PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

CEFEPIME 1 g FRESENIUS powder for injection or infusion

CEFEPIME 2 g FRESENIUS powder for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CEFEPIME 1 g FRESENIUS

Each vial contains 1 g cefepime (as cefepime dihydrochloride monohydrate)

CEFEPIME 2 g FRESENIUS

Each vial contains 2 g cefepime (as cefepime dihydrochloride monohydrate)

Sugar free

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion. White to pale yellow powder.

The pH of the reconstituted solution is 4,0-6,0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

CEFEPIME FRESENIUS is indicated in the treatment of the infections listed below when caused by susceptible bacteria. Culture and susceptibility studies should be performed to determine susceptibility of the causative organism(s) to cefepime.

Lower respiratory tract infections:

Nosocomial and community-acquired pneumonia caused by *Staphylococcus aureus* (methicillin susceptible strains), *Pseudomonas aeruginosa*, Klebsiella species (including *Klebsiella pneumoniae*), Enterobacter species*, Escherichia coli*, *Proteus mirabilis*, *Streptococcus pneumoniae* (including intermediate penicillin resistant strains), *Haemophilus influenzae* (including beta-lactamase producing strains), *Haemophilus parainfluenzae* and *Moraxella (Branhamella) catarrhalis* (including beta-lactamase producing strains), including cases associated with bacteraemia.

When *P. aeruginosa* is isolated or suspected, combination therapy with an aminoglycoside should be used.

Acute bacterial exacerbation of chronic bronchitis and acute bronchitis due to *Streptococcus pneumoniae* (including intermediate penicillin resistant strains), *Haemophilus influenzae* (including beta-lactamase-producing strains), *Moraxella (Branhamella) catarrhalis* (including beta-lactamase producing strains).

Urinary tract infections:

Complicated urinary tract infections caused by *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Proteus mirabilis* and Enterobacter species, including cases associated with bacteraemia. When *P. aeruginosa* is isolated or suspected, combination therapy with an aminoglycoside should be used.

Uncomplicated urinary tract infections due to *Escherichia coli, Proteus mirabilis*, Klebsiella species and Enterobacter species.

Skin and skin structure infections:

Skin and skin structure infections caused by *Staphylococcus aureus* (methicillin susceptible strains), *Streptococcus pyogenes* (Group A streptococci),

Streptococcus agalactia (Group B streptococci), other β-haemolytic Streptococcus species, Enterobacter species, Klebsiella species, *Proteus mirabilis*, *Morganella morganii, Escherichia coli, Serratia marcescens* and *Acinetobacter calcoaceticus*.

Intra-abdominal infections:

Complicated intra-abdominal infections including peritonitis and biliary tract infections caused by *Escherichia coli,* sensitive *Pseudomonas aeruginosa*. Peritonitis is often polymicrobial and may include anaerobic micro-organisms such as Bacteroides species which are resistant to cefepime. When resistant anaerobes are suspected, CEFEPIME FRESENIUS should be combined with an antibiotic effective against these micro-organisms, including cases associated with bacteraemia.

In patients who are at risk of mixed aerobic-anaerobic infection, including infections in which *Bacteroides fragilis* may be present, concurrent therapy with an anti-anaerobic medicine is recommended.

Empiric treatment in febrile neutropenia:

CEFEPIME FRESENIUS is indicated for empiric monotherapy of febrile neutropenia. Combination of cefepime with other appropriate medicines should be considered in patients at high risk for severe infection (including patients with a history of recent bone marrow transplantation, hypotension at presentation, an underlying haematologic malignancy, or severe or prolonged neutropenia) or when called for by host or local epidemiological factors.

Paediatrics

CEFEPIME FRESENIUS is indicated in paediatric patients (2 months and older) for the treatment of the infections listed below when caused by susceptible bacteria, (when *P. aeruginosa* is isolated or suspected, combination therapy with an aminoglycoside should be used):

Lower respiratory tract infection:

Pneumonia caused by *S. aureus, S. pneumoniae, H. influenzae*.

