SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SANPIME - 1000
Cefepime for Injection USP 1000mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Sterile Cefepime Hydrochloride USP equivalent to anhydrous Cefepime 1000mg
L-Arginine for pH adjustment

Sr. No	Material	Specification	Quantity/Unit in mg	Function
1	Cefepime for Injection	USP	1984.0*	Active Pharmaceutical Ingredient

Remarks:
*Standard quantity is based on 90.0% w/w assay value as Cefepime, 4.0% w/w water content and 40% L-Arginine.

3. PHARMACEUTICAL FORM

Dry powder for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Pneumonia
- Empiric Therapy For Febrile Neutropenic Patients
- Uncomplicated And Complicated Urinary Tract Infections (Including Pyelonephritis)
- Uncomplicated Skin And Skin Structure Infections
- Complicated Intra-Abdominal Infections (Used In Combination With Metronidazole)

4.2 Posology and method of administration

Dosage For Adults

The recommended adult dosages and routes of administration are outlined in Table 1 below for patients with creatinine clearance greater than 60 mL/min. Administer Cefepime intravenously over approximately 30 minutes.

Table 1: Recommended Dosage Schedule for Cefepime in Adult Patients with Creatinine Clearance (CrCL) Greater Than 60 mL/min

Site and Type of infection	Dose	Frequency	Duration(Days)
Adults			

Moderate to severe Pneumonia	1 – 2g IV	Every 8 to 12 hours	10
Empiric therapy for febrile neutropenic patients	2g IV	Every 8 hours	7*
Mild to moderate Uncomplicated or Complicated Urinary Tract Infections	0.5 – 1g IV/IM**	Every 12 hours	7 - 10
Severe Uncomplicated or Complicated Urinary Tract Infections	2g IV	Every 12 hours	10
Moderate to severe Uncomplicated Skin and Skin structure Infections	2g IV	Every 12 hours	10
Complicated Intra-abdominal Infections[§]	2g IV	Every 12 hours	7 - 10

*or until resolution of neutropenia. In patients whose fever resolves but who remain neutropenic for more than 7 days, the need for continued antimicrobial therapy should be re-evaluated frequently.

**Intramuscular route of administration is indicated only for mild to moderate, uncomplicated or complicated UTIs due to *E. coli.*

[§] For *P. aeruginosa*, use 2 g IV every 8 hours.

Pediatric Patients (2 Months Up To 16 Years)

The maximum dose for pediatric patients should not exceed the recommended adult dose.

The usual recommended dosage in pediatric patients up to 40 kg in weight for durations as given above for adults is:

- 50 mg per kg per dose, administered every 12 hours for uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, and pneumonia (see below).

- For moderate to severe pneumonia due to *P. aeruginosa* give 50 mg per kg per dose, every 8 hours.
- 50 mg per kg per dose, every 8 hours for febrile neutropenic patients.

Dosage Adjustments In Patients With Renal Impairment
Adult Patients

Adjust the dose of Cefepime in patients with creatinine clearance less than or equal to 60 mL/min to compensate for the slower rate of renal elimination. In these patients, the recommended initial dose of cefepime should be the same as in patients with CrCL greater than 60 mL/min except in patients undergoing hemodialysis. The recommended doses of cefepime in patients with renal impairment are presented in Table 2.

When only serum creatinine is available, the following formula (Cockcroft and Gault equation)[1]may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

Males: $\frac{\textbf{(weight in kg) x (140 – age)}}{\text{(72) x serum creatinine (mg/100 mL)}}$

Females: (0.85) x (above value)

Table 2: Recommended Dosing Schedule for Cefepime in Adult Patients With Creatinine Clearance Less Than or Equal to 60 mL/min

Creatinine Clearance (mL/min)	**Recommended Maintenance Schedule**			
Greater than 60 Normal recommended dosing schedule	500mg Every 12 hours	1g Every 12 hours	2g Every 12 hours	2g Every 8 hours
30 - 60	500mg every 24 hours	1g every 24 hours	2g every 24 hours	2g every 12 hours
11 - 29	500mg every 24 hours	500mg every 24 hours	1g every 24 hours	2g every 24 hours
Less than 11	250mg every 24 hours	250mg every 24 hours	500mg every 24 hours	1g every 48 hours
CAPD	500mg every 48 hours	1g every 48 hours	2g every 48 hours	2g every 48 hours

Hemodialysis*	1 g on day 1, then 500mg every 24 hours thereafter	1g every 24 hours

*On hemodialysis days, Cefepime should be administered following hemodialysis. Whenver possible, Cefepime should be administered at the same time each day.

