1.3.1 SUMMARY PRODUCT OF CHARACTERISTICS (SmPC)

Attached overleaf

Summary Product Characteristics (SPC)

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1. Name of the Drug product

Cefuroxime for Injection USP 750mg

Cefuroxime for Injection USP 1500mg

2. Qualitative and quantitative composition

Label claim:

Each vial contains:

Sterile Cefuroxime Sodium USP equivalent to anhydrous Cefuroxime ……750mg

Each vial contains:

Sterile Cefuroxime Sodium USP equivalent to anhydrous Cefuroxime ……1500mg

3. Pharmaceutical form

Dry powder for Injection

Description: Sterile, white or faintly yellow powder, distributed in sealed containers and which, when shaken with the prescribed volume of sterile liquid rapidly form clear and practically particle free solution.

4. Clinical particulars

4.1 Therapeutic indications

Cefuroxime sodium for injection is indicated for the treatment of the infections listed below in adults and children, including neonates (from birth).

• Community acquired pneumonia.

• Acute exacerbations of chronic bronchitis.

• Complicated urinary tract infections, including pyelonephritis.

• Soft-tissue infections: cellulitis, erysipelas and wound infections.

• Intra-abdominal infections

• Prophylaxis against infection in gastrointestinal (including oesophageal), orthopaedic, cardiovascular, and gynaecological surgery (including caesarean section).

In the treatment and prevention of infections in which it is very likely that anaerobic organisms will be encountered, cefuroxime should be administered with additional appropriate antibacterial agents.

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

4.2 Posology and method of administration

Table 1. Adults and children ≥ 40kg

Indication	**Dosage**
Community acquired pneumonia and acute exacerbations of chronic bronchitis	750 mg every 8 hours (intravenously or intramuscularly)
Soft-tissue infections: cellulitis, erysipelas and wound infections	
Intra-abdominal infections	
Complicated urinary tract infections, including pyelonephritis	1.5g every 8 hours (intravenously or intramuscularly)
Severe infections	750 mg every 6 hours (intravenously) 1.5 g every 8 hours (intravenously)
Surgical prophylaxis for gastrointestinal, gynaecological (including caesarean section) and orthopaedic operations	1.5 g with the induction of anaesthesia. This may be supplemented with two 750 mg doses (intramuscularly) after 8 hours and 16 hours.
Surgical prophylaxis for cardiovascular and oesophageal operations	1.5 g with induction of anaesthesia followed by 750 mg (intramuscularly) every 8 hours for a further 24 hours.

Table 2. Children < 40kg

	Infants and toddlers > 3 weeks and children < 40 kg	**Infants (birth to 3 weeks)**
Community acquired pneumonia	30 to 100 mg/kg/day (intravenously) given as 3 or 4 divided doses; a dose of 60 mg/kg/day is appropriate for most infections	30 to 100 mg/kg/day (intravenously) given as 2 or 3 divided doses
Complicated urinary tract infections, including pyelonephritis		
Soft-tissue infections: cellulitis, erysipelas and wound infections		

Intra-abdominal infections		

Renal impairment

Cefuroxime is primarily excreted by the kidneys. Therefore, as with all such antibiotics, in patients with markedly impaired renal function it is recommended that the dosage of Cefuroxime should be reduced to compensate for its slower excretion.

Table 3. Recommended doses for Cefuroxime *in renal impairment*

Creatinine clearance	**$T_{1/2}$ (hrs)**	**Dose mg**
> 20 mL/min/1.73 m^2	1.7–2.6	It is not necessary to reduce the standard dose (750 mg to 1.5 g three times daily).
10-20 mL/min/1.73 m^2	4.3–6.5	750 mg twice daily
< 10 mL/min/1.73 m^2	14.8–22.3	750 mg once daily
Patients on haemodialysis	3.75	A further 750 mg dose should be given intravenously or intramuscularly at the end of each dialysis; in addition to parenteral use, cefuroxime sodium can be incorporated into the peritoneal dialysis fluid (usually 250 mg for every 2 litres of dialysis fluid).
Patients in renal failure on continuous arteriovenous haemodialysis (CAVH) or high-flux haemofiltration (HF) in intensive therapy units	7.9–12.6 (CAVH) 1.6 (HF)	750 mg twice daily; for low-flux haemofiltration follow the dosage recommended under impaired renal function.

Hepatic impairment

Cefuroxime is primarily eliminated by the kidney. In patients with hepatic dysfunction this is not expected to affect the pharmacokinetics of cefuroxime.

