SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SANFUR - 1500 (Cefuroxime for Injection USP 1500mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Label claim:
Each vial contains:

Sterile Cefuroxime Sodium USP equivalent to anhydrous Cefuroxime 1500mg

3. PHARMACEUTICAL FORM

Dry powder for Injection
Appearance of powder: Sterile, white or faintly yellow powder, distributed in sealed container and which when shaken with the prescribed volume of sterile liquid, rapidly form clear and practically particle-free solution

4. CLINICAL PARTICULARS

Cefuroxime sodium for injection is indicated for the treatment of infections listed below in adultsand 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 gynecological 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.

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Table 1. Adults and children ≥ 40 kg

Indication	**Dosage**
Community acquired pneumonia and acuteexacerbations 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	1.5 g every 8 hours
pyelonephritis	(intravenously or intramuscularly)
Severe infections	750 mg every 6 hours (intravenously) 1.5 g every 8 hours (intravenously)
Surgical prophylaxis for gastrointestinal, gynecological surgery (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 andoesophageal operations	1.5 g with induction of anaesthesia followed by750 mg (intramuscularly) every 8 hours for a further 24 hours.

Table 2. Children < 40 kg

Indication	Infants and toddlers > 3 weeksand 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 Cefuroximeshould be reduced to compensate for its slower excretion.

Table 3. Recommended doses for Cefuroxime in renal impairment

Creatinine clearance	**T1/2 (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 hemodialysis	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 hemofiltration follow the dosage recommended under impaired renal function.

Hepatic impairment

Cefuroxime is primarily eliminated by the kidney. In patients with hepatic dysfunction this is notexpected 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. Intramuscular injections should be injected well within the bulk of a relatively large muscle and not more than 750 mg should be injected at one site. For doses greater than 1.5 g intravenous administration should be used.

Compatibility:
Compatible below Recommended Diluents are

i) 0.9% sodium chloride solution

ii) 5% dextrose solution

iii) 10% dextrose solution

iv) 0.9% sodium chloride +5% dextrose solution

v) WFI

It is found compatible for 24 hours at room temperature.

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)

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.

Cephalosporin antibiotics may, in general, be given safely to patients who are hypersensitive to penicillins, although cross-reactions have been reported. Special care is indicated in patients whohave experienced an anaphylactic reaction to penicillin.

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

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.

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. 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.

Interference with diagnostic tests

The development of a positive Coombs Test associated with the use of cefuroxime may interferewith cross matching of blood.
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.

Intracameral use and eye disorders

Cefuroxime is not formulated for intracameral use. Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intracameral use of cefuroxime sodium compounded from vials approved for intravenous/intramuscular administration. These reactions included macular oedema, retinal oedema, retinal detachment, retinal toxicity, visual impairment, visual acuity reduced, vision blurred, corneal opacity and corneal oedema.

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.

Interactions 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 probenecid is not recommended. Concurrent administration of probenecid prolongs the excretionof Cefuroxime 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).

Fertility, Pregnancy and Lactation

Pregnancy

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.

Breastfeeding

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 forthe child and the benefit of therapy for the woman.

Fertility

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

Effects on Ability to Drive and Use Machines

No studies on the effects of Cefuroxime on the ability to drive and use machines have been performed. However, based on known adverse reactions, Cefuroxime is unlikely to have an effect on the ability to drive and use machines.

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.

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

Data from clinical trials were used to determine the frequency of very common to rare adverse reactions. The frequencies assigned to all other adverse reactions (i.e. those occurring at <1/10,000) were mainly determined using post-marketing data, and refer to a reporting rate rather than a true frequency.

Treatment related adverse reactions, all grades, are listed below by MedDRA body system organclass, frequency and grade of severity. The following convention has been utilized 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 beestimated from the available data).

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 Coombs'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 creatinineclearance
General disorders and administration site conditions	injection site reactions which may include pain and thrombophlebitis		
Description of selected adverse reactions Cephalosporins as a class tend to be absorbed onto the surface of red cell 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 or bilirubin have been observed which are usually reversible. Pain at the intramuscular injection site is more likely at higher doses. However, it is unlikely to bea cause for discontinuation of treatment.			

