National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

SYNOFEPIM (Cefepime for Injection USP 1000 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Vial Contains:
Sterile Cefepime Hydrochloride USP
Eq. To Cefepime.....1000 mg
(Sterile mixture of Cefepime Hydrochloride and L-Arginine)

Batch size: 10,000 Vial

Sr. No.	Ingredients	Specifications	Label Claim	Qty/ Vial (mg)	Qty/ Batch (Kg)	Reason For Inclusion
1	Sterile mixture of Cefepime Hydrochloride and L-Arginine	USP	1000 mg	1959	19.59	Active

USP: United State Pharmacopoeia

3. PHARMACEUTICAL FORM

White to pale yellow powder, Powder for Injection, pH is about 4.0 to 6.0

4. Clinical particulars

4.1 Therapeutic indications

Sterile mixture of Cefepime Hydrochloride and L-Arginine 1000 mg (**SYNOFEPIM)** is indicated in the treatment of infections caused by bacteria that are cefepime-sensitive:

- Lower respiratory tract infections, including nosocomial pneumonia and community acquired pneumonia, acute bacterial exacerbation of chronic bronchitis and secondary bacterial infection of acute bronchitis;
- Uncomplicated and complicated urinary tract infections, including pyelonephritis;
- Skin and subcutaneous infections;
- Intra-abdominal infections, including peritonitis and biliary tract infections;
- Gynaecological infections;
- Bacterial meningitis in infants and children;
- In combination with other antibacterial agents in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection;
- Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

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

4.2 Posology and method of administration

Posology

SYNOFEPIM can be administered via intravenous use or intramuscular use.

After reconstitution, the solution is yellow to yellow-brown.

The usual dose and the route of administration vary in accordance with the severity of the infection, the renal function and the general conditions of the patient.

The IV route of administration is preferable in the patients with severe infections or in a life-threatening

situation, particularly if there is the possibility of shock.

Adults and children weighing > 40 kg with normal renal function:

Severity of the infection	**Dosage and route of administration**	**Interval between the doses**
Mild to moderate urinary tract infections (UTI)	500 mg to 1 g IV or IM	every 12 h
Other mild to moderate infections (non UTI)	1 g IV or IM	every 12 h
Severe infections	2 g IV	every 12 h
Very severe or life-threatening infections	2 g IV	every 8 h

The usual treatment duration is 7 to 10 days; more severe infections can require a more prolonged treatment.

In the empirical treatment of febrile neutropenia, the usual treatment duration should not be less than 7 days or until the resolution of the neutropenia.

In patients weighing ≤ 40 kg, the posology indicated for the children is recommended.

Elderly:

No dose adjustment is required in patients with normal renal function; the dose adjustment is recommended in patients with impaired renal function (see section 4.4).

Adults with renal insufficiency:

The cefepime dose should be adjusted to compensate the slower renal elimination rate. In adult patients with mild to moderate renal insufficiency, the initial dose of cefepime recommended should be the same as for patients with normal renal function. The recommended maintenance dose should be in accordance with the instructions of the table below.

When only the serum creatinine values are available, the (Cockcroft and Gault) formula can be used to calculate the creatinine clearance. The serum creatinine should represent a steady-state of renal function:

Man: Creatinine clearance (ml/min) = weight (kg) x (140 - age)

72 x serum creatinine (mg/dl)

Woman: 0.85 x value calculated using the man formula

Creatinine clearance (ml/min)	**Recommended maintenance dose**			
> 50	Usual dose, no dose adjustment is required			
	2 g, 3x day 2x day	2 g, 2x day	1 g, 2x day	500 mg,
30 to 50	2 g, 2x day	2 g, 1x day	1 g, 1x day	500 mg, 1x day
11 to 29	2 g, 1x day	1 g, 1x day	500 mg, 1x day	500 mg, 1x day
< 10	1 g, 1x day	500 mg, 1x day	250 mg, 1x day	250 mg, 1x day
Haemodialysis*	500 mg, 1x day	500 mg, 1x day	500 mg, 1x day	500 mg, 1x day

*The pharmacokinetic models indicate that it is necessary to reduce the dose in these patients. In patients

receiving cefepime and doing haemodialysis, the dose is 1 gram as loading dose in the first day of treatment followed by 500 mg daily for all the infections, except febrile neutropenia which is 1 gram daily. In the dialysis days, cefepime should be administered after dialysis. Cefepime should be administered, whenever possible, at the same time every day.

