SUMMARY OF PRODUCT CHARACTERISTICS

CEROXIM
(Cefuroxime Axetil 500 mg Tablets)

1. NAME OF THE MEDICINAL PRODUCT

CEROXIM

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CEROXIM

Each film coated tablet contains:
Cefuroxime Axetil Ph. Eur.
equivalent to Cefuroxime 250 mg/500 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet

4. CLINICAL PARTICULARS[1]

4.1 Therapeutic indications

CEROXIM is indicated for the treatment of the infections listed below in adults and children from the age of 3 months (see **sections 4.4** and **5.1**).

- Acute streptococcal tonsillitis and pharyngitis.
- Acute bacterial sinusitis.
- Acute otitis media.
- Acute exacerbations of chronic bronchitis.
- Cystitis.
- Pyelonephritis.
- Uncomplicated skin and soft tissue infections.
- Treatment of early Lyme disease.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

The usual course of therapy is seven days (may range from five to ten days).

Table: Adults and children (≥40 kg)

Indication	Dosage
Acute tonsillitis and pharyngitis, acute bacterial sinusitis	250 mg twice daily
Acute otitis media	500 mg twice daily
Acute exacerbations of chronic bronchitis	500 mg twice daily
Cystitis	250 mg twice daily
Pyelonephritis	250 mg twice daily
Uncomplicated skin and soft tissue infections	250 mg twice daily
Lyme disease	500 mg twice daily for 14 days (range of 10 to 21 days)

Table: Children (<40 kg)

Indication	Dosage
Acute tonsillitis and pharyngitis, acute bacterial sinusitis	10 mg/kg twice daily to a maximum of 125 mg twice daily
Children aged two years or older with otitis media or, where appropriate, with more severe infections	15 mg/kg twice daily to a maximum of 250 mg twice daily
Cystitis	15 mg/kg twice daily to a maximum of 250 mg twice daily
Pyelonephritis	15 mg/kg twice daily to a maximum of 250 mg twice daily for 10 to 14 days
Uncomplicated skin and soft tissue infections	15 mg/kg twice daily to a maximum of 250 mg twice daily
Lyme disease	15 mg/kg twice daily to a maximum of 250 mg twice daily for 14 days (10 to 21 days)

There is no experience of using 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 reported.

Cefuroxime is primarily excreted by the kidneys. In patients with markedly impaired renal function it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion. Cefuroxime is effectively removed by dialysis.

Table: Recommended doses for cefuroxime in renal impairment

Creatinine clearance	**$T_{1/2}$ (hrs)**	**Recommended dosage**
≥30 ml/min/1.73 m^2	1.4–2.4	No dose adjustment necessary (standard dose of 125 mg to 500 mg given twice daily)
10-29 ml/min/1.73 m^2	4.6	Standard individual dose given every 24 hours
<10 ml/min/1.73 m^2	16.8	Standard individual dose given every 48 hours
During haemodialysis	2-4	A single additional standard individual dose should be given at the end of each dialysis

Hepatic impairment

There are no reported 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.

Method of administration

Oral use

CEROXIM should be taken after food for optimum absorption.

CEROXIM should not be crushed and are therefore unsuitable for treatment of patients who cannot swallow tablets. In children cefuroxime oral suspension may be used.

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 betalactam antibacterial agent (penicillins, monobactams and carbapenems)

4.4 Special warnings and precautions for use

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

Severe cutaneous adverse reactions (SCARS)
Severe cutaneous adverse reactions including: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) anddrug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with cefuroxime treatment (see **section 4.8**).

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, cefuroxime should be withdrawn immediately and an alternative treatment considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of cefuroxime, treatment with cefuroxime must not be restarted in this patient at any time.

Jarisch-Herxheimer reaction
The Jarisch-Herxheimer reaction has been reported following cefuroxime axetil 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. enterococci and *Clostridium difficile*), which may require interruption of treatment (see **section 4.8**).

Antibacterial agent–associated pseudomembranous colitis have been reported with nearly all antibacterial agents, including cefuroxime 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. Discontinuation of therapy with cefuroxime and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given (see **section 4.8**).

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

As 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 cefuroxime.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs 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 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.

Concomitant use with oral anticoagulants may give rise to increased INR.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data reported on use of cefuroxime in pregnant women. Studies in animals have reported no harmful effects on pregnancy, embryonal or foetal development, parturition or postnatal development. Cefuroxime should be prescribed to pregnant women only if the benefit outweighs the risk.

Lactation
Cefuroxime 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. The possibility of sensitisation should be taken into account. Cefuroxime should only be used during breastfeeding after benefit/risk assessment by the physician in charge.

Fertility
There are no data on the effects of cefuroxime axetil on fertility in humans. Reported 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 reported. 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 reported are *Candida* overgrowth, eosinophilia, headache, dizziness, gastrointestinal disturbances and transient rise in liver enzymes.

The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data for calculating incidence were not available. In addition the incidence of adverse reactions associated with cefuroxime axetil may vary according to the indication.

Data reported from large clinical studies were used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e. those occurring at <1/10,000) were mainly determined using post-marketing data and refer to a reporting rate rather than true frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Treatment related adverse reactions, all grades, are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been utilised for the classification of frequency: very common ≥ 1/10; common ≥ 1/100 to < 1/10, uncommon ≥ 1/1,000 to < 1/100; rare ≥ 1/10,000 to < 1/1,000; very rare < 1/10,000 and not known (cannot be estimated from the available data).