Paediatric population

The safety profile for Cefuroxime sodium in children is consistent with the profile in adults.

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 hemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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

Mechanism of action

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) extended-spectrum beta-lactamases (ESBLs), and Amp-C enzymes, that may be induced or stably derepressed in certain aerobic Gram-negative bacterial 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 sodium breakpoints

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

Microorganism	**Breakpoints (mg/L)**	
	Susceptible	Resistant
Enterobacteriaceae (Enterobacterales)[1, 2]	≤8	>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
Kingella kingae	≤0.5	>0.5
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 isolates that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as tested, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. ESBL detection and characterization are recommended for public health and 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 cefoxitin susceptibility except for cefixime, ceftazidme, ceftazidime-avibactam, ceftibuten and ceftolozane-tazobactam,

which do not have breakpoints and should not be used for staphylococcal infections.

[4] The susceptibility of streptococcus groups A, B, C and G is inferred from the benzylpenicillinsusceptibility.

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

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 known and the utility of the agent 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)* $ *Streptococcus pyogenes Streptococcus agalactiae*
Gram-negative aerobes: *Haemophilus parainfluenzae* *Moraxella catarrhalis*
Microorganisms for which acquired resistance may be a problem
Gram-positive aerobes: *Streptococcus pneumoniae* *Streptococcus mitis* (viridans group)
Gram-negative aerobes: *Citrobacter spp. not including C. freundii*

Enterobacter spp. not including *E. aerogenes* and *E. cloacae* *Escherichia coli* *Haemophilus influenzae* *Klebsiella pneumoniae* *Proteus mirabilis* *Proteus* spp. not including *P. penneri and 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. *Burkholderia cepacia* *Campylobacter* spp. *Citerobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Morganella morganii* *Proteus penneri*

Proteus vulgaris Pseudomonas aeruginosa Serratia marcescens Stenotrophomonas maltophilia
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.

In vitro the activities of Cefuroxime sodium and aminoglycoside antibiotics in combination havebeen shown to be at least additive with occasional evidence of synergy.

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 from 33 to 40 µg/mL for a 1000 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_{max} appear to increase linearly with increase in dose over the single dose range of 250 to 1000 mg following IM and IV administration. There was no evidence of accumulation of Cefuroxime in the serum from normal volunteers following repeat intravenous administration of1500 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 ranges from 9.3 to 15.8 L/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 metabolized.

Elimination

Cefuroxime is excreted by Glomerular filtration and tubular secretion. The serum half-life after either intramuscular or intravenous administration 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 m^2 following IM or IV administration overthe 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 sal

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

Paediatrics

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).

Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional 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

List of excipients

None

Incompatibilities

Cefuroxime is compatible with most commonly used intravenous fluids and electrolyte solutions.

The pH of 2.74% w/v sodium bicarbonate injection BP considerably affects the colour of solutions and therefore this solution is not recommended for the dilution of Cefuroxime. However, if required, for patients receiving sodium bicarbonate injection by infusion the Cefuroxime solution may be introduced into the tube of the giving set.

Cefuroxime should not be mixed in the syringe with aminoglycoside antibiotics.

Shelf life

24 months

Special precautions for storage

Store at temperature below 30° C. Protect from light.

The reconstituted solution should be used immediately after preparation

KEEP OUT OF REACH OF CHILDREN

Nature and contents of container

Cefuroxime for injection USP 1500mg is filled in 15ml USP Type III vial sealed with 20mm Grey butyl rubber stopper and 20mm flip off seal. One such unit is packed along with pack insertand sterile water for Injection USP 10ml in a printed carton.

Special precautions for disposal and other handling

None

7. MARKETING AUTHORISATION HOLDER

Sance Laboratories Private Limited.
VI/51B, P.B.No: 2, Kozhuvanal-686573,
Pala, Kottayam District, Kerala,
India.

8. MARKETING AUTHORISATION NUMBER(S)

TAN 21 HM 0090

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

March 19, 2021

10. DATE OF REVISION OF THE TEXT

March, 2021