SECTION 2: SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Cefepime

1 g powder for solution for injection or infusion

Cefepime (as cefepime dihydrochloride monohydrate)

1. NAME OF THE MEDICINAL PRODUCT

Cefepime 1 g powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cefepime 1 g powder for solution for injection or infusion

Each vial contains 1 g cefepime as cefepime dihydrochloride monohydrate.

Excipients:

Each vial contains L-arginine 730 mg per g of cefepime.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

White to pale yellow powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adults and adolescents

Infections caused by cefepime-susceptible pathogens:

- 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 soft-tissue infections

- intra-abdominal infections, including peritonitis and biliary tract infections

- gynaecological infections

- empirical treatment of patients with febrile neutropenia. Cefepime as monotherapy is

indicated in patients with febrile neutropenia that is suspected to be due to a bacterial infection. In patients at high risk of severe infections (e.g. patients with recent bone marrow transplantation, with hypotension at presentation, with an underlying hematological malignancy, or severe or prolonged neutropenia), combination antimicrobial therapy should be considered

- treatment of patients with septicemia that occurs in association with, or is suspected to be associated with, any of the infections listed above

Cefepime may be used for peri-operative prophylaxis in surgical procedures such as intra-abdominal surgery in patients who have a definite risk of post-operative infections.

Children (2 months to 12 years) and with a body weight of ≤ 40 kg

For the treatment of infections caused by cefepime-susceptible pathogens:

- bacterial meningitis

- pneumonia

- uncomplicated and complicated urinary tract infections, including pyelonephritis

- skin and soft-tissue infections

- empirical treatment of patients with febrile neutropenia. Cefepime as monotherapy is indicated in patients with febrile neutropenia that is suspected to be due to a bacterial infection. In patients at high risk of severe infections (e.g. patients with recent bone marrow transplantation, with hypotension at presentation, with an underlying hematological malignancy, or severe or prolonged neutropenia), combination antimicrobial therapy should be considered.

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

4.2. Posology and method of administration

The tables below provide general recommendations for dosing.

The dose of Cefepime administered and the duration of treatment are guided by the nature and severity of infection, pathogen susceptibility, renal function and the patient's overall constitution.

Cefepime can either be administered intravenously as an injection or as a short infusion (over 30 min) or via deep intramuscular injection into a large muscle mass.

Intravenous administration is to be preferred in patients with severe or life-threatening infections, particularly when the possibility of shock is present.
Intravenous injections should be given over a period of 3 to 5 minutes, directly into a vein or into the tube of an infusion set during infusion of a compatible IV fluid.
Adults and adolescents over 40kg body weight (approximately over 12 years) 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, including empiric therapy for febrile neutropenic patients	2 g IV	every 8 h

For prophylaxis in intra-abdominal surgery, a single dose of 2 g is administered as a 30-minute infusion 60 minutes before the procedure; thereafter, 500 mg metronidazole should be given by slow intravenous infusion. Due to incompatibility between Cefepime and metronidazole, these two active substances must not be administered together (see section 6.2). Prior to infusing metronidazole, it is recommended that the infusion tube be flushed with a compatible fluid. If the procedure lasts for more than 12 hours, the infusions should be repeated after 12 hours.

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).

Impaired hepatic function in adults: No dose adjustment is required in patients with impaired hepatic function.

Impaired renal function in adults:

Cefepime is excreted via the kidneys almost exclusively by glomerular filtration. The cefepime dose must therefore be adjusted in patients with renal dysfunction (GFR < 50 ml/min), in order to compensate for the reduced renal elimination rate. The recommended starting dose for patients with renal dysfunction (except in cases of dialysis, see below) is the same as for patients with normal renal function.

If only the serum creatinine level (SCR mg/dl) is available, creatinine clearance (CrCL) can be approximated using Cockcroft's equation. The serum creatinine should represent a steady state of renal function:

Male patients: CRCL (ml/min) = $\frac{\text{weight (kg) x (140 - age)}}{\text{(72 x SCR mg/ dl)}}$

Female patients: CRCL (ml/min) = 0.85 x the male value.

The following table gives the maintenance dose for adults with renal dysfunction:

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

* Pharmacokinetics shows that a dose reduction is required for dialysis patients. For these patients, cefepime should be dosed as follows: 1 g cefepime on Day 1 as a starting dose, followed by 500 mg / day for all infections with the exception of febrile neutropenia. On dialysis days, cefepime should be administered following hemodialysis. If possible, cefepime should always be administered at the same time of day.

Dialysis patients: If hemodialysis is performed, approximately 68% of the total amount of cefepime at the start of dialysis will be removed during a 3-hour dialysis session.

In cases of continuous ambulatory peritoneal dialysis, cefepime can be administered at the usual doses recommended for patients with normal renal function, but at 48-hour intervals only.