Urinary tract infections:

Caused by *E. coli.*

Skin and skin structure:

Infections caused by *Staphylococcus epidermidis, Streptococcus, S. aureus, S. pyogenes.*

Empiric treatment in febrile neutropenia:

CEFEPIME FRESENIUS is indicated for empiric monotherapy of febrile neutropenia. Combination of CEFEPIME FRESENIUS with other appropriate antimicrobial medicines should be considered in patients at high risk for severe infection (including patients with a history of recent bone marrow transplantation, hypotension at presentation, an underlying haematologic malignancy, or severe or prolonged neutropenia) or when called for by host or local epidemiological factors.

4.2 Posology and method of administration

Posology

CEFEPIME FRESENIUS can be administered either intravenously or intramuscularly.

The dosage and route depend upon the severity of the infection, susceptibility of causative organisms, site and type of infection, and upon age and renal function of the patient.

Adults

TABLE 1*:* Recommended dosage schedule for adults and paediatric patients > 40 kg (or older than 12 years of age) with normal renal function:*

SITE AND TYPE OF INFECTION	DOSE	FREQUENCY

Mild to moderate urinary tract infections (uncomplicated and complicated)	500 mg - 1g IV or IM	12-hourly
Mild to moderate infections including bronchitis, skin and skin structure infections	1 g IV or IM	12 hourly
Severe infections including pneumonia, urinary tract infections, complicated intra-abdominal infections, including cases with an associated bacteraemia	2 g IV	12 hourly
Empiric treatment of fever in neutropenic patients	2 g IV	8 hourly

* Usual duration of therapy is 7-10 days; more severe infections may require longer treatment. In the treatment of beta-haemolytic streptococcal infections a therapeutic dose should be administered for at least 10 days. For empirical treatment of febrile neutropenia, usual duration of therapy is 7 days or until resolution of neutropenia.

Special populations

Elderly

Dose adjustment is not required, unless there is concurrent renal impairment.

Adults with impaired renal function

In patients with impaired renal function, the dose of CEFEPIME FRESENIUS should be adjusted to compensate for the slower rate of renal elimination. The recommended initial dose of CEFEPIME FRESENIUS in patients with mild to moderate renal impairment should be the same as in patients with normal renal

function.

The recommended maintenance doses of CEFEPIME FRESENIUS in patients with renal impairment are presented in TABLE 2.

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

Males: Creatinine clearance (ml/min) =

$$\frac{\text{Weight (kg)} \times (140 - \text{age})}{0{,}82 \times \text{serum creatinine (micromole/L)}}$$

Females: 0,85 x value calculated using the formula for males.

Maintenance dose schedule for adults and adolescents (>12 years) with renal impairment:

TABLE 2: Maintenance dosing schedule in adult patients with renal impairment

Creatinine clearance (ml/min)	**Recommended maintenance dosage**			
> 50	Usual dose, no adjustment necessary			
	2 g 8 hourly	2 g 12 hourly	1 g 12 hourly	500 mg 12 hourly
30 - 50	1 g 8 hourly	2 g 24 hourly	1 g 24 hourly	500 mg 24 hourly
11 - 29	1 g 12 hourly	1 g 24 hourly	500 mg 24 hourly	500 mg 24 hourly
≤ 10	1 g 24 hourly	500 mg 24 hourly	250 mg 24 hourly	250 mg 24 hourly
Haemodialysis*	500 mg 24 hourly	500 mg 24 hourly	500 mg 24 hourly	500 mg 24 hourly

* Pharmacokinetic modelling indicates that reduced dosing for these patients is necessary. Patients receiving CEFEPIME FRESENIUS who are undergoing

concomitant haemodialysis should be dosed as follows: 1 gram loading dose on the first day of CEFEPIME FRESENIUS therapy and 500 mg per day thereafter. On dialysis days, CEFEPIME FRESENIUS should be administered following dialysis. Whenever possible CEFEPIME FRESENIUS should be administered at the same time each day.

