SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

NECPIME 1 g(Cefepime for Injection USP 1 g)

1.1. Strength

1 g

1.2. Pharmaceutical Form

Powder for Injection

2. Qualitative & Quantitative Composition

<u>For Cefepime for injection USP 1 g</u>

Each vial contains

Cefepime USP..... 1 g

(As Cefepime Hydrochloride)

A blend of Sterile Cefepime Hydrochloride & Sterile Arginine

3. Pharmaceutical form

Powder for Injection *(PI)*

- White to pale yellow powder filled in Clear, transparent glass vial with grey coloured bromobutyl rubber stopper and coloured polypropylene disc.

4. Clinical Particulars

4.1. Therapeutic Indications

Cefepime for Injection USP 1 g is indicated in the treatment of following infection caused by susceptible strains of following organisms.

- Pneumonia (moderate to severe): caused by *Streptococcus pneumoniae,*including caeses associated with concurrent bacteremia, *Pseudomonas aeruginosa, Klebseilla pneumonia or Enterobacter species.*

- Empiric Therapy for Febrile Neutropenic patients: Cefepime as monotherapy is indicated for empiric treatment of febrile neutropenic patients. In patients at high risk for svere infections (including patients with history of recent bone marrow transplantation,with hypotension at presentation, with an underlying hemotologic malignancy,or with severe or prolonged neutropenia),antimicrobial monotherapy may not be appropriate.

- Uncomplicated and Complicated Urinary Tract Infections (including pyelonephritis): caused by *Escherichia coli or Klebsiella pneumonia*, when the infection is severe, or caused by *Escherichia coli , Klebsiella pneumonia or Proteus mirabilis,* when the infection is mild to moderate, including cases associated with concurrent bacteremia with these microorganisms.

- Uncomplicated Skin and Skin structure Infections: caused by *Staphylococcus aureus* (methicillin susceptible strains only) or *Streptococcus pyogenes.*

- Complicated Intra-abdominal Infections: (used in Combination with metronidazole) caused by *Escherichia coli*, viridians group S*treptococci, Pseudomonas aeruginosa, Klebsiella pneumonia, Enterobacter species or Bacteroides fragilis.*

  To reduce the development of drug-resistant bacteria and maintain the effectiveness of *Cefepime for injection USP* 500 *mg/1 g* and other antibacterial drugs, it should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy.

4.2. Posology & Method of administration

Method of Administration : Intramuscular/Intravenous

The recommended adult and pediatric dosages are outlined in the following table:

Table 1: *Recommended Dosage Schedule in Patients with Creatinine clearance > 60 ml/min*

Site & Type of Infection	***Dose***	***Frequency***	***Duration (Days)***
Adults			
Moderate to Severe Pneumonia	1 to 2 g IV	Every 12 hours	10
Empiric therapy for Febrile Neutropenic patients	2 g IV	Every 8 hours	7*
Mild to Moderate Uncomplicated or Complicated Urinary Tract Infections	0.5 to 1 g IV/IM**	Every 12 hours	7 to 10
Severe Uncomplicated or Complicated Urinary tract Infections	2 g IV	Every 12 hours	10
Moderate to Severe Uncomplicated Skin and Skin structure Infections	2 g IV	Every 12 hours	10
Complicated Intra-abdominal Infections	2 g IV	Every 12 hours	7 to 10
Pediatric Patients (2 months upto 16 years) The maximum dose for pediatric patients should not exceed the recommended adult dose. The usual recommended dosage in pediatric patients upto 40 kg in weight for Uncomplicated and Complicated urinary tract infections,uncomplicated Skin and Skin structure infections and Pneumonia is 50 mg per kg per dose, administered every 12 hours.			
*Or until resolution of Neutropenia. In patients whose fe3ver 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* when the intramuscular route is considered to be a more appropriate route of drug administration.			

Patients with Hepatic Impairment

No adjustment is necessary for patients with hepatic impairment.