Patients doing dialysis

In the patient doing dialysis, about 68% of the total quantity of cefepime present in the body in the beginning of the dialysis will be removed during a 3 hour dialysis. In the patient doing continuous ambulatory peritoneal dialysis, cefepime can be administered in the same dosages that are recommended for the patients with normal renal function, i.e. 500 mg, 1 g or 2 g, depending on the severity of the infection, but with an interval of 48 hours between doses.

Children with normal renal function

In the child, the usual recommended dose is:

- *Pneumonia, urinary tract infection, skin and subcutaneous tissue infection*:

• Children aged more than 2 months and weighing ≤ 40 kg: 50 mg/kg every 12 hours for 10 days; in more severe infections, 8 hours interval between the intakes should be done.

- *Bacteraemia that occurs in association with infections, bacterial meningitis and empirical treatment of febrile neutropenia*:

• Children aged more than 2 months and weighing ≤ 40 kg: 50 mg/kg every 8 hours for 7 to 10 days.

The experience in children aged less than 2 months is limited. Despite the experience having been obtained with the 50 mg/kg dose, data from pharmacokinetic models obtained in children aged more than 2 months suggest that, in children from 1 month to 2 months old, a dose of 30 mg/kg every 12 or 8 hours can be considered. The administration of Synofepim in these patients should be carefully monitored.

In the child weighing > 40 kg, it is recommended to use the dose indicated for adults. The maximum recommended dose for adults (2 g every 8 hours) should not be exceeded. The experience with the intramuscular use in children is limited.

Children with renal insufficiency:

As renal excretion is the main route of elimination of cefepime, the dose should be adjusted in children with renal insufficiency. A dose of 50 mg/kg in children from 2 months to 12 year old and a dose 30 mg/kg in children 1 month to 2 months are comparable to a 2 g dose in the adult.

The same interval between the doses is recommended or the same dose reduction indicated for the renal insufficient adult.

Patients with hepatic function impairment:

No dose adjustment is required in patients with hepatic insufficiency

4.3 Contraindications

Hypersensitivity to cefepime, to any other cephalosporin or to any of the excipients listed in section 6.1.

History of severe hypersensitivity reaction (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, severe and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefepime 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 cefepime, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if cefepime is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Cefepime should be administered with caution to patients with a history of asthma or allergic diathesis. The patient must be carefully monitored during the first administration. If an allergic reaction occurs, treatment must be discontinued immediately.

Serious hypersensitivity reactions may require epinephrine and other supportive therapy.

Antibiotics should be administered with caution to patients that have shown some form of allergy, particularly to drugs. If there is an allergic reaction to Synofepim, the medicine should be stopped and adequate treatment applied.

Use in Patients with Renal Impairment

In patients with creatinine clearance less than or equal to 60 mL/min, adjust the dose of SYNOFEPIM (cefepime hydrochloride) to compensate for the slower rate of renal elimination [see DOSAGE AND ADMINISTRATION]. 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.

Neurotoxicity

During post marketing surveillance, 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), myoclonus, seizures, and nonconvulsive status epilepticus (see ADVERSE REACTIONS: Post marketing Experience). 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 them 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, consider discontinuing cefepime or making appropriate dosage adjustments in patients with renal impairment.

Antibacterial activity of cefepime

Due to the relatively limited spectrum of antibacterial activity of cefepime it is not suitable for the treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there

is a very high suspicion that the most likely pathogen(s) would be suitable for treatment with cefepime (see section 5.1).

As with other antibiotics, the use of Synofepim can lead to the development of resistant micro-organisms. If superinfection occurs during treatment, adequate measures should be taken.