Patients doing dialysis

In patients undergoing haemodialysis, 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.

In patients undergoing continuous ambulatory peritoneal dialysis (CAPD), CEFEPIME FRESENIUS may be administered at the same dose recommended for patients with normal renal function at intervals of 48 hours.

Paediatric population

Paediatrics (aged 2 month up to 12 years with normal renal function and body weight of ≤ 40 kg)

Pneumonia, urinary tract infections, and skin structure infections:

50 mg/kg twelve hourly for 10 days. For more severe infections, an eight hourly dosage schedule can be used.

Empiric treatment of febrile neutropenia:

Patients ≥ 2 months of age with body weight ≤ 40 kg:

50 mg/kg eight hourly for 7-10 days.

Experience with the use of CEFEPIME FRESENIUS in paediatric patients < 2 months of age is limited. Administration of CEFEPIME FRESENIUS in these patients should be carefully monitored.

For paediatric patients with body weights > 40 kg, adult dosing recommendations apply (see TABLE 1). For patients older than 12 years who are ≤ 40 kg, the dosage recommendations for younger patients ≤ 40 kg should be used. Dosage in paediatric patients should not exceed the maximum recommended dosage in adults (2 g eight hourly). Experience with intramuscular administration in paediatric patients is limited.

Children with impaired renal function

Since urinary excretion is the primary route of elimination of cefepime in paediatric patients (see section 5.2), an adjustment of the dosage of CEFEPIME FRESENIUS should also be considered in patients < 12 years of age with renal impairment.

Method of administration

After reconstitution, CEFEPIME FRESENIUS can be administered via intravenous or intramuscular route.

The reconstituted solution is yellow to yellow-brown.

Intravenous (IV) administration: The IV route of administration is preferable for patients with severe or life-threatening infections, particularly if the possibility of shock is present.

The prepared solution (see section 6.6 for instructions) should be injected directly into the vein over a period of three to five minutes or injected into the tubing of an administration set while the patient is receiving a compatible IV fluid (see section 6.6 for a list of compatible fluids). For physical and chemical incompatibilities, refer to section 6.6.

For intravenous infusion, reconstitute the 1 g, or 2 g vial, as described in section 6.6 for direct IV administration. Dilute it further by adding the appropriate quantity of the resulting solution to an IV container with one of the compatible IV fluids identified in

section 6.6. IV infusions of a volume between 50 ml and 100 ml should be administered over a period of approximately 30 minutes.

Intramuscular (IM) administration: CEFEPIME FRESENIUS should be reconstituted with one of the diluents described in section 6.6, then administered by deep IM injection into a large muscle mass (such as the upper outer quadrant of the gluteus maximus).

4.3 Contraindications

- Hypersensitivity to cefepime or any of the excipients of CEFEPIME FRESENIUS.
- Patients with history of hypersensitivity reactions to the cephalosporin class of antibiotics or beta-lactam antibiotics (e.g. penicillins, monobactams and carbapenems).

4.4 Special warnings and precautions for use

Hypersensitivity

Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to medicines. Severe and occasionally fatal hypersensitivity reactions have been reported.

If an allergic reaction to CEFEPIME FRESENIUS occurs, discontinue the medicine and treat the patient appropriately. Severe immediate hypersensitivity reactions may require epinephrine and other supportive therapy.