Patients with Renal Impairment

In patients with Creatinine clearance less than or equal to 60 ml/min, the dose of *Cefepime for injection USP 1 g* should be adjusted to compensate for the slower rate of renal elimination. The recommended initial dose should be the same as in patients with normal renal function except in patients undergoing hemodialysis. The recommended doses in patient with Renal impairment is given in *Table 2*.

Table 2: *Recommended Dosing Schedule in Adult Patients*

Creatinine Clearance (ml/min)	***Recommended Maintenanace Schedule***			
Greater than 60 Normal recommended dosing schedule	500 mg every 12 hours	1 g every 12 hours	2 g every 12 hours	2 g every 8 hours
30 to 60	500 mg every 24 hours	1 g every 24 hours	2 g every 24 hours	2 g every 12 hours
11 to 29	500 mg every 24 hours	500 mg every 24 hours	1 g every 24 hours	2 g every 24 hours
Less than 11	250 mg every 24 hours	250 mg every 24 hours	500 mg every 24 hours	1 g every 24 hours
CAPD	500 mg every 48 hours	1 g every 48 hours	2 g every 48 hours	2 g every 48 hours
Hemodialysis*	1 g on day 1, then 500 mg every 24 hours thereafter			1 g every 24 hours
*on Hemodialysis days, cefepime should be administered following hemodialysis. Whenever possible, cefepime should be administered at the same time each day.				

In patients undergoing Hemodialysis, approximately 68% of the total amount of Cefepime present in the body at the star of dialysis will be removed during a 3 hour dialysis period. The dosage 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.

4.3. Contraindications

It is contraindicated in patients who have shown immediate hypersensitivity reactions to Cefepime or the Cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics.

4.4. Special warnings and precautions for use

4.4.1. Warnings

- *Hypersensitivity reactions :*

Before therapy with *Cefepime for Injection USP 1 g* is instituted, careful injury should be made to determine whether the patient has had previous immediate hypersensitivity reactions to Cefepime, Cephalosporins, Penicillins or other drugs. Exercise caution if this product is to be given to penicillin-ssensitive patients because cross-hypersensitivity among beta-lactam antibiotics has been clearly documented and may occur in upto 10 % of patients with a history of penicillin allergy. If an allergic reaction occurs, discontinue the drug.

- *Use in patients wirh Renal Impairment :*

In patients with Creatinine clearance less than or equal to 60 ml/min, adjust the dose to compensate for slower rate of renal elimination. Because high and prolonged serum cefepime concentrations can occur from usual dosages in patients with renal impairment, the Cefepime dosage should be reduced when it is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms.

- *Clostridium difficile Associated Diarrhea :*

CDAD has been reported with use of nearly all antibacterial agents 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.*

If CDAD is suspected or confirmed, ongoing antibiotic use need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C.difficle* and surgical evaluation should be instituted as clinically indicated.

4.4.2. Precautions

Prescribing *Cefepime for injection USP 1 g* 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 may result in overgrowth of nonsusceptible microorganisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Many cephalosporins, including cefepime, have been associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk, and exogenous vitamin K administered as indicated.

Positive direct Coombs' tests have been reported during treatment with *Cefepime for injection USP 500 mg/1g*. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Arginine has been shown to alter glucose metabolism and elevate serum potassium transiently when administered at 33 times the amount provided by the maximum recommended human dose. The effect of lower doses is not presently known.

4.5. Interaction with other medicinal products and other interactions

- Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with Cefepime because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide.

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

4.6. Fertility,pregnancy and lactation

- *Pregnancy*

Cefepime was not teratogenic or embryocidal when administered during the period of organogenesis to rats at doses up to 1000 mg/kg/day (1.6 times the recommended maximum human dose calculated on a mg/m2 basis) or to mice at doses up to 1200 mg/kg (approximately equal to the recommended maximum human dose calculated on a mg/m2 basis) or to rabbits at a dose level of 100 mg/kg (0.3 times the recommended maximum human dose calculated on a mg/m2 basis).

