually active against the following microorganisms *in vitro*.

Microorganisms for which acquired resistance may be a problem:

Gram-positive aerobes:

Streptococcus pneumoniae

Gram-negative aerobes:

Citrobacter freundii

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Klebsiella pneumoniae

Proteus mirabilis

Proteus spp. (other than *P. vulgaris)*

Providencia spp.

Gram-positive anaerobes:

Peptostreptococcus spp.

Propionibacterium spp.

Gram-negative anaerobes:

Fusobacterium spp.

Bacteroides spp.

Inherently resistant microorganisms:

Gram-positive aerobes:

Enterococcus faecalis

Enterococcus faecium

Gram-negative aerobes:

Acinetobacter spp.

Campylobacter spp.

Morganella morganii

Proteus vulgaris

Pseudomonas aeruginosa

Serratia marcescens

Gram-negative anaerobes:

Bacteroides fragilis

Others:

Chlamydia spp.

Mycoplasma spp.

Legionella spp.

5.2 Pharmacokinetic properties

Absorption

Cefuroxime axetil is an oral prodrug of cefuroxime. After oral administration, cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the intestinal mucosa and blood to release cefuroxime into the circulation. Optimum absorption occurs when it is administered shortly after a meal. Following administration of cefuroxime axetil

tablets peak serum levels (2,1 µg/ml for a 125 mg dose, 4,1 µg/ml for a 250 mg dose, 7,0 µg/ml for a 500 mg dose and 13,6 µg/ml for a 1000 mg dose) occur approximately 2 to 3 hours after dosing, when taken with food.

The pharmacokinetics of cefuroxime is linear over the oral dose range of 125 to 1000 mg. No accumulation of cefuroxime occurred following repeat oral doses of 250 to 500 mg.

Distribution

Protein binding has been stated as 33 % to 50 % depending on the methodology used. Following a single dose of cefuroxime axetil 500 mg tablet to 12 healthy volunteers, the apparent volume of distribution was 50 L (CV % = 28 %). Concentrations of cefuroxime in excess of 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 humour. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.

Biotransformation

Cefuroxime is not metabolised.

Elimination

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

Special patient 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 doses up to the normal maximum of 1 g per day. Elderly patients are more likely to have decreased renal function; therefore, the dose should be adjusted in accordance with the renal function in the elderly (see section 4.2).

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, as with all such antibiotics, in patients with markedly impaired renal function (i.e. Clcr < 30 ml/minute) it is recommended that the dose of cefuroxime should be reduced to compensate for its slower excretion (see section 4.2). 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 minimum inhibitory concentration (MIC) of cefuroxime for individual target species (i.e. %T > MIC).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipient core: Copovidone, croscarmellose sodium, crospovidone, magnesium stearate, mannitol granulated, microcrystalline cellulose, silica colloidal anhydrous, sodium lauryl sulphate, talc.

Excipient coating: Hypromellose, polyethylene glycol, polysorbate 80, titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Do not remove the blisters from the carton until required for use.

6.5 Nature and contents of container

Printed cardboard cartons containing 10 or 100 tablets in Alu/Alu blister with PE coating or unit dose Alu/Alu blister with polyamide/PE coating or blister aluminium foil with polyester/PE coating.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBERS

ZINUROZ 250: 37/20.1.1/0055

ZINUROZ 500: 37/20.1.1/0056

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 July 2004

10. DATE OF REVISION OF THE TEXT

29 June 2023

[1]Company Reg. No.: 1990/001979/07