Colitis and antibiotic-associated colic and diarrhoea

Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis *Clostridium difficile*- associated diarrhoea, has been reported with nearly all broad-spectrum antibiotics, including CEFEPIME FRESENIUS. It may range in severity from mild diarrhoea to fatal colitis. It is

therefore important to consider this diagnosis in patients who develop diarrhoea in association with the use of CEFEPIME FRESENIUS. Careful medical history is necessary since *Clostridium difficile* associated diarrhoea has been reported to occur over two months after the administration of antibacterial medicines. Mild cases of colitis may respond to discontinuation of CEFEPIME FRESENIUS; moderate to severe cases may require more elaborate management. Medicines inhibiting peristalsis are contraindicated in this situation.

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).

Use of CEFEPIME FRESENIUS may result in overgrowth of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Renal impairment

Cefepime is predominantly excreted by the kidney and the risk of toxic reactions to CEFEPIME FRESENIUS is greater in patients with impaired renal function (see section 5.2 and “Elderly patients” below).

Renal function should be monitored carefully if medicines with nephrotoxic potential, such as aminoglycosides and potent diuretics, are administered with CEFEPIME FRESENIUS.

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 FRESENIUS 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 FRESENIUS 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 were reported: reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures (including nonconvulsive status epilepticus), and/or renal failure (see section 4.8). Most cases occurred in patients with renal impairment who received doses of CEFEPIME FRESENIUS that exceeded recommendations.

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

Elderly patients (65 years and older)

In clinical studies, when elderly patients received the usual recommended adult dose, clinical efficacy and safety were comparable to clinical efficacy and safety in younger adult patients unless the patients had renal insufficiency. There was a modest prolongation in elimination half-life and lower renal clearance values compared with those seen in younger people. Dosage adjustments are recommended if renal function is compromised (see section 4.2).

Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection and renal function should be monitored (see section 4.8, 5.2 and “Renal impairment” above).

Severe adverse events, including reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma) myoclonus, convulsions (including nonconvulsive status epilepticus), and/or renal failure have occurred in elderly patients with renal insufficiency given the usual dose of CEFEPIME FRESENIUS (see section 4.8).

Interference with serological testing

A positive Coombs test, without evidence of haemolysis, has been described in patients treated with CEFEPIME FRESENIUS twice daily (see section 4.5).

Cephalosporin antibiotics (including CEFEPIME FRESENIUS) 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 (see section 4.5).

4.5 Interactions with other medicines and other forms of interaction

Concomitant treatment with bacteriostatic antibiotics may interfere with the action of beta-lactam antibiotics.

Renal function should be monitored if CEFEPIME FRESENIUS is used in combination with potentially nephrotoxic medicines, such as aminoglycosides and potent diuretics.

CEFEPIME FRESENIUS may potentiate the action of coumarin anticoagulants (warfarin).

The renal excretion of CEFEPIME FRESENIUS may be inhibited by probenecid.

Interaction with diagnostic tests (see section 4.4)

In patients treated with cefepime, a 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).

False positives are not seen with glucose oxidase methods.

For incompatibility information, see section 6.2.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of CEFEPIME FRESENIUS during pregnancy has not been established.

Breastfeeding

Cefepime is excreted in human breast milk in very low quantities. The safety of CEFEPIME FRESENIUS during lactation has not been established.

Fertility

There is no information available on the effect of CEFEPIME FRESENIUS on fertility.

4.7 Effects on ability to drive and use machines

Dizziness, confusional states and altered state of consciousness may be possible side effects of CEFEPIME FRESENIUS. Patients should be advised not to drive or use machinery if they experience any of these effects.

4.8 Undesirable effects

a. Summary of the safety profile

The most common side effects were gastrointestinal symptoms and hypersensitivity reactions. Adverse events that occurred are listed below by system organ class and frequency of occurrence.