There are, however, no adequate and well-controlled studies of cefepime use in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

- *Breast feeding*

Cefepime is excreted in human breast milk in very low concentrations (0.5 mcg/mL).

Caution should be exercised when cefepime is administered to a nursing woman.

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. However, as this medicine may cause dizziness, patients should be warned to be cautious when driving or operating machinery.

4.8. Undesirable Effects

The following adverse events were thought to be related to Cefepime during Evaluation of the drug in Clinical Trials conducted.

Incidence equal to or Greater than 1 %	Local reactions (3%), including Phlebitis (1.3%), pain or inflammation (0.6%)*, Rash (1.1%)
Incidence less than 1 % but greater than 0.1 %	Colitis (including pseudomembranous colitis), Diarrhea, Erythema, fever, headache, nausea, oral moniliasis, pruritus, urticaria, vaginitis, vomiting, anemia
*Local reactions,irrespective of relationship to cefepime in those patients who received intravenous infusion.	

At the higher dose of 2 g every 8 hours, the incidence of probably related adverse events was higher among the 795 patients who received this dose of Cefepime. They considered of rash (4%), Diarrhea (3%), nausea (2%), vomiting (1%), pruritus (1 %), fever (1%) and headache (1%).

4.9. Overdose

Patients who receive an overdose should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis, not peritoneal dialysis, is recommended to aid in the removal of cefepime from the body. Accidental overdosing has occurred when large doses were given to patients with impaired renal function. Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, neuromuscular excitability and nonconvulsive status epilepticus.

5. Pharmacological Properties

5.1. Pharmacodynamic Properties

Cefepime is a bactericidal agent 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. Cefepime has a low affinity for chromosomally-encoded beta-lactamases. Cefepime is highly resistant to hydrolysis by most beta-lactamases and exhibits rapid penetration into Gram-negative bacterial cells. Within bacterial cells, the molecular targets of cefepime are the penicillin binding proteins (PBP).

Cefepime has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections.

- Aerobic Gram-Negative Microorganisms:

Enterobacter
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

- Aerobic Gram-Positive Microorganisms:

Staphylococcus aureus (methicillin-susceptible isolates only)
Streptococcus pneumoniae
Streptococcus pyogenes (Lancefield's Group A *Streptococci*)
Viridans group *Streptococci*

The following *in vitro* data are available, ***but their clinical significance is unknown***.

Cefepime has been shown to have *in vitro* activity against most isolates of the following microorganisms; however, the safety and effectiveness of cefepime in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

- Aerobic Gram-Positive Microorganisms:

Staphylococcus epidermidis (methicillin-susceptible isolates only)
Staphylococcus saprophyticus
Streptococcus agalactiae (Lancefield's Group B *Streptococci*)

NOTE: Most isolates of *Enterococci,* eg, *Enterococcus faecalis,* and methicillin-resistant *Staphylococci* are resistant to cefepime.

- Aerobic Gram-Negative Microorganisms:

Acinetobacter calcoaceticus subsp. *lwoffii*
Citrobacter diversus
Citrobacter freundii
Enterobacter agglomerans
Haemophilus influenzae (including beta-lactamase producing isolates)
Hafnia alvei
Klebsiella oxytoca
Moraxella catarrhalis (including beta-lactamase producing isolates)
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

NOTE: Cefepime is inactive against many isolates of *Stenotrophomonas* (formerly *Xanthomonas maltophilia* and *Pseudomonas maltophilia*). Cefepime is inactive against most isolates of *Clostridium difficile.*

5.2. Pharmacokinetic Properties

The average plasma concentrations of cefepime observed in healthy adult male volunteers (n=9) at various times following single 30-minute infusions (IV) of cefepime 500 mg, 1 g, and 2 g are summarized in *Table 1*. 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.

Absorption

The average plasma concentrations of cefepime and its derived pharmacokinetic parameters after intravenous (IV) administration are portrayed in *Table 1*.