Renal impairment

In patients with impaired renal function, such as reduction of urinary output because of renal insufficiency (creatinine clearance ≤ 50 mL/min) or other conditions that may compromise renal function, the dosage of cefepime should be adjusted to compensate for the slower rate of renal elimination. Because high and prolonged serum antibiotic concentrations can occur from usual dosages in patients with renal insufficiency or other conditions that may compromise renal function, the maintenance dosage should be reduced when cefepime is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection and susceptibility of the causative organisms (see sections 4.2 and 5.2).

During post-marketing surveillance, the following serious adverse events have been reported: reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures (including non-convulsive status epilepticus), and/or renal failure (see section 4.8 - Undesirable effects). Most cases occurred in patients with renal impairment who received doses of cefepime that exceeded the recommendations.

In general, symptoms of neurotoxicity resolved after discontinuation of cefepime and/or after haemodialysis, however, some cases included a fatal outcome.

Clostridium difficile associated diarrhoea

Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, has been reported in association with the use of nearly all antibiotics including cefepime and may range in severity from mild diarrhoea to fatal colitis. Therefore, it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of cefepime. If antibiotic-associated diarrhoea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including cefepime, should be discontinued and adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in this situation.

It is known that cefepime is excreted substantially by the kidney and the risk of toxic reactions to this drug can be higher in the patients with renal insufficiency. Because elderly patients are more susceptible to have a decreased renal function, caution should be taken in the selection of the dose and renal function should be monitored (see section 5.2). In elderly patients with renal failure to whom the usual dose of cefepime was administered, severe adverse events occurred (see section 4.8) including reversible encephalopathy (conscience disturbance, including confusion, hallucinations, stupor and coma), myoclonus, convulsions (including non-convulsive status epilepticus) and/or renal failure.

Interference with serological testing

A positive Coombs test, without evidence of haemolysis, has been described in patients treated with cefepime twice daily.

Cephalosporin antibiotics may produce a false-positive reaction for glucose in the urine with copper reduction tests (Benedict's or Fehling's solution or with Clinitest tablets), but not with enzyme-based tests (glucose oxidase) for glycosuria. Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

PRECAUTION:

General

Prescribing SYNOFEPIM 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 SYNOFEPIM may result in overgrowth of non-susceptible microorganisms. Repeated evaluation of the patient's condition is essential. Should superinfection occur 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 SYNOFEPIM. 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.

SYNOFEPIM (cefepime hydrochloride) should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

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 of SYNOFEPIM. The effect of lower doses is not presently known.

Information for Patients

Patients should be counseled that antibacterial drugs including SYNOFEPIM should only be used to treat bacterial infections. They do not treat viral infections (eg, the common cold). When SYNOFEPIM is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by SYNOFEPIM or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Patients should be advised of neurological adverse events that could occur with SYNOFEPIM use. Patients

should be instructed to inform their healthcare provider at once of any neurological signs and symptoms, including encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures, for immediate treatment, dosage adjustment, or discontinuation of SYNOFEPIM.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant treatment with bacteriostatic antibiotics may interfere with the action of beta-lactam antibiotics.
The monitoring of renal function is recommended during the treatment with Synofepim if other drugs that have nephrotoxic potential are administered (i.e., aminoglycosides and potent diuretics).
Cephalosporins can potentiate the action of coumarin anticoagulants.
Interaction with diagnostic tests

In patients treated with Synofepim positive Coombs test was described with no evidence of haemolysis.
In the glycosuria test, a false positive result may occur due to reduction of copper (the enzymatic method should preferably be used).

4.6 Pregnancy and Lactation

Pregnancy
In what concerns cefepime there are no sufficient data on its exposure in pregnancy.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, labour or post-natal development (see section 5.3).
This medicinal product should only be prescribed to pregnant women with great caution.
Breastfeeding
Cefepime is excreted in human milk in very low quantities, so caution is recommended when administered to the breast-feeding woman.
Fertility
There are no data on the use of cefepime in human fertility. Reproduction studies in animals did not reveal any effects on fertility.

4.7 Effects on ability to drive and use machines

The effects of the medicinal product on the ability to drive and use machines have not been studied. However, possible adverse reactions like altered state of consciousness, dizziness, confusional state or hallucinations may alter the ability to drive and use machines

4.8 Undesirable effects

In clinical trials (N=5598), the more common adverse events were gastrointestinal symptoms and hypersensitivity reactions. The undesirable effects considered as definitively, probably or possibly related to cefepime are listed.