b. Tabulated summary of adverse reactions

System organ class/ Frequency	Adverse reactions (MedDRA term)
Infections and infestations	
Less frequent:	Vaginitis, candidiasis (vaginal and oral), *Clostridium difficile* associated diarrhoea, colitis, pseudomembranous colitis.
Frequency not known:	Overgrowth of non-susceptible organisms
Blood and lymphatic system disorders	
Frequent:	Anaemia, eosinophilia
Less frequent:	Thrombocytopenia, leukopenia, neutropenia
Frequency not known:	Agranulocytosis, aplastic or haemolytic anaemia
Immune system disorders	
Less frequent:	Anaphylactic reaction, angioedema
Frequency not known:	Anaphylactic shock
Psychiatric disorders	
Frequency not known:	State of confusion, hallucination
Nervous system disorders	
Less frequent:	Headache, convulsions, paraesthesia, dysgeusia, dizziness
Frequency not known:	Coma, stupor, encephalopathy, altered state of consciousness, myoclonus
Vascular disorders	

Frequent:	Phlebitis at the infusion site
Less frequent:	Vasodilation
Frequency unknown:	Haemorrhage
Respiratory, thoracic and mediastinal disorders	
Less frequent:	Dyspnoea
Gastrointestinal disorders	
Frequent:	Diarrhoea
Less frequent:	Nausea, vomiting, abdominal pain, constipation
Frequency not known:	Gastrointestinal disorder
Hepatobiliary disorders	
Frequent:	Increased alkaline phosphatase, alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin
Frequency not known:	Hepatitis, cholestatic jaundice
Skin and subcutaneous tissue disorders	
Frequent:	Skin rash
Less frequent:	Erythema, urticaria, pruritus
Frequency unknown:	Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Renal and urinary disorders	
Less frequent:	Increased blood urea, increased blood creatinine
Frequency not known:	Renal failure, toxic nephropathy

Reproductive system and breast disorders	
Less frequent:	Genital pruritus
General disorders and administration site conditions	
Frequent:	Infusion site reaction, injection site inflammation and pain
Less frequent:	Pyrexia, infusion site inflammation, chills
Investigations	
Frequent:	Coombs test positive, prolonged prothrombin time, prolonged partial thromboplastin time
Frequency not known:	False-positive glycosuria

c. Description of selected adverse reactions

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 who received cefepime doses that exceeded those recommended (see sections 4.2 and 4.4).

Anaphylaxis, including anaphylactic shock, transient leukopenia, neutropenia, agranulocytosis and thrombocytopenia were reported.

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 otherwise) 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

Treatment should be symptomatic and supportive.

In case of severe overdosage, especially in patients with compromised renal function, haemodialysis will aid in the removal of cefepime from the body; peritoneal dialysis is of no value. Accidental overdosing has occurred when large doses were given to patients with impaired renal function (see sections 4.2 and 4.8).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.20.1.1 Broad and medium spectrum antibiotics

Cefepime is a fourth generation cephalosporin.

Mechanism of action

Cefepime is bactericidal and acts by inhibition of bacterial cell wall synthesis. It has a spectrum of activity against a range of Gram-positive and Gram-negative bacteria.

Cefepime is highly resistant to hydrolysis by a number of beta-lactamases, has a low affinity for chromosomally encoded beta-lactamases, and exhibits rapid penetration into Gram-negative bacterial cells.

Cefepime minimum bactericidal concentrations were < 2 times the minimum inhibitory concentration for the majority of organisms tested.

Resistance

Gram-positives aerobes:

Enterococci like *Enterococcus faecalis,* methicillin-resistant staphylococci and *Listeria* are resistant to cefepime.

Gram-negative aerobes:

Cefepime is inactive against most strains of *Xanthomonas maltophilia (Pseudomonas maltophilia).* Not all pseudomonas strains are susceptible.

Species with acquired resistance include *Burkholderia cepacian, Legionella, Stenotrophomonas maltophilia.*

Anaerobes:

Cefepime is inactive against *Bacteroides fragilis* and *Clostridium difficile.*

Other microorganisms:

Chlamydia, Mycoplasma

5.2 Pharmacokinetic properties

Absorption:

Following intramuscular injection, cefepime is completely absorbed. Therapeutic concentrations are found in various body fluids such as urine, bile, peritoneal fluid, blister fluid and sputum, and tissues such as bronchial mucosa, prostate, appendix and gallbladder, following intravenous administration of a single dose of cefepime.