In patients undergoing continuous ambulatory peritoneal dialysis, Cefepime may be administered at normally recommended doses at a dosage interval of every 48 hours(see Table 2).

In patients undergoing hemodialysis, approximately 68% of the total amount of cefepime present in the body at the start of dialysis will be removed during a 3-hour dialysis period. The dosage of cefepime for hemodialysis patients is 1 g on Day 1 followed by 500 mg every 24 hours for the treatment of all infections except febrile neutropenia, which is 1 g every 24 hours.

Cefepime should be administered at the same time each day and following the completion of hemodialysis on hemodialysis days (see Table 2).

Pediatric Patients

Data in pediatric patients with impaired renal function are not available; however, since cefepime pharmacokinetics are similar in adults and pediatric patients changes in the dosing regimen proportional to those in adults (see Tables 1 and 2) are recommended for pediatric patients.

4.3 Contraindications

cefepime is contraindicated in patients who have shown immediate hypersensitivity reactions to cefepime or the cephalosporin class of antibacterial drugs, penicillins or other beta-lactam antibacterial drugs.

4.4 Special warnings and precautions for use

WARNINGS

Included as part of the **"PRECAUTIONS"** Section

PRECAUTIONS

Hypersensitivity Reactions

Before therapy with cefepime for Injection is instituted, careful inquiry should be made to determine whether the patient has had previous immediate hypersensitivity reactions to cefepime, cephalosporins, penicillins, or other beta-lactams. Exercise caution if this product is to

be given to penicillin-sensitive patients because cross-hypersensitivity among beta-lactam antibacterial drugs has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to cefepime occurs, discontinue the drug and institute appropriate supportive measures.

Neurotoxicity

Serious adverse reactions have been reported including life-threatening or fatal occurrences of the following: encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), aphasia, myoclonus, seizures, and nonconvulsive status epilepticus [see **ADVERSE REACTIONS**]. Most cases occurred in patients with renal impairment who did not receive appropriate dosage adjustment.

However, some cases of neurotoxicity occurred in patients receiving a dosage adjustment appropriate for their degree of renal impairment. In the majority of cases, symptoms of neurotoxicity were reversible and resolved after discontinuation of cefepime and/or after hemodialysis. If neurotoxicity associated with cefepime therapy occurs, discontinue cefepime and institute appropriate supportive measures.

Clostridioides Difficile-Associated Diarrhea

Clostridioides difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including MAXIPIME, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C.difficile.*

C.difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C.difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C.difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C.difficile,* and surgical evaluation should be instituted as clinically indicated.

Development Of Drug-Resistant Bacteria

Prescribing MAXIPIME in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other antimicrobials, prolonged use of MAXIPIME may result in overgrowth of nonsusceptible microorganisms. Repeated evaluation of the patient's condition is essential. Should superinfection occur during therapy, appropriate measures should be taken.

4.5 Interaction with other medicinal products and other forms of interaction

Drug/Laboratory Test Interactions

The administration of cefepime may result in a false-positive reaction for glucose in the urine with certain methods. It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

Aminoglycosides

Monitor renal function if aminoglycosides are to be administered with MAXIPIME because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibacterial drugs.

Diuretics

Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide. Monitor renal function when cefepime is concomitantly administered with potent diuretics.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no cases of cefepime exposure during pregnancy reported from postmarketing experience or from clinical trials. Available data from published observational studies and case reports over several decades with cephalosporin use in pregnant women have not established drug-associated risks of major birth defects, miscarriage or adverse maternal or fetal outcomes .

Cefepime was not associated with adverse developmental outcomes in rats, mice, or rabbits when administered parenterally during organogenesis. The doses used in these studies were 1.6 (rats), approximately equal to (mice), and 0.3 times (rabbits) the recommended maximum human dose .

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other

adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Fertility

No animal carcinogenicity studies have been conducted with cefepime. In chromosomal aberration studies, cefepime was positive for clastogenicity in primary human lymphocytes, but negative in Chinese hamster ovary cells. In other *in vitro* assays (bacterial and mammalian cell mutation, DNA repair in primary rat hepatocytes, and sister chromatid exchange in human lymphocytes), cefepime was negative for genotoxic effects. Moreover, *in vivo* assessments of cefepime in mice (2 chromosomal aberration and 2 micronucleus studies) were negative for clastogenicity. No untoward effects on fertility were observed in rats when cefepime was administered subcutaneously at doses up to 1000 mg/kg/day (1.6 times the recommended maximum human dose based on body surface area).