System organ class	**Common**	**Uncommon**	**Not known**
Infections and infestations	*Candida* overgrowth		*Clostridium difficile* overgrowth
Blood and lymphatic system disorders	eosinophilia	positive Coomb's test, thrombocytopenia, leukopenia	haemolytic anaemia

		(sometimes profound)	
Immune system disorders			drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction
Nervous system disorders	headache, dizziness		
Gastrointestinal disorders	diarrhoea, nausea, abdominal pain	vomiting	pseudomembranous colitis (see **section 4.4**)
Hepatobiliary disorders	transient increases of hepatic enzyme levels		jaundice (predominantly cholestatic), hepatitis
Skin and subcutaneous tissue disorders		skin rashes	urticaria, pruritus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematic necrolysis) (*see Immune system disorders*), angioneurotic edema, Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS)

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 reported which are usually reversible.

Paediatric population

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

4.9 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**).

Serum levels of cefuroxime can be reduced by haemodialysis and peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES[1]

5.1 Pharmacodynamic properties

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

Mechanism of action
Cefuroxime axetil 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.

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 depressed 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 local prevalence of resistance is such that the utility of cefuroxime axetil in at least some types of infections is questionable.

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

Commonly susceptible species

Gram-positive aerobes: *Staphylococcus aureus (methicillin susceptible)*, Coagulase negative staphylococcus (methicillin susceptible), Streptococcus pyogenes, Streptococcus agalactiae*

Gram-negative aerobes*: Haemophilus influenza, Haemophilus parainfluenzae, Moraxella catarrhalis*

Spirochaetes: Borrelia burgdorferi

Microorganisms for which acquired resistance may be a problem

Gram-positive aerobes: *Streptococcus pneumonia*

Gram-negative aerobes: *Citrobacter freundii, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella pneumonia, 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.*

* All methicillin-resistant *S. aureus* are resistant to cefuroxime.

5.2 Pharmacokinetics properties

Absorption

After oral administration, cefuroxime axetil is reported to be absorbed from the gastrointestinal tract and rapidly hydrolysed in the intestinal mucosa and blood to release

cefuroxime into the circulation. It has been reported that optimum absorption occurs when it is administered shortly after a meal.

Following administration of cefuroxime axetil tablets peak serum levels (2.1 mcg/ml for a 125 mg dose, 4.1 mcg/ml for a 250 mg dose, 7.0 mcg/ml for a 500 mg dose and 13.6 mcg/ml for a 1000 mg dose) is reported occur approximately 2 to 3 hours after dosing, when taken with food. The pharmacokinetics of cefuroxime has been reported to be linear over the oral dosage range of 125 to 1000 mg. No accumulation of cefuroxime has been reported following repeat oral doses of 250 to 500 mg.

Distribution

Protein binding has been reported as 33 to 50% depending on the methodology used. Following a single dose of cefuroxime axetil 500 mg tablet to healthy volunteers, the apparent volume of distribution was reported as 50 L (CV%=28%). Concentrations of cefuroxime in excess of the minimum inhibitory levels for common pathogens is reported to be achieved in the tonsilla, sinus tissues, bronchial mucosa, bone, pleural fluid, joint fluid, synovial fluid, interstitial fluid, bile, sputum and aqueous humor. Cefuroxime has been reported to pass the blood-brain barrier when the meninges are inflamed.

Biotransformation

It has been reported that cefuroxime is not metabolised in the body.

Elimination

The serum half-life has been reported to be between 1 and 1.5 hours. Cefuroxime is excreted by glomerular filtration and tubular secretion. The renal clearance has been reported to be in the region of 125 to 148 ml/min/1.73 m^2.

Special patient populations

Gender

No differences in the pharmacokinetics of cefuroxime have been reported 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, the dose should be adjusted in accordance with the renal function in the elderly (see **section 4.2**).

Pediatrics

In older infants (aged >3 months) and in children, the pharmacokinetics of cefuroxime are similar to that reported 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 reported. Cefuroxime is primarily excreted by the kidneys. Therefore, as with all such antibiotics, in patients with markedly impaired renal function (i.e. C1cr <30 ml/minute) it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion (see **section 4.2**). Cefuroxime is effectively removed by dialysis.

Hepatic impairment

No data has been reported 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 reported 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).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on reported studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. No carcinogenicity studies have been reported; however, there is no evidence to suggest carcinogenic potential.

Gamma glutamyl transpeptidase activity in rat urine is inhibited by various cephalosporins, however, the level of inhibition is less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Lauryl Sulfate, Colloidal Anhydrous Silica, Microcrystalline Cellulose (PH101), Croscarmellose Sodium, Hydrogenated Vegetable oil, Colloidal Anhydrous Silica, Microcrystalline Cellulose, Croscarmellose Sodium, Hydrogenated Vegetable oil, Opadry White OY-S-58910, Purified water

6.2 Incompatibilities

NA

6.3 Shelf life

24 months

6.4 Special precautions for storage

NA

6.5 Nature and contents of container

Each blister pack contains 10's tablets

6.6 Special precautions for disposal and other handling

NA

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

04-4942

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

January 2024

REFERENCES

1. Summary of Product Characteristics of Zinnat Tablets 250 mg Tablets, Sandoz Pharmaceuticals d.d., Slovenia, UK, June 2023.