Method of administration

Cefuroxime should be administered by intravenous injection over a period of 3 to 5 minutes directly into a vein or via a drip tube or infusion over 30 to 60 minutes, or by deep intramuscular injection. For instructions on reconstitution of the medicinal product before administration, see section 6.6.

750mg, 1.5 g powder for solution for infusion.

For instructions on preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Contra-indicated in patients hypersensitive to the cephalosporin group of 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

Hypersensitivity reactions

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.

Concurrent treatment with potent diuretics or aminoglycosides

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as furosemide or aminoglycosides. Renal

impairment has been reported during use of these combinations. Renal function should be monitored in the elderly and those with known pre-existing renal impairment (see section 4.2).

Overgrowth of non-susceptible microorganisms

Use of cefuroxime 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 has been reported with use of 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.

Intra-abdominal infections

Due to its spectrum of activity, cefuroxime is not suitable for the treatment of infections caused by Gram-negative non-fermenting bacteria (see section 5.1).

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).

Slight interference with copper reduction methods (Benedict's, Fehling's, Clinitest) may be observed. However, this should not lead to false-positive results, as may be experienced with some other cephalosporins.

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 sodium.

Important information about excipients

Cefuroxime powder for solution for injection and infusion contains sodium. This should be considered for patients who are on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Cefuroxime 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 prolongs the excretion of the antibiotic and produces an elevated peak serum level.

Potential nephrotoxic drugs and loop diuretics

High-dosage treatments with cephalosporins should be carried out with caution on patients who are taking strong-acting diuretics (such as furosemide) or potential nephrotoxic preparations (such as aminoglycoside antibiotics), since impairment of renal function through such combinations cannot be ruled out.

Other Interactions

Determination of blood/plasma glucose levels: Please refer to section 4.4.

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

4.6 Pregnancy and lactation

There are limited amounts of data from the use of cefuroxime in pregnant women. Studies in animals have shown no reproductive toxicity. Cefuroxime should be prescribed to pregnant women only if the benefit outweighs the risk.

Cefuroxime has been shown to cross the placenta and attain therapeutic levels in amniotic fluid and cord blood after intramuscular or intravenous dose to the mother.

Cefuroxime is excreted in human milk in small quantities. Adverse reactions at therapeutic doses are not expected, although a risk of diarrhoea and fungus infection of the mucous membranes cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from cefuroxime therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Cefuroxime is not known to affect the ability to drive or use machines.

4.8 Undesirable effects

The most common adverse reactions are neutropenia, eosinophilia, transient rise in liver enzymes or bilirubin, particularly in patients with pre-existing liver disease, but there is no evidence of harm to the liver and injection site reactions.

System organ class	Common	Uncommon	Not known
Infections and infestations			*Candida* overgrowth, overgrowth of *Clostridium difficile*
Blood and lymphatic system disorders	neutropenia, eosinophilia, decreased haemoglobin concentration	leukopenia, positive Coomb's test	thrombocytopenia, haemolytic anaemia
Immune system disorders			drug fever, interstitial nephritis, anaphylaxis, cutaneous vasculitis
Gastrointestinal disorders		gastrointestinal disturbance	pseudomembranous colitis
Hepatobiliary disorders	transient rise in liver enzymes	transient rise in bilirubin	
Skin and subcutaneous tissue disorders		skin rash, urticaria and pruritus	erythema multiforme, toxic epidermal necrolysis and Stevens-Johnson syndrome, angioneurotic oedema
Renal and urinary disorders			elevations in serum creatinine, elevations in blood urea nitrogen and decreased creatinine clearance (see section 4.4)
General disorders and administration site conditions	injection site reactions which may include pain and thrombophlebitis		

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Cefuroxime is a cephalosporin antibiotic, ATC code J01DC02 (Cephalosporins and Related Substances). All cephalosporins (β-lactam antibiotics) inhibit cell wall production and are selective inhibitors of peptidoglycan synthesis. The initial step in drug action consists of binding of the drug to cell receptors, called penicillin-binding proteins. After a β-lactam antibiotic has

bound to these receptors, the transpeptidation reaction is inhibited and peptidoglycan synthesis is blocked. Bacterial lysis is the end result.

Susceptibility

The following MIC breakpoints separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are used.

Microorganism	Breakpoints (mg/L)	
	S	R
Enterobacteriaceae[1]	≤8[2]	>8
Staphylococcus spp.	Note[3]	Note[3]
Streptococcus A, B, C and G	Note[4]	Note[4]
Streptococcus pneumoniae	≤0.5	>1
Streptococcus (other)	≤0.5	>0.5
Haemophilus influenzae	≤1	>2
Moraxella catarrhalis	≤4	>8
Non-species related breakpoints[1]	≤4[5]	>8[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] Breakpoint relates to a dosage of 1.5 g × 3 and to *E. coli, P. mirabilis* and *Klebsiella spp.* only

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

[5] Breakpoints apply to daily intravenous dose of 750 mg × 3 and a high dose of at least 1.5 g × 3.