Lactation

Cefepime is present in human breast milk at low concentrations (approximately 0.5 mcg/mL) following a single intravenous dose of 1000 mg. A nursing infant consuming approximately 1000 mL of human milk per day would receive approximately 0.5 mg of cefepime per day . There is no information regarding the effects of cefepime on the breastfed infant or on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for cefepime and any potential adverse effects on the breastfed child from cefepime or from the underlying maternal condition.

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 performed.

4.8 Undesirable effects

The following adverse reactions are discussed in the Warnings and Precautions section and below:

- Hypersensitivity Reactions [see **WARNINGS AND PRECAUTIONS**]
- Neurotoxicity [see **WARNINGS AND PRECAUTIONS**]
- *Clostridioides difficile*-Associated Diarrhea [see **WARNINGS AND PRECAUTIONS**]
- Anaphylaxis including anaphylactic shock,
  transient leukopenia, neutropenia, agranulocytosis and thrombocytopenia, have been reported.

- In addition to the adverse reactions listed above that have been observed in patients treated with cefepime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibacterial drugs:
- Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic dysfunction including choestasis, and pancytopenia.

Pediatric Use

- The safety and effectiveness of cefepime in the treatment of uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, pneumonia, and as empiric therapy for febrile neutropenic patients have been established in the age groups 2 months up to 16 years. Use of MAXIPIME in these age groups is supported by evidence from adequate and well-controlled studies of cefepime in adults with additional pharmacokinetic and safety data from pediatric trials.
- Safety and effectiveness in pediatric patients below the age of 2 months have not been established. There are insufficient clinical data to support the use of MAXIPIME in pediatric patients for the treatment of serious infections in the pediatric population where the suspected or proven pathogen is H. influenzae type b. In those patients in whom meningeal seeding from a distant infection site or in whom meningitis is suspected or documented, an alternate agent with demonstrated clinical efficacy in this setting should be used.

Geriatric Use

- Of the more than 6400 adults treated with MAXIPIME in clinical studies, 35% were 65 years or older while 16% were 75 years or older. When geriatric patients received the usual recommended adult dose, clinical efficacy and safety were comparable to clinical efficacy and safety in non-geriatric adult patients.
- Serious adverse events have occurred in geriatric patients with renal insufficiency given unadjusted doses of cefepime, including life-threatening or fatal occurrences of the following: encephalopathy, myoclonus, and seizures.
- This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.

Renal Impairment

- Adjust the dose of MAXIPIME in patients with creatinine clearance less than or equal to 60 mL/min to compensate for the slower rate of renal elimination.

4.9 Overdose
In cases of severe overdose, particularly in patients with impaired renal function, haemodialysis can assist in eliminating Cefepime from the body. Peritoneal dialysis has no benefit. Unintentional overdose has occurred when patients with renal dysfunction were administered high doses (see sections 4.2 and 4.4). Symptoms of an overdose include encephalopathy (impaired consciousness, including confusion, hallucinations, stupor and coma), myoclonic seizures and neuromuscular excitability (see section 4.8).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other beta-lactam antibiotics, 4th-generation cephalosporins; ATC code: J01DE01

Mode of action

Cefepime is a bactericidal drug that acts by inhibition of bacterial cell wall synthesis. Cefepime has a broad spectrum of *in vitro* activity that encompasses a wide range of Gram-positive and Gram-negative bacteria. Within bacterial cells, the molecular targets of cefepime are the penicillin binding proteins (PBP).

Antimicrobial Activity

Cefepime has been shown to be active against most isolates of the following microorganisms, both *in vitro*and in clinical infections as described in the Indications and Usage section (1).

Gram-negative Bacteria

Enterobacter spp.
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

Gram-positive Bacteria

Staphylococcus aureus(methicillin-susceptible isolates only)
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans group streptococci

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for cefepime against isolates of similar genus or organism group. However, the efficacy of cefepime in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-positive Bacteria

Staphylococcus epidermidis (methicillin-susceptible isolates only)
Staphylococcus saprophyticus
Streptococcus agalactiae

NOTE: Most isolates of enterococci, e.g.,*Enterococcus faecalis*,and methicillin-resistant staphylococci are resistant to cefepime.

