SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Renapime 2 g powder for solution for injection/infusion

Renapime

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Renapime

Renapime 2 g powder for solution for injection or infusion:

One vial contains 2 g of cefepime (as dihydrochloride monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion

White to pale yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Renapime 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

Renapime 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 2 g, 2x day 1 g, 2x day 500 mg, 2x day			
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 Renapime 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 Renapime, the medicine should be stopped and adequate treatment applied.

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 Renapime 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 $\leq$ 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.

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 Renapime 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 Renapime 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 Fertility, 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 (see sections 4.4, 4.8 e 4.9).

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	Rare	Genital pruritus

breast disorders		
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%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at:

www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic 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 and *Moraxella catarrhalis*	S ≤ 0.25 mg/l	R > 0.25 mg/l
Streptococcus pneumoniae *Streptococci* A, B, C and G[b] *Staphylococcus*[c]	S ≤ 1 mg/l	R > 2 mg/l

[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 Renapime 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 Renapime is required in this population.

5.3 Preclinical safety data

No long term studies were performed in the animal to assess the carcinogenic potential. In *in vitro* and *in vivo* genotoxicity tests, cefepime did no show to be genotoxic. In the rat no decreased fertility was seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-arginine

6.2 Incompatibilities

Cefepime must not be mixed with other medicinal products or solutions except those mentioned in section 6.6 “Special precautions for disposal and other handling”.

There is a physical-chemical incompatibility with metronidazole, vancomycin, gentamicin, tobramycin, netilmicin and aminophylline. In the cases where a concomitant intravenous administration is indicated, these active substances should not be administered together with cefepime or through the same intravenous route.

6.3 Shelf life

Medicinal product in the original container:

3 years.

Reconstituted solution for injection, reconstituted with water for injections:

The in use physical and chemical stability was demonstrated for 18 hours at room temperature (15 - 25ºC) and for 7 days in a refrigerator (2 - 8ºC).

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use time and storage conditions prior to administration are users' responsibility and, usually, should not exceed 24 hours at 2º-8º C, unless reconstitution has occurred under validated aseptic controlled conditions.

The reconstituted solution for infusion, reconstituted with other solvents (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 1/6M solution):

The in use physical and chemical stability was demonstrated for 4 hours at room temperature (15 - 25ºC).

Do not refrigerate.

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use time and storage conditions prior to administration are users' responsibility, unless reconstitution has occurred under validated aseptic controlled conditions.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep the container in the outer carton.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless type II 20 ml glass vial closed with chlorobutyl rubber stopper and sealed with an aluminium cap and a plastic flip-off.

Pack size: 1, 5, 10, 20, 25, 50 and 100 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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 MARKETING AUTHORISATION HOLDER

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