The frequency of adverse reactions listed below, reported during the clinical experience or post-marketing experience, is defined using the following convention:

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 be estimated from the available data).

The side effects are presented by decreasing order of severity within each class of frequency.

System organ class	**Frequency**	**MedDRA term**
Infections and Infestations	Uncommon	Oral candidiasis, vaginal infection
	Rare	Candidiasis
Blood and lymphatic system disorders	Common	Anaemia, eosinophilia
	Uncommon	Thrombocytopenia, leukopenia, neutropenia
	Not known	Aplastic anaemia[a], haemolytic anaemia[a], agranulocytosis
Immune system disorders	Rare	Anaphylactic reaction, angioedema
	Not known	Anaphylactic shock
Psychiatric disorders	Not known	State of confusion, hallucination
Nervous system Disorders	Uncommon	Headaches
	Rare	Convulsions, paraesthesia, digeusia, dizziness
	Not known	Coma, stupor, encephalopathy, altered state of conscience, myoclonus
Vascular disorders	Common	Phlebitis at the infusion site
	Rare	Vasodilatation
	Not known	Haemorrhage
Respiratory, thoracic and mediastinal disorders	Rare	Dyspnoea
Gastrointestinal Disorders	Common	Diarrhoea
	Uncommon	Pseudomembranous colitis, colitis, nausea, vomiting
	Rare	Abdominal pain, constipation
	Not known	Gastrointestinal disorder
Skin and subcutaneous tissue disorders	Common	Skin rash
	Uncommon	Erythema, urticaria, pruritus
	Not known	Toxic epidermal necrolysis[a], Stevens-Johnson syndrome, erythema multiforme
Renal and urinary disorders	Uncommon	blood urea increased, blood creatinine increased
	Not known	Renal failure, toxic nephropathy[a]
Reproductive system and breast disorders	Rare	Genital pruritus
General disorders and administration site conditions	Common	Infusion site reaction, injection site inflammation and pain
	Uncommon	Pyrexia, infusion site inflammation
	Rare	Chills

Investigations	Very common	Positive Coombs test
	Common	Alkaline phosphatase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, prothrombin time prolonged, partial thromboplastin time prolonged
	Not known	False positive glycosuria

[a] – Adverse reactions generally accepted as being attributable to other compounds of the same class.

The safety profile of cefepime in infants and children is similar to that seen in the adult.

As with other drugs of the class of cephalosporins, encephalopathy (conscience disorder, including confusion, hallucinations, stupor and coma), convulsions, myoclonus and/or renal failure were reported. Most cases occurred in patients with renal impairment which received cefepime doses that exceeded those recommended (see section 4.4).

Such as with other cephalosporins, anaphylaxis, including anaphylactic shock, transient leukopenia, neutropenia, agranulocytosis and thrombocytopenia were reported.

During clinical tests, changes in laboratory tests were transient in the patients with normal baseline values. The changes that occurred with a frequency between 1% and 2% (except when indicated other frequency) were: increased alanine aminotransferase (3.6%), aspartate aminotransferase (2.5%), alkaline phosphatase, total bilirubin, anaemia, eosinophilia, increased prothrombin time and thromboplastin time (2.8%) and positive Coombs test with no haemolysis (18.7%). The transient increases of uraemia, serum creatinine and thrombocytopenia were observed in 0.5% to 1% of the patients. Transient leukopenia and neutropenia were observed (< 0.5%).

4.9 Overdose

In case of severe overdose, especially in patients with renal function impairment, haemodialysis can help remove cefepime from the body (peritoneal dialysis is not useful).

Accidental overdose occurred with the administration of high doses to patients with decreased renal function (see sections 4.2 and 4.4).

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, and neuromuscular excitability.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antibacterials for systemic use. Other beta-lactam antibacterials. Fourth-generation cephalosporins, ATC code: J01DE01

Mechanism of action

Cefepime is a broad-spectrum, bactericidal antibiotic, with activity against a wide range of Gram-positive and Gram-negative bacteria, including many strains resistant to aminoglycosides or third generation cephalosporins.