Children (> 2 months up to approximately 12 years of age, to a body weight of 40 kg) with normal renal function

Site and Type of Infection	Dose and route of administration	Frequency	Duration (days)
Pneumonia, urinary tract infections, skin and soft tissue infections	50 mg/kg	Every 12 hours severe infections: every 8 hours	10
Moderate to severe pneumonia due to *P. aeruginosa*	50 mg/kg	Every 8 hours	10
Bacterial meningitis Empiric therapy for febrile neutropenic patients	50 mg/kg	Every 8 hours	7-10

Infants from 1 to less than 2 months with normal renal function

Experience is limited with children below 2 months of age. On the basis of data obtained in the age group >2 months, it is recommended, based on a pharmacokinetic model, that children between 1 and 2 months of age should be administered doses of 30 mg/kg every 12 hours or every 8 hours. The 50 mg/kg dose for patients >2 months and the 30 mg/kg dose for patients between 1 and 2 months are comparable with an adult dose of 2 g. These patients should be carefully monitored when administering Cefepime.

The pediatric dosage should not exceed the maximum daily dose for adults (2 g every 8 hours). There is only limited experience with regard to intramuscular injection in children. Data on absorption of cefepime administered intramuscularly are limited in children.

For children > 40 kg, the dosage instructions for adults apply.

Impaired renal function in children:

As elimination primarily takes place via the kidneys (see section 5.2), the dose should also be adjusted for patients below 12 years of age with impaired renal function. A dosage of

50 mg/kg (patients between 2 months and 12 years of age) and a dose of 30 mg/kg (patients between 1 and 2 months) are comparable with doses of 2 g in adults.

If only the serum creatinine level (SCR) is available, creatinine clearance (CrCL) can be determined using the following formula.

$$\text{CrCL (ml/ min/ 1.73 m}^3\text{)} = \frac{0.55 \times \text{height (cm)}}{\text{SCR (mg/ dl)}}$$

or

$$\text{CrCL (ml/ min/ 1.73 m}^3\text{)} = \frac{0.52 \times \text{height (cm)} - 3.6}{\text{SCR (mg/ dl)}}$$

The following table gives maintenance dose for children aged between 2 months and 12 years with impaired renal function:

Creatinine clearance (ml/min)	**Severe infections**	**Very severe infections**
> 50	Usual dosage, no adjustment required	
	50 mg/kg every 12h	50 mg/kg every 8h
30 - 50	50 mg/kg every 24h	50 mg/kg every 12h
11 - 29	25 mg/kg every 24h	50 mg/kg every 24h
≤ 10	12.5 mg/kg every 24h	25 mg/kg every 24h

The following table gives maintenance dose for infants from 1 to less than 2 months with impaired renal function:

Creatinine clearance (ml/min)	**Severe infections**	**Very severe infections**
> 50	Usual dosage, no adjustment required	
	30 mg/kg every 12h	30 mg/kg every 8h
30 - 50	30 mg/kg every 24h	30 mg/kg every 12h
11 - 29	15 mg/kg every 24h	30 mg/kg every 24h

≤ 10	7.5 mg/kg every 24h	15 mg/kg every 24h

Children with impaired hepatic function: No dose adjustment is required in children with impaired hepatic function.

Duration of treatment is guided by the clinical picture. In general, treatment should always be continued for another few days following abatement of fever and resolution of pathological symptoms. 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.

Method of administration

Cefepime should be reconstituted before use. For instructions on reconstitution of the product before administration, see section 6.6.

4.3. Contraindications

Hypersensitivity to cefepime, to any other cephalosporin antibiotics 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 any history of allergy, particularly to medicinal products, or in patients with bronchial asthma, urticaria and hay fever. The patient must be carefully monitored during the first administration. If an allergic reaction occurs, treatment must be discontinued immediately.

Severe hypersensitivity reactions require emergency treatment.

Renal Impairment

In patients with impaired renal function, e.g. reduced urine output due to renal impairment (creatinine clearance < 50 ml/min), or other conditions that can impair renal function, the dose of Cefepime must be adjusted, in order to compensate for the reduced renal elimination rate. As high and prolonged antibiotic serum concentrations may occur at the conventional dosage in patients with renal impairment or other conditions that may impair renal function, the maintenance dose of cefepime must be reduced in such patients. Continued dosage is guided by the degree of renal dysfunction, the severity of infection and susceptibility of the causative pathogens (see sections 4.2 and 5.2).

As cefepime is mainly excreted via the kidneys, the risk of toxic effects is greater in patients with renal dysfunction. As the likelihood of suffering from reduced renal function is greater in elderly patients, caution should be exercised when selecting the dose for these patients and renal function should be monitored (see section 4.8 and 5.2). Severe adverse reactions occurred in elderly patients with renal impairment whose cefepime dose was not adjusted, including reversible encephalopathy (impaired consciousness with confusion, hallucinations, stupor and coma), myoclonus, seizures (including non-convulsive status epilepticus) and/or renal failure (see section 4.8).

Renal function should be carefully monitored if medications with a nephrotoxic potential, e.g. aminoglycosides or potent diuretics, are administered at the same time as Cefepime.