Gram-negative Bacteria

Acinetobacter calcoaceticus subsp. *lwoffii*
Citrobacter diversus
Citrobacter freundii
Enterobacter agglomerans
Haemophilus influenzae
Hafnia alvei
Klebsiella oxytoca
Moraxella catarrhalis
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

NOTE: Cefepime is inactive against many isolates of *Stenotrophomonas maltophilia.*

5.2 Pharmacokinetic properties

Pharmacokinetic parameters for cefepime in healthy adult male volunteers (n=9) following single 30-minute infusions (IV) of cefepime 500 mg, 1 g, and 2 g are summarized in Table 7. Elimination of cefepime is principally via renal excretion with an average (±SD) half-life of 2 (±0.3) hours and total body clearance of 120 (±8) mL/min in healthy volunteers. Cefepime pharmacokinetics are linear over the range 250 mg to 2 g. There is no evidence of accumulation in healthy adult male volunteers (n=7) receiving clinically relevant doses for a period of 9 days.

Mean Pharmacokinetic Parameters for Cefepime (±SD), Intravenous Administration

CEFEPIME	
Parameter	**1G IV**
Cmax, mcg/mL	**81.7 (5.1)**
AUC, h•mcg/mL	**148.5 (15.1)**

Number of subjects (male)	**9**

Pharmacokinetic parameters for cefepime following a single intramuscular injection are summarized in Table . The pharmacokinetics of cefepime are linear over the range of 500 mg to 2 g intramuscularly and do not vary with respect to treatment duration.

Mean Pharmacokinetic Parameters for Cefepime (±SD), Intramuscular Administration cefepime

Cefepime	
Parameter	**1g IM**
Cmax, mcg/mL	29.6 (4.4)
Tmax, h	1.6 (0.4)
AUC, h•mcg/mL	137 (11)
Number of subjects (male)	6

Absorption

Following intramuscular (IM) administration, cefepime is completely absorbed.

Distribution

The average steady-state volume of distribution of cefepime is 18 (±2) L. The serum protein binding of cefepime is approximately 20% and is independent of its concentration in serum.

Concentrations of cefepime achieved in specific tissues and body fluids are listed in Table 9.

Table 9: Mean Concentrations of Cefepime in Specific Body Fluids (mcg/mL) or Tissues (mcg/g)

Tissue or Fluid	**Dose/Route**	**# of patients**	**Mean Time of sample Post-Dose (h)**	**Mean concentration**
Urine	1g IV	12	0 to 4	926 mcg/mL

Data suggest that cefepime does cross the inflamed blood-brain barrier. The clinical relevance of these data is uncertain at this time.

Metabolism And Excretion

Cefepime is metabolized to N-methylpyrrolidine (NMP) which is rapidly converted to the N-oxide (NMP-N-oxide). Urinary recovery of unchanged cefepime accounts for approximately 85% of the administered dose. Less than 1% of the administered dose is recovered from urine as NMP, 6.8% as NMP-N-oxide, and 2.5% as an epimer of cefepime. Because renal excretion is a significant pathway of elimination, patients with renal dysfunction and patients undergoing hemodialysis require dosage adjustment [see **DOSAGE AND ADMINISTRATION**].

5.3 Preclinical safety data

Although no long-term animal studies have been performed to evaluate carcinogenic potential, *in vivo* and *in vitro* testing has shown that Cefepime is not genotoxic.

Studies in animals have shown that daily doses of up to 10 times the recommended dose in humans do not have any direct or indirect harmful effects on reproduction, embryonal/foetal development, duration of gestation or peri/postnatal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

NA

6.2 Incompatibilities

Solutions of Cefepime must not be mixed with the following antibiotics: metronidazole, vancomycin, gentamicin, tobramycin sulphate and netilmicin sulphate, because
physical or chemical incompatibilities may arise. Should concomitant therapy be indicated, such agents must be administered separately.

If the solution or container permits, all parenteral products should be visually inspected for particles prior to administration.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a cool dry place at temperature below 30°C. Protect from light.
Reconstituted solution should be used immediately after preparation
KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

15ml Type III colorless glass vial closed with 20mm Grey butyl rubber stopper and 20 mm taxim blue flip off seal, Such 01 vial is packed in mono carton along with pack insert and 10ml Sterile Water For Injection.

7. Marketing authorization holder

Sance Laboratories Pvt. Ltd.
VI/51B, P.B. No.2,
Kozhuvanal, Pala

Kottayam 686 573,
Kerala, India

8. Marketing authorization number(s)
03819/5072/VAR/2017

9. Date of first authorization/renewal of the authorization
Date of renewal: 18/04/2023

10. Date of revision of the text
11/07/2023