Distribution

The serum protein binding of cefepime averages 16,4 % and is independent of concentration in the serum.

Biotransformation

Urinary recovery of unchanged cefepime represents approximately 85 % of dose, resulting in high concentrations of cefepime in the urine.

Elimination

The average elimination half-life of cefepime is approximately two hours.

There is no evidence of accumulation in healthy persons receiving doses up to 2 g intravenously every 8 hours for a period of 9 days. Total body clearance averages 120 ml/min.

The average renal clearance of cefepime is 110 ml/min, demonstrating that cefepime is eliminated almost exclusively by renal mechanisms, primarily glomerular filtration.

Special populations

Elderly

Healthy volunteers 65 years old or older, who received a single 1 g intravenous dose of cefepime had higher area under the concentration-time curve and lower renal clearance values compared to younger healthy adults. Dosage adjustments in the

elderly are recommended if renal function is compromised (see sections 4.4 and 4.2).

Paediatrics

The pharmacokinetics with respect to single and multiple doses of cefepime have been evaluated in patients aged between 2 months and 16 years who received doses of 50 mg/kg, administered by IV infusion or IM injection; multiple doses were administered every 8 or 12 hours for a period of at least 48 hours.

Mean plasma concentrations of cefepime after the first dose were similar to those at steady state, with only slight accumulation seen upon repeated dosing.

Following IM injection under steady state conditions, mean peak cefepime plasma concentrations of 68 µg/ml were achieved at a median time of 0,75 hours, compared to 185,6 µg/ml after IV. The mean trough concentration after IM injection at steady state was 6,0 µg/ml at 8 hours. Bioavailability averaged 82 % after IM injection.

Other pharmacokinetic parameters in infants and children were not different between first dose and steady state determinations, regardless of dosing schedule (12-hourly or 8-hourly).

Following a single IV dose, total body clearance (in children over 6 months) averaged 3,4 ml/min/kg and average volume of distribution was 0,3 L/kg.

The overall mean elimination half-life was 1,6 hours in children.

The urinary recovery of unchanged cefepime was 60,4 % of the administered dose, and renal clearance was the primary pathway of elimination, averaging 2,0 ml/min/kg.

Elimination was slower in children 2-6 months ($t_{1/2}$ 1,89 hours, clearance 2,97 ml/min/kg).

Impaired hepatic function:

The pharmacokinetics of cefepime is unaltered in patients with impaired hepatic function who receive a single 1 g dose.

Impaired renal function:

Elimination half-life is prolonged in patients with renal insufficiency with a linear relationship between the individual body clearance and the creatinine clearance.

The average elimination half-life in dialysis patients is 13 hours (haemodialysis) and 19 hours for continuous ambulatory peritoneal dialysis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L- arginine

6.2 Incompatibilities

Cefepime Fresenius should not be mixed with other medicines or solution except those mentioned in section 6.6.

Physical-chemical incompatibility have been reported between solutions of CEFEPIME FRESENIUS and solutions of metronidazole, vancomycin, gentamycin, tobramycin sulphate or netilmicin sulphate. In cases where a concomitant intravenous administration is indicated, these active substances should neither be administered together with CEFEPIME FRESENIUS, nor should it be administered through the same intravenous route.

6.3 Shelf life

Vial with powder:

2 years

Solutions for intravenous use:

Chemical and physical in-use stability has been demonstrated. From a microbiological point of view, the product should be used immediately after reconstitution and dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

CEFEPIME FRESENIUS at concentrations between 1 and 40 mg/ml in one of the compatible IV infusion fluids listed in section 6.6 are physically and chemically stable for 2 hours at room temperature at or below 25 ºC.