Table 1: ***Average Plasma Concentrations in mcg/mL of Cefepime and Derived Pharmacokinetic Parameters (±SD), Intravenous Administration***

	Cefepime for Injection USP 500 mg/1 g		
Parameter	**500 mg IV**	**1 g IV**	**2 g IV**
0.5 h	38.2	78.7	163.1
1 h	21.6	44.5	85.8
2 h	11.6	24.3	44.8
4 h	5	10.5	19.2
8 h	1.4	2.4	3.9
12 h	0.2	0.6	1.1
Cmax, mcg/mL	39.1 (3.5)	81.7 (5.1)	163.9 (25.3)
AUC, h•mcg/mL	70.8 (6.7)	148.5 (15.1)	284.8 (30.6)
Number of subjects (male)	9	9	9

Following intramuscular (IM) administration, cefepime is completely absorbed. The average plasma concentrations of cefepime at various times following a single intramuscular injection are summarized in *Table 2*. 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.

Table 2: ***Average Plasma Concentrations in mcg/mL of Cefepime and Derived Pharmacokinetic Parameters (±SD), Intramuscular Administration***

	Cefepime for Injection USP 500 mg/1 g		
Parameter	**500 mg IM**	**1 g IM**	**2 g IM**
0.5 h	8.2	14.8	36.1
1 h	12.5	25.9	49.9
2 h	12	26.3	51.3
4 h	6.9	16	31.5
8 h	1.9	4.5	8.7
12 h	0.7	1.4	2.3
Cmax,mcg/mL	13.9 (3.4)	29.6 (4.4)	57.5 (9.5)
Tmax,h	1.4 (0.9)	1.6 (0.4)	1.5 (0.4)
AUC, h•mcg/mL	60 (8)	137 (11)	262 (23)
Number of subjects (male)	6	6	12

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.

Cefepime is excreted in human milk. A nursing infant consuming approximately 1000 mL of human milk per day would receive approximately 0.5 mg of cefepime per day.

Concentrations of cefepime achieved in specific tissues and body fluids are listed in *Table 3.*

Table 3: ***Average Concentrations of Cefepime in Specific Body Fluids (mcg/mL) or Tissues (mcg/g)***

Tissue or Fluid	Dose/Route	# of Patients	Average Time of Sample Post-Dose (h)	Average Concentration
Blister Fluid	2 g IV	6	1.5	81.4 mcg/mL
Bronchial Mucosa	2 g IV	20	4.8	24.1 mcg/g
Sputum	2 g IV	5	4	7.4 mcg/mL
Urine	500 mg IV	8	0 to 4	292 mcg/mL
	1 g IV	12	0 to 4	926 mcg/mL
	2 g IV	12	0 to 4	3120 mcg/mL
Bile	2 g IV	26	9.4	17.8 mcg/mL
Peritoneal Fluid	2 g IV	19	4.4	18.3 mcg/mL
Appendix	2 g IV	31	5.7	5.2 mcg/g
Gallbladder	2 g IV	38	8.9	11.9 mcg/g
Prostate	2 g IV	5	1	31.5 mcg/g

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.

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.

6. Pharmaceutical Particulars

6.1. List of Excipients

======Not Applicable========

6.2. Incompatibilities

======Not Applicable========

6.3. Shelf life

36 months from date of manufacture

6.4. Special precautions for Storage

Store in dry place at temperature below 30° C.
Keep out of the sight and reach of children.

6.5. Nature and Contents of container

White to pale yellow powder filled in Clear, transparent 15 ml vials with 20 mm Grey colored bromobutyl rubber stopper and coloured flip off seal.

7. Marketing Authorization Holder

Nectar Lifesciences Limited

8. Marketing Authorisation Number (s)

04836/5739/NMR/2017

9. Date of first Authorisation/Renewal of Authorization

Dec 18, 2019

10. Date of Revision of Text

=====Not applicable=====

Reference : Using **Maxipime** Injection (Hospira) as Innovator product.