SUMMARY OF PRODUCT CHARACTERISTICS

CEROXIM SUSPENSION
(Cefuroxime Axetil for Oral Suspension 125 mg/5 ml & 250 mg/5 ml)

1. NAME OF THE MEDICINAL PRODUCT

CEROXIM SUSPENSION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cefuroxime Axetil for Oral Suspension 125 mg/5 ml:
Each 5 ml of the constituted suspension contains
Cefuroxime Axetil USP
equivalent to cefuroxime 125 mg

Cefuroxime Axetil for Oral Suspension 250 mg/5 ml
Each 5 ml of the constituted suspension contains
Cefuroxime Axetil USP
equivalent to cefuroxime 250 mg

For list of excipients please see **section** 6.1

3. PHARMACEUTICAL FORM

Powder for Oral Suspension

4. CLINICAL PARTICULARS [1]

4.1 Therapeutic indications

Ceroxim Suspension is indicated for the treatment of the infections listed below in adults and children from the age of 3 months (see **section 4.4**).

- 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 reported experience of using cefuroxime axetil in children under the age of 3 months.

In infants (from the age of 3 months) and children with a body mass of less than 40 kg, it may be preferable to adjust dosage according to weight or age. The dose in infants and children 3 months to 18 years is 10 mg/kg twice daily for most infections, to a maximum of 250 mg daily. In otitis media or more severe infections the recommended dose is 15 mg/kg twice daily to a maximum of 500 mg daily.

The following two tables, divided by age group, serve as a guideline for simplified administration, e.g measuring spoon (5 ml) for the 125 mg/5 ml or the 250 mg/5 ml multi-dose suspension if provided.

Table: 10 mg/kg dosage of Cefuroxime axetil for Oral Suspension for most infections

Age	Dose (mg) twice daily	Volume per dose (ml)	
		125 mg	250 mg
3 to 6 months	40 to 60	2.5	-
6 months to 2 years	60 to 120	2.5 to 5	-
2 to 18 years	125	5	2.5

Table: 15 mg/kg dosage of Cefuroxime axetil for Oral Suspension for otitis media and more serious infections

Age	Dose (mg) twice daily	Volume per dose (ml)	
		125 mg	250 mg
3 to 6 months	60 to 90	2.5	-
6 months to 2 years	90 to 180	5 to 7.5	2.5
2 to 18 years	180 to 250	7.5 to 10	2.5 to 5

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 axetil for Oral Suspension 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 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

For optimal absorption cefuroxime axetil suspension should be taken with food.

For instructions on reconstitution of the medicinal product before administration, **see section 6.6**

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.

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 (see **section 4.8**).

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 axetil.

Excipients
This medicinal product contains aspartame. It is a source of phenylalanine which may not be suitable for people with phenylketonuria.

It also contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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 probenicid 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 reported data from the use of cefuroxime in pregnant women. No harmful effects on pregnancy, embryonal or foetal development, parturition or

postnatal development have been reported in animals. 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 reported 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 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 example from placebo-controlled studies) for calculating incidence were not available. In addition the incidence of adverse reactions associated with cefuroxime axetil may vary according to the indication.

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	eosinophilia	positive Coomb's test,	haemolytic anaemia

disorders		thrombocytopenia, leukopenia (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 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 reported which are usually reversible.

Paediatric population
The safety profile for cefuroxime axetil in children has been reported to be 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: antibacterials 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 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 axetil in at least some types of infections is questionable.

Cefuroxime has been reported to be 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 influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis

Spirochaetes:
Borrelia burgdorferi

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.

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

5.2 Pharmacokinetics properties

Absorption
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 has been reported when it is administered shortly after a meal.

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 to be as 33 to 50%. Following a single dose of cefuroxime axetil 500 mg tablet to healthy volunteers, the apparent volume of distribution was reported to be 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 humor. Cefuroxime has been reported to pass the blood-brain barrier when the meninges are inflamed.

Biotransformation
Cefuroxime is not metabolised.

Elimination
The serum half-life is reported to be between 1 and 1.5 hours. 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.

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 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**).

Paediatrics
In older infants (aged >3 months) and in children, the pharmacokinetics of cefuroxime are reported to be similar to that reported in adults.

There is no reported data 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
There are no reported data 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

No special hazard for humans has been reported based on the 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 has been reported to be less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CEROXIM SUSPENSION 125 mg/5 ml: Aspartame, Silicon dioxide, Colloidal silicon dioxide Mono sodium citrate, Stearic acid, Flavour tutti frutti, Flavour peppermint, Sodium chloride, Sucrose and Flavour Grenadine.

CEROXIM SUSPENSION 250 mg/5 ml: Aspartame, Silicon dioxide, Colloidal silicon dioxide Mono sodium citrate, Stearic acid, Flavour tutti frutti, Flavour peppermint, Sodium chloride, Sucrose and Flavour Grenadine.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Before reconstitution, store dry powder between 20-25°C. After reconstitution, store the suspension between 2-8°C, in a refrigerator.

Keep the bottle tightly closed.

6.5 Nature and contents of container

100 ml HDPE bottle

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Limited

8. MARKETING AUTHORISATION NUMBER(S)

04-6077 & 04-6057

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/10/2004

10. DATE OF REVISION OF THE TEXT

September 2021

REFERENCES

1. Summary of Product Characteristics of Zinnat Suspension 125 mg, GlaxoSmithKline UK Limited, November 2019.