It is highly resistant to hydrolysis caused by most beta-lactamases. It has a reduced affinity for beta-lactamases changed via chromosomes and has a rapid penetration in the cells of the Gram-negative bacteria.

Resistance

The bacterial resistance to cefepime can depend on one or several mechanisms:

- Hydrolysis via beta-lactamases. Cefepime is stable to most beta-lactamases changed by plasmids and via chromosomes, but it can be hydrolysed effectively by certain beta-lactamases with broad-spectrum which are present mostly in *Escherichia coli* and *Klebsiella pneumoniae* and by enzymes changed by the chromosomes.
- Reduced affinity of the penicillin-binding proteins (PBPS) to cefepime. The resistance developed to *Streptococcus pneumoniae* and other streptococci caused by PBPs mutation; resistance of the staphylococci to methicillin caused by the production of additional PBPs with reduced affinity to cefepime.
- Non penetrable exterior membrane.
- Drugs efflux pumps.

There may be simultaneously more than one mechanism of resistance in each cell wall. Depending on the mechanism(s) present, there may be crossed resistance to several or to all other beta-lactam and/or antibacterial drugs of other types.

During treatment, resistance to the following species can develop: *Citrobacter*, *Pseudomonas* (especially *P. aeruginosa*), *Morganella* and *Serratia*.

Critical concentration values (Breakpoints)

The critical concentration values to differentiate susceptible (S) pathogens from resistant (R) pathogens, in accordance with EUCAST (2009-05-25) are:

Microorganism	**Susceptible**	**Resistant**
Critical concentration values related to species	non S ≤ 4 mg/l	R > 8 mg/l
Enterobacteriaceae	S ≤ 1 mg/l	R > 8 mg/l
Pseudomonas[a]	S ≤ 8 mg/l	R > 8 mg/l
Haemophilus influenzae	S ≤ 0.25 mg/l	R > 0.25 mg/l
and *Moraxella catarrhalis*		
Streptococcus pneumoniae	S ≤ 1 mg/l	R > 2 mg/l
Streptococci A, B, C and G[b]		
Staphylococcus[c]		

[a] Critical concentration value is valid in high dose (2g x 3).

[b] Based on the critical concentration value for benzylpenicillin.

[c] Based on the critical concentration value for methicillin.

The prevalence of acquired resistance may vary geographically and with time for selected species and it is desirable to have local information on resistance, particularly when treating severe infections. As necessary,

expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in, at least some types of infections, is questionable.

Commonly susceptible species	
Gram-positive aerobes	*Staphylococcus aureus* and coagulase negative staphylococci including beta-lactamase producing strains Streptococci. Pneumococci
Gram-negative aerobes	*Acinetobacteria* *Aeromonas spp* *Citrobacter* Enterobacteriae *Escherichia coli* *Haemophilus influenzae* including beta-lactamase producing stains *Klebsiella* *Moraxella catarrhalis* including beta-lactamase producing stains *Morganella morganii* *Proteus* *Providencia* *Pseudomonas* *Serratia*
Species with acquired resistance	
Gram-positive aerobes	*Enterococos* *Listeria*
Gram-negative aerobes	*Burkholderia cepacia* *Legionella* *Stenotrophomonas maltophilia*
Anaerobes	Anaerobic bacteria including *Bacteroides and Clostridium difficile*
Other microorganisms	*Chlamydia, Mycoplasma*

5.2 Pharmacokinetic properties

Absorption

Cefepime is completely absorbed after IM administration.

Distribution

Adults: Average plasma concentrations of cefepime observed in the male adult, after a single IV infusion (30 minutes) or after the IM injection of doses of 500 mg, 1 g and 2 g are summarized in table 1; in table 2 are presented the average concentrations in the tissues and biological fluids. After the intramuscular administration, cefepime is completely absorbed.