S=susceptible, R=resistant.

The prevalence of resistance may vary geographically and with time for selected species and local information is desirable, particularly when treating several infections. This information gives only an approximate guidance on probabilities whether organisms will be susceptible to Cefuroxime or not.

Table 2: Cefuroxime is usually active against the following microorganisms *in vitro*.

Commonly susceptible species
Gram-positive aerobes:
Staphylococcus aureus (methicillin-suscpetible) $
Streptococcus pyogenes
Streptococcus agalactiae
Streptococcus mitis (viridans group)
Gram-negative aerobes:
Haemophilus influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis
Microorganisms for which acquired resistance may be a problem
Gram-positive aerobes:
Streptococcus pneumoniae
Gram-negative aerobes:
Citrobacter freundii
Enterobacter cloacae
Enterobacter aerogenes
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Proteus spp. (other than *P. vulgaris*)
Providencia spp.
Salmonella 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.
Morganella morganii
Proteus vulgaris
Pseudomonas aeruginosa
Serratia marcescens
Gram-positive anaerobes:
Clostridium difficile
Gram-negative anaerobes:
Bacteroides fragilis
Others:
Chlamydia spp.
Mycoplasma spp.
Legionella spp

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

Mechanisms of Resistance to Cefuroxime

Known mechanisms of resistance in targeted pathogens are the following:

• Production of β-lactamases which are able to hydrolyse cefuroxime efficiently (eg, several of the extended-spectrum and chromosomally-mediated β-lactamases).

• Reduced affinity of penicillin-binding proteins for cefuroxime (eg, penicillin-resistant *Streptococcus pneumoniae*).

• Cell wall impermeability.

• Efflux pumps.

5.2 Pharmacokinetic properties

Absorption

After intramuscular (IM) injection of cefuroxime to normal volunteers, the mean peak serum concentrations ranged from 27 to 35 μg/mL for a 750 mg dose and were achieved within 30 to 60

minutes after administration. Following intravenous (IV) doses of 750 and 1500 mg, serum concentrations were approximately 50 and 100 μg/mL, respectively, at 15 minutes.

AUC and C appear to increase linearly with increase in dose over the single dose range of 250 to 1000 mg following IM and IV max administration. There was no evidence of accumulation of cefuroxime in the serum from normal volunteers following repeat intravenous administration of 1500 mg doses every 8 hours.

Distribution

Protein binding has been stated as 33 to 50%, depending on the methodology used. The average volume of distribution 15.8L/1.73 m^2 following IM or IV administration over the dosage range of 250 to 1000 mg. 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

Cefuroxime is excreted by glomerular filtration and tubular secretion. The serum half-life after either intramuscular or intravenous injection is approximately 70 minutes. There is an almost complete recovery (85 to 90%) of unchanged cefuroxime in urine within 24 hours of administration. The majority of the cefuroxime is excreted within the first 6 hours. The average renal clearance ranges from 114 to 170 mL/min/1.73 m2 following IM or IV administration over the dosage range of 250 to 1000 mg.

Special patient populations

Gender

No differences in the pharmacokinetics of cefuroxime were observed between males and females following a single IV bolus injection of 1000 mg of cefuroxime as the sodium salt.

Elderly

Following IM or IV administration, the absorption, distribution and excretion of cefuroxime in elderly patients are similar to younger patients with equivalent renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in cefuroxime dose selection, and it may be useful to monitor renal function.

Pediatrics

The serum half-life of cefuroxime has been shown to be substantially prolonged in neonates according to gestational age. However, in older infants (aged >3 weeks) and in children, the serum half-life of 60 to 90 minutes is similar to that observed in adults.

Renal impairment

Cefuroxime is primarily excreted by the kidneys. As with all such antibiotics, in patients with markedly impaired renal function (i.e. C1cr <20 mL/minute) it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion.

Cefuroxime is effectively removed by haemodialysis and peritoneal dialysis.

Hepatic impairment

Since cefuroxime is primarily eliminated by the kidney, hepatic dysfunction is not expected to have an effect on the pharmacokinetics of cefuroxime.

PK/PD 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

There is no experimental evidence of embryopathic or teratogenic effects attributable to cefuroxime.

6. Pharmaceutical particulars

6.1 List of excipients

Not Applicable.

