Professional Information

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

CEFUGEN 250 Film-coated tablets

CEFUGEN 500 Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains 155.28 mg sodium per tablet.

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

Contains 310.56 mg sodium per tablet.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CEFUGEN 250: Film-coated tablets

White to off-white, film coated, capsule shaped tablets with ‘A 33’ debossed on one side and plain on the other side.

CEFUGEN 500: Film-coated tablets

White to off-white, film coated, capsule shaped tablets with ‘A 34’ debossed on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

CEFUGEN is indicated for the treatment of patients with infections caused by susceptible organisms in the following diseases:

• **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. CEFUGEN is generally effective in the eradication of streptococci from the oral pharynx. CEFUGEN is not indicated for the prophylaxis of subsequent rheumatic fever because data to support such use is not available).
• **Otitis Media** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (ampicillin-susceptible and ampicillin-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-susceptible strains), and *Haemophilus parainfluenzae* (ampicillin-susceptible strains).
• **Acute uncomplicated cystitis** caused by *Escherichia coli* and *Klebsiella pneumoniae*.
• **Lyme Disease** caused by the spirochaete *Borrelia burgdorferi*. CEFUGEN is indicated for the treatment of early Lyme disease and subsequent prevention of late Lyme disease in adults and children over 12 years old.

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: 250 mg twice daily for seven days (range 5-10 days).
Acute and chronic 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: 500 mg twice daily for 14 days. (range 10-21 days).

Children 12 years and older

Lyme disease in children over the age of 12 years: the usual dose is 500 mg twice daily for 14 days. (range 10-21 days).

Special Populations

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 Table 1: Recommended doses for renal impairment below*).

Renal impairment:

Cefuroxime is primarily excreted by the kidneys. It is recommended that the dosage for patients with markedly impaired renal function (i.e. CrCl <30 ml/minute) should be reduced to compensate for the slower excretion **(***see Table 1: Recommended doses for renal impairment below)*.

Table 1: Recommended doses for 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:

Since cefuroxime is primarily eliminated by the kidney, the presence of hepatic dysfunction is expected to have no effect on the pharmacokinetics of cefuroxime.

Paediatric population:

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. Only children older than 12 years may use CEFUGEN.

Method of Administration

For oral administration only.

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

Because of the bitter taste of cefuroxime axetil, CEFUGEN tablets should not be crushed and are therefore unsuitable for treatment of patients who cannot swallow tablets.

4.3 Contraindications

- Hypersensitivity to cephalosporin antibiotics, the active substance, or to any of the excipients listed in section 6.1.
- History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial medicine (penicillins, monobactams and carbapenems).

4.4 Special warnings and precautions for use

Prescribers must adhere to the principles of antibiotic stewardship

Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactam antibiotics.
There is a risk of cross-sensitivity.
In the case of severe hypersensitivity reactions, treatment with CEFUGEN must be discontinued immediately and adequate emergency measures must be initiated.

CEFUGEN should be used with caution in patients with:

- a history of gastro-intestinal 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

Serious and occasionally fatal hypersensitivity reactions have been reported. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8)

Before beginning treatment with CEFUGEN, 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 CEFUGEN is given to patients with a history of non-severe hypersensitivity to other beta-lactam medicine.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following cefuroxime 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

Use of CEFUGEN 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 discontinuation of treatment (see section 4.8).

Pseudomembranous colitis

Antibacterial medicine–associated pseudomembranous colitis have been reported with cefuroxime as in CEFUGEN and may range in severity from mild to life threatening. This diagnosis should be considered in patients who develop abdominal or stomach cramps, abdominal tenderness, severe and watery diarrhoea (which may be bloody) and fever during or subsequent to the administration of CEFUGEN. If the diagnosis of pseudomembranous colitis is suspected, discontinue therapy with CEFUGEN 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 serological testing

Slight interference with copper reduction methods (Benedict's, Fehling's, Clinitest) may be observed. However, this should not lead to false-positive results. Cefuroxime does not interfere with enzyme-based tests for glucosuria.

Cefuroxime may cause false-negative reactions in the ferricyanide test.

Hence it is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving cefuroxime axetil as in CEFUGEN.
Cefuroxime can cause a falsely high reading in the alkaline picrate assay for creatinine, although the degree of elevation is unlikely to be of clinical importance. It is possible that cefuroxime may also interfere with this determination.
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).

Important information about excipients
This medicine contains less than 1 mmol of sodium (23 mg) per tablet.

4.5 Interaction with other medicines and other forms of interaction
Medicines which reduce gastric acidity: Concurrent use with CEFUGEN may result in a lower bioavailability of cefuroxime compared with that of the fasting state and tend to cancel the effect of enhanced absorption after food.

Probenecid: CEFUGEN is excreted by glomerular filtration and tubular secretion. Concomitant use of probenecid is not recommended as probenecid significantly increases the peak concentration area under the serum concentration time curve and elimination half-life of cefuroxime·
Concomitant use of ceroxim and furosemide should be avoided when possible, due to enhanced nephrotoxicity.

The combined use of cephalosporins and aminoglycosides should be undertaken with caution, due to nephrotoxicity.

Oral contraceptives: CEFUGEN may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Oral anticoagulants: Concomitant use with oral anticoagulants may give rise to increased international normalised ratio (INR).

4.6 Fertility, Pregnancy and Lactation

Women of childbearing potential / Contraception in males and females

Concurrent use of CEFUGEN and oral contraceptives decreases the efficacy of the oral contraceptive. Patients should be strongly advised to use an alternative or additional method of contraception while taking CEFUGEN (see section 4.5).