Table 1: Average plasma concentrations of cefepime (micrograms/ml)

Cefepime dose	**0.5 h**	**1 h**	**2 h**	**4 h**	**8 h**	**12 h**
500 mg IV	38.2	21.6	11.6	5.0	1.4	0.2
1 g IV	78.7	44.5	24.3	10.5	2.4	0.6
2 g IV	163.1	85.8	44.8	19.2	3.9	1.1
500 mg IM	8.2	12.5	12.0	6.9	1.9	0.7

1 g IM	14.8	25.9	26.3	16.0	4.5	1.4
2 g IM	36.1	49.9	51.3	31.5	8.7	2.3

Cefepime concentrations in specific tissues and biological fluids are in Table 2.

The binding of cefepime to serum proteins is, on average, 16.4% and is independent of the serum concentration.

Table 2: Average concentrations of cefepime in several tissues (micrograms/g) and biological fluids (micrograms/g)

Tissue or Fluid	**Dose (IV)**	**Time after the collection (h)**	**Average Concentration**
Urine	500 mg	0 – 4	292
	1 g	0 – 4	926
	2 g	0 – 4	3120
Bile	2 g	9.4	17.8
Peritoneal fluid	2 g	4.4	18.3
Blister fluid	2 g	1.5	81.4
Bronchial mucosa	2 g	4.8	24.1
Expectoration	2 g	4.0	7.4
Prostate	2 g	1.0	31.5
Appendix	2 g	5.7	5.2
Gall bladder	2 g	8.9	11.9

Biotransformation

Cefepime is metabolised in N-methylpyrrolidinium, being converted quickly in N-oxide. About 85% of the administered dose is eliminated unchanged; high concentrations of unchanged cefepime are detected in urine. Less than 1% of the administered dose is eliminated in urine as N-methylpyrrolidinium, 6.8% as N-oxide and 2.5% as cefepime epimer.

Elimination

The elimination average half-life of cefepime is about 2 hours, and is independent of the dose for the range of 250 mg to 2 g. There is no evidence of accumulation in the healthy individuals receiving doses up to 2 g IV every 8 hours for 9 days. The total body clearance is 120 ml/min. The average renal clearance of cefepime is 110 ml/min, suggesting an elimination almost exclusively via the kidneys, mainly by glomerular filtration.

Pharmacokinetic/pharmacodynamic (PK/PD) relationship

The antibacterial activity depends on the time during which the free concentration serum/urine exceeds the minimum inhibitory concentration (MIC).

Special populations

Renal dysfunction: The elimination half-life is increased in patients with several degrees of renal failure, so the dosage adjustment is recommended.

Liver dysfunction: Cefepime pharmacokinetics was not changed in patients with hepatic insufficiency that received a dose of 1 g. It is not necessary to change the posology of Synofepim in this population.

Elderly: healthy voluntary individuals of 65 years old or more that received a single dose of 1 g IV of cefepime

presented higher AUC values and lower renal clearance values when compared with younger adults.

It is recommended the dose adjustment in the elderly patient with renal function impairment (see sections 4.2 and 4.4).

From the more than 6400 adults treated with cefepime in clinical studies, 35% were aged 65 years old or more and 16% were aged 75 years old or more. In clinical studies when the elderly patient received the recommended dose for the adult patient, the clinical efficacy and safety were comparable to the clinical efficacy and safety in the non-elderly adult patient, unless the patient had renal failure. There was a mild increase in the elimination half-life time and lower renal clearance values when compared with those seen in younger individuals. Dose adjustments are recommended if the renal function is impaired (see section 4.2).

Children: Cefepime pharmacokinetics with single and multiple doses was assessed in patients aged between 2.1 months and 11.2 years, with doses 50 mg/kg in IV infusion or IM injection; multiple doses were administered with intervals of 8 or 12 hours for at least 48 hours.

After the single IV administration, the total clearance was 3.3 ml/min/kg, with a distribution value of 0.3 l/kg. The elimination half-life was 1.7 hour, with an average recovery in urine of unchanged cefepime around 60.4% of the administered dose, being the renal clearance the main route of elimination (2.0 ml/min/kg).

The average plasma concentrations of cefepime in steady state after the administration of multiple IV doses were similar to those seen after the 1st dose, only with mild accumulation after repeated doses.