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at temperature below 30°C.

Reconstituted Solution: Store at 2° to 8°C.

Keep out of reach of Children.

6.5 Nature and contents of container

Cefuroxime for Injection USP 750mg: 10 ml vial USP Type III with 20mm Grey butyl rubber stopper and 20mm flip off seal packed in a Carton along with a leaflet.

Cefuroxime for Injection USP 1500mg: 15 ml vial USP Type III with 20mm Grey butyl rubber stopper and 20mm flip off seal packed in a Carton along with a leaflet.

6.6 Special precautions for disposal and other handling

Instructions for constitution

Table 4. Addition volumes and solution concentrations, which may be useful when fractional doses are required.

Addition volumes and solution concentrations, which may be useful when fractional doses are required			
Vial size		Amount of water to be added (ml)	Approximate cefuroxime concentration (mg/mL)**
750 mg powder for solution for injection or infusion			
750 mg	intramuscular	3 mL	216
	intravenous bolus	at least 6 mL	116
	intravenous infusion	at least 6 mL	116
1.5 g powder for solution for injection or infusion			
1.5 g	intramuscular	6 mL	216
	intravenous bolus	at least 15mL	94
	intravenous infusion	15 mL*	94

* Reconstituted solution to be added to 50 or 100 ml of compatible infusion fluid (see information on compatibility, below)
** The resulting volume of the solution of cefuroxime in reconstitution medium is increased due the displacement factor of the drug substance resulting in the listed concentrations in mg/ml.

CEROXIM 750 mg and 1.5 g powder for solution for infusion (Monovial presentation)

Preparation of solution for intravenous infusion

The contents of the monovial are added to small volume infusion bags containing 0.9% Sodium Chloride Injection, or 5% Dextrose Injection, or another compatible fluid.

1. Peel off the removable top part of the label and remove the cap.
2. Insert the needle of the monovial into the additive port of the infusion bag.
3. To activate, push the plastic needle holder of the monovial down onto the vial shoulder until a "click" is heard.
4. Holding it upright, fill the vial to approximately two-thirds capacity by squeezing the bag several times.
5. Shake the vial to reconstitute the cefuroxime sodium.
6. With the vial uppermost, transfer the reconstituted cefuroxime sodium into the infusion bag by squeezing and releasing the bag.
7. Repeat steps 4 to 6 to rinse the inside of the vial.

Dispose of the empty monovial safely. Check that the powder has dissolved, and that the bag has no leaks.

Compatibility

1.5 g cefuroxime sodium constituted with 15 mL Water for Injection may be added to metronidazole injection (500 mg/100 ml) and both retain their activity for up to 24 hours below 25°C.

1.5 g cefuroxime sodium is compatible with azlocillin 1 g (in 15 ml) or 5 g (in 50 ml) for up to 24 h at 4°C or 6 h below 25°C.

Cefuroxime sodium (5 mg/ml) in 5% w/v or 10% w/v xylitol injection may be stored for up to 24 h at 25°C.

Cefuroxime sodium is compatible with aqueous solutions containing up to 1% lidocaine hydrochloride.

Cefuroxime sodium is compatible with the following infusion fluids. It will retain potency for up to 24 hours at room temperature in:

Sodium Chloride Injection BP 0.9% w/v

5% Dextrose Injection BP

0.18% w/v Sodium Chloride plus 4% Dextrose Injection BP

5% Dextrose and 0.9% Sodium Chloride Injection

5% Dextrose and 0.45% Sodium Chloride Injection

5% Dextrose and 0.225% Sodium Chloride Injection

10% Dextrose Injection

10% Invert Sugar in Water for Injection

Ringer's Injection USP

Lactated Ringer's Injection USP

M/6 Sodium Lactate Injection

Compound Sodium Lactate Injection BP (Hartmann's Solution).

The stability of cefuroxime sodium in Sodium Chloride Injection BP 0.9% w/v and in 5% Dextrose Injection is not affected by the presence of hydrocortisone sodium phosphate.

Cefuroxime sodium has also been found compatible for 24 h at room temperature when admixed in i.v. infusion with: Heparin (10 and 50 units/ml) in 0.9% Sodium Chloride Injection; Potassium Chloride (10 and 40 mEqL) in 0.9% Sodium Chloride Injection.

Disposal

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

7. Marketing authorization holder

Sun Pharmaceuticals Ind. Ltd.
Sun House, 201 B/1,
Western Express Highway,
Goregaon (East), Mumbai - 400063, India

8. Marketing authorization number(s)

C4-0168

9. Date of first authorization/renewal of the authorization

November 2019