Pregnancy

Safety in pregnancy has not been established (see section 4.3).

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

Breastfeeding

Safety in lactation has not been established (see section 4.3).

CEFUGEN is excreted in human milk in small quantities. Adverse effects at therapeutic doses are not expected, although the possibility of sensitisation should be taken into account and the 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 is no data available on the effects of CEFUGEN on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

4.7 Effects on ability to drive and use machines

CEFUGEN 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 following undesirable effects have been observed and reported during treatment with cefuroxime:

Tabulated list of adverse reactions

MedDRA System organ class	**Frequency**	**Adverse reactions**
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, cutaneous vasculitis, bronchospasm, drug fever, serum sickness and anaphylaxis, Jarisch-Hexheimer reaction
Cardiac disorders	Frequency unknown	Kounis syndrome (see section 4.4)
Nervous system disorders	Frequency unknown	convulsions.
	Frequent	Headache, dizziness
Ear and labyrinth disorders	Less frequent	Hearing loss in children with meningitis.
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, abdominal pain.
	Less frequent	A particular form of enterocolitis (pseudomembranous colitis) (see section 4.4
	Frequency unknown	Vomiting, diarrhoea accompanied by blood in the stools which may be a symptom of enterocolitis.

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	porphyria, skin rashes.
	Frequency unknown	Urticarial, pruritus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematic ncerolysis) (see Immune system disorders), angioneurotic oedema, Linear IgA disease.
Renal and urinary disorders	Less frequent	Acute interstitial nephritis, nephrotoxicity when CEROXIM is used in combination with aminoglycosides or furosemide.
Reproductive system and breast disorders	Frequency unknown	Vaginal candidiasis.
Investigations	Frequency unknown	Positive antiglobulin (Coombs') 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 cross-matching 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 CEFUGEN 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.

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 sections 4.2 and 4.4).

Treatment of overdose

Treatment is symptomatic and supportive.

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

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

Pharmacological Classification:

A 20.1.1 Broad and medium spectrum antibiotics

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

Cefuroxime is a bactericidal 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 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 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.

Cefuroxime axetil breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Microoganism	**Breakpoints (mg/L)**	
	S	R
Enterobacteriaceae [1, 2]	≤ 8	>8
Staphylococcus spp.	Note[3]	Note[3]
Streptococcus A, B, C and G	Note[4]	Note[4]
Streptococcus pneumoniae	≤ 0,25	> 0,5
Moraxella catarrhalis	≤ 0,125	> 4
Haemophilus influenzae	≤ 0,125	> 1
Non-species related breakpoints[1]	IE[5]	IE[5]

[1] The cephalosporin breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL and plasmid mediated AmpC). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. In many areas, ESBL detection and characterization is recommended or mandatory for infection control purposes.

[2] Uncomplicated UTI (cystitis) only (see section 4.1).

[3] Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility except for ceftazidme and cefixime and ceftibuten, which do not have breakpoints and should not be used for staphylococcal infections.

[4] The beta-lactam susceptability of beta-haemolytic streptococci groups A, B, C and G is inferred from the penicillin susceptibility.

[5] insufficient evidence that the species in question is a good target for therapy with the medicine-. An MIC with a comment but without an accompanying S or R-categorization may be reported.

S=susceptible, R=resistant

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

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 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 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 (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) occur approximately two to three hours after oral dosing when taken with food.

The rate of absorption of cefuroxime from the suspension is reduced compared with the tablets, leading to later, lower peak serum levels and reduced systemic bioavailability (4 to 17% less). Cefuroxime axetil oral suspension was not bioequivalent to cefuroxime axetil tablets when tested in healthy adults and therefore is not substitutable on a milligram-per-

milligram basis (see section 4.2).The pharmacokinetics of cefuroxime is linear over the oral dosage range of 125 to 1000 mg. No accumulation of cefuroxime occurred following repeat oral doses of 250 to 500 mg.

Distribution

Protein binding is approximately 33 % to 50 %. . 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 humor. Cefuroxime passes the blood- brain barrier when the meninges are inflamed.

Biotransformation

Cefuroxime is not metabolised and is excreted unchanged in the urine by glomerular filtration and tubular secretion.

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 m2 . 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, the dose should be adjusted in accordance with the renal function in the elderly.

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. CrCl <30 ml/minute) it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion. Cefuroxime is effectively removed by dialysis.

Hepatic impairment:

There is 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.

Paediatric population:

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.

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).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. No carcinogenicity studies have been performed; 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

Tablet core:

Cellulose, Microcrystalline

Croscarmellose Sodium

Sodium Lauryl Sulfate

Silica, Colloidal Anhydrous

Hydrogenated Vegetable Oil

Tablet film coating:

Hypromellose

Titanium dioxide

Macrogol 400

Purified water

6.2 Incompatibilities

A positive Coombs' test has been reported during treatment with cephalosporins - this phenomenon can interfere with cross-matching of blood **(see section 4.4 and 4.8)**.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Triple laminated cold form film - aluminium foil blister pack further packed in pre-printed cartons.

Pack sizes

CEFUGEN tablets are available in blister packs of 10 tablets.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd
Corner Birch Road & Bluegum Avenue,
Anchorville,
Lenasia, 1827

8. REGISTRATION NUMBER(S)

CEFUGEN 250 : 50/20.1.1/0561

CEFUGEN 500 : 50/20.1.1/0562

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 FEBRUARY 2021

10. DATE OF REVISION OF THE TEXT

04 December 2024