After the IM administration in steady state conditions, maximum cefepime plasma concentrations around 68 micrograms/ml were obtained in average in 0.75 hours. The bioavailability was in average 82% after intramuscular administration.

The cefepime concentrations in cerebrospinal fluid (CSF) in relation to plasma are the following:

Table 3: Average concentrations in plasma and in CSF in children*

Sample collection (h)	**N**	**Plasma concentration (micrograms/ml)**	**CSF concentration (micrograms/ml)**	**CSF/plasma relation**
0.5	7	67.1 (51.2)	5.7 (7.3)	0.12 (0.14)
1	4	44.1 (7.8)	4.3 (1.5)	0.10 (0.04)
2	5	23.9 (12.9)	3.6 (2.0)	0.17 (0.09)
4	5	11.7 (15.7)	4.2 (1.1)	0.87 (0.56)
8	5	4.9 (5.9)	3.3 (2.8)	1.02 (0.64)

* The age of the patients ranged from 3.1 month to 12 years. The patients with suspicion of CNS infection received 50 mg/kg every 8 hours, in 5 to 20 minutes infusion. The plasma and CSF were collected in the times determined in relation to the end of the infusion on the 2nd or 3rd day of treatment.

Other: clinical improvement was seen with cefepime in the treatment of acute pulmonary exacerbations in patients with cystic fibrosis. Pharmacokinetics of cefepime did not change in patients with hepatic function impairment which received a single dose of 1 g and in patients with cystic fibrosis. No dose adjustment of Synofepim is required in this population.

5.3 Preclinical safety data

Drug/Laboratory Test Interactions

The administration of cefepime may result in a false-positive reaction for glucose in the urine when using Clinitest™ tablets. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™) be used.

Carcinogenesis, Mutagenesis, Impairment of 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 calculated on a mg/m2 basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not Aapplicable

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 Month

6.4 Special precautions for storage

Store below 30°C. Protect From light.

Keep out of reach of children.

6.5 Nature and contents of container

White to pale yellow powder filled in clear vials closed with grey butyl rubber stopper & sealed with flip of aluminum seal. Such 1 Vial packed in printed carton along with pack insert.

6.6 Special precautions for disposal and other handling

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

Preparation and administration of the reconstituted solution:
Renapime, powder for solution for injection/infusion should be dissolved in:
a) water for injections
or in one of the solutions listed in b) below for intravenous administration
b) sodium chloride 0.9% solution
sodium chloride 0.9% with glucose 5% solution
glucose 5% or 10% solution
Ringer lactate solution
Ringer lactate with glucose 5% solution
sodium lactate 1/6 M solution.
For Intravenous Injection, the volume of the solvent to be added to each vial and the resulting concentration of cefepime are presented in the following table:

Quantity of cefepime per vial	**Volume of solvent added (ml)**	**Approximate final volume (ml)**	**Approximate concentration of cefepime (mg/ml)**
1.0 g I.V.	10.0	11.4	90
2.0 g I.V.	10.0	12.8	160

For Intravenous Infusion, the volume of the solvent for infusion (solution listed in b)) to be used for reconstitution and the resulting concentration of cefepime are presented in the following table:
The volume of the solvent for infusion to be used for each vial and the resulting concentration of cefepime are presented in the following table:

Quantity of cefepime per vial	**Volume of solvent added (ml)**	**Approximate final volume (ml)**	**Approximate concentration of cefepime (mg/ml)**
1.0 g I.V.	50.0	51.4	19
2.0 g I.V.	50.0	52.8	38

The resulting solution should be administered over approximately 30 minutes.
For Intramuscular Injection, reconstitute the 1 g vial by using 3.0 ml of water for injections.
Note:
The *reconstituted* solutions, which are prepared correctly, can present a yellow to yellow-brown colour. This does not mean that efficacy of Renapime may be compromised.
The content of the vial is meant for a single usage. The remaining *reconstituted* solution should be discarded.
Inspect the vial before using. It can only be used if the solution does not present particles.

7. APPLICANT/MANUFACTURER

JFL LIFESCIENCES PVT LTD.

615, G.I.D.C. Kerala, Bavla,

Dist. Ahmedabad,

Gujarat, India