Solutions for intramuscular use:

CEFEPIME FRESENIUS reconstituted as directed (TABLE 4, section 6.6) is stable for 24 hours at room temperature below 25 ^{0}C or for 7 days under refrigeration (2 - 8 ^{0}C) when using the following diluents: sterile water for injection, 0,9 % sodium chloride, 5 % dextrose injection, bacteriostatic water for injection with parabens or benzyl alcohol, or 0,5 % or 1 % lidocaine hydrochloride.

6.4 Special precautions for storage

Store at or below 25 ^{0}C. Protect from light.

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

6.5 Nature and contents of container

Cefepime 1 g Fresenius:

15 or 20 ml Type II or Type III clear glass vial closed with chlorobutyl rubber stopper with blue aluminium cap.

Cefepime 2 g Fresenius:

15 or 20 ml Type II or Type III clear glass vial closed with chlorobutyl rubber stopper with red aluminium cap.

Outer container: carton boxes.

Pack sizes: 1's and 10's. Not all packing sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Preparation and administration of the reconstituted solution

CEFEPIME FRESENIUS powder is to be reconstituted using the volumes of diluent shown in TABLE 4. The compatible diluents are listed below.

TABLE 4 Preparation of solutions of CEFEPIME FRESENIUS

	Amount of diluent to be added (ml)	**Approx. available volume (ml)**	**Approx. cefepime concentration (mg/ml)**
Intravenous			
1g vial	10	11,4	90
2g vial	10	12,8	160
Intramuscular			
1g vial	3,0	4,4	230

Intravenous (IV):

Direct IV administration:

Compatible diluents: sterile water for injection, 5 % dextrose injection or 0,9 % sodium chloride.

Reconstitute CEFEPIME FRESENIUS with one of the above compatible diluents, using the diluent volumes shown in TABLE 4. The resulting solution should be injected directly into the vein over a period of three to five minutes.

Intravenous infusion:

Compatible IV fluids: CEFEPIME FRESENIUS is compatible at concentrations between 1 and 40 mg/ml with the following IV infusion fluids: 0,9 % sodium chloride injection, 5 % and 10 % dextrose injection, m/6 sodium lactate injection, 5 % dextrose and 0,9 % sodium chloride injection, lactated ringers and 5 % dextrose injection.

Reconstitute the 1 g, or 2 g vial, as noted above for direct IV administration.

Inject the appropriate quantity of the resulting solution into the tubing of an administration set while the patient is receiving a compatible IV fluid mentioned above. IV infusions of a volume between 50 ml and 100 ml should be administered over a period of approximately 30 minutes. See section 4.2.

Intramuscular (IM):

CEFEPIME FRESENIUS should be reconstituted with one of the following diluents, using the volumes shown in TABLE 4: sterile water for injection, 0,9 % sodium chloride injection, 5 % dextrose injection, or bacteriostatic water for injection with parabens or benzyl alcohol.

Although CEFEPIME FRESENIUS can be reconstituted with 0,5 % or 1,0 % lidocaine hydrochloride, it is usually not necessary because CEFEPIME FRESENIUS causes little or no pain upon IM administration.

NOTE:

The *reconstituted* solutions, which are prepared correctly, can present a yellow to yellow-brown colour. The colour may darken on storage. This does not mean that efficacy of CEFEPIME FRESENIUS may be compromised.

The content of the vial is meant for a single usage only.

Any remaining reconstituted solution should be discarded.

Inspect the vial before using. It can only be used if the solution is free from visible particles.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

Stand 7 Growthpoint Business Park

162 Tonetti Street

Halfway House extension 7

Midrand

Gauteng

Telephone number: (011) 545 0000

8 REGISTRATION NUMBERS

Cefepime 1 g Fresenius: 47/20.1.1/0005

Cefepime 2 g Fresenius: 47/20.1.1/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 March 2021

10 DATE OF REVISION OF TEXT