Neurotoxicity

Severe adverse reactions have been reported during post-marketing, including reversible encephalopathy (impaired consciousness with confusion, hallucinations, stupor and coma), myoclonus, seizures (including non-convulsive status epilepticus) and/or renal failure (see section 4.8). In most cases, those affected were patients with renal dysfunction who had received Cefepime at dosages higher than those recommended. In general, symptoms of neurotoxicity regressed upon discontinuation of therapy and/or hemodialysis, but there have also been cases with a fatal outcome.

Clostridium difficile associated diarrhea

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

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

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

Development of drug-resistant bacteria

As with other antibiotics, increased growth of non-susceptible organisms may also occur with Cefepime. Should superinfection occur during treatment, appropriate measures should be taken.

Cefepime contains sodium.

Cefepime 1.0 g: This medicinal product contains approximately 4.0 mEq of sodium per 1.0 g dose which should be taken into consideration by patients on a controlled sodium diet.

4.5. Interaction with other medicinal products and other forms of interaction

The monitoring of renal function is recommended during the treatment with Cefepime if other drugs that have nephrotoxic potential are administered (i.e., aminoglycosides and potent diuretics).

Coombs' tests: In rare cases during cefepime treatment, the Coombs' test may show a false-positive result (see section 4.8).

Urinary glucose: 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.

4.6. Fertility, pregnancy and lactation

Pregnancy: The safety of using cefepime in pregnant women has not been substantiated. During pregnancy, cefepime should only be used when the anticipated benefit justifies the potential risk.

Breast-feeding: 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

No studies on the effect on the ability to drive and use machines have been performed. However, possible adverse reactions like altered state of consciousness, dizziness or confusional state may alter the ability to drive and use machines

4.8. Undesirable effects

a. *Summary of the safety profile*

In clinical trials using multiple doses of cefepime, 4 137 patients were treated with the recommended dosages of cefepime (500 mg to 2 g intravenous every 12 hours). There were no deaths or permanent disabilities thought related to drug toxicity. Sixty-four (1.5%) patients discontinued medication due to adverse reactions. Thirty-three (51%) of these 64 patients who discontinued therapy did so because of rash. The percentage of cefepime-treated patients who discontinued study drug because of drug-related adverse reactions was similar at daily doses of 500 mg, 1 g, and 2 g every 12 hours (0.8%, 1.1%, and 2%, respectively). However, the incidence of discontinuation due to rash increased with the higher recommended doses.

At the higher dose of 2 g every 8 hours, the incidence of adverse reactions was higher among the 795 patients who received this dose of cefepime. They consisted of rash (4%), diarrhea (3%), nausea (2%), vomiting (1%), pruritus (1%), fever (1%), and headache (1%).

b. *Tabulated list of adverse reactions*

For estimation of development frequency of side effects the following criteria are used: very common (≥1/10), common (from ≥1/100 to <1/10), uncommon (from ≥1/1000 to <1/100), rare (from ≥1/10 000 to <1/1000), very rare (from <1/10 000 including individual case safety report), and "the frequency is not known" (according to the available data, it is not possible to estimate the frequency).

System Organ Class	Frequency	Event
Infections and infestations	Uncommon	oral candidiasis, vaginal infection
	Rare	candidiasis
Blood and lymphatic system disorders	Common	anemia, eosinophilia

	Uncommon	thrombocytopenia, leukopenia, neutropenia
	Not known	aplastic anemia, hemolytic anemia, agranulocytosis
Immune system disorders	Rare	anaphylactic reaction
	Not known	anaphylactic shock
Psychiatric disorders	Not known	confusion, hallucinations
Nervous system disorders	Uncommon	headaches
	Rare	seizures, paresthesia, dysgeusia, dizziness
	Not known	coma, stupor, encephalopathy, impaired consciousness, myoclonus
Vascular disorders	Common	phlebitis at the injection/infusion site
	Rare	vasodilation
	Not known	hemorrhage
Respiratory, thoracic and mediastinal disorders	Rare	dyspnea
Gastrointestinal disorders	Common	diarrhea
	Uncommon	colitis (incl. pseudomembranous colitis), nausea, vomiting
	Rare	abdominal pain, constipation
	Not known	gastrointestinal complaints
Skin and subcutaneous tissue disorders	Common	Skin rash
	Uncommon	erythema, urticaria, pruritus
	Not known	toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
Renal and urinary disorders	Uncommon	increase in BUN and serum creatinine
	Not known	renal failure, toxic nephropathy
General disorders and administration site conditions	Common	Infusion site reaction, injection site inflammation and pain
	Uncommon	fever
	Rare	shivering
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

Pediatric population

The safety profile of cefepime in infants and children is similar to that seen in the adult. In clinical studies, rash was the most commonly occurring adverse reaction to have any causal relationship with cefepime.

Reporting of suspected adverse reactions. Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

To report any side effect(s):

- _____:

- _____

Fax: _____

Call _____ at _____, Exts: _____.

Toll free phone: _____

E-mail____@_____

Website: _____

4.9. Overdose

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

5. PHARMACODYNAMIC PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: other beta-lactam antibiotics, 4th-generation cephalosporins.

ATC code: J01DE01.

Mechanism of Action

The mechanism of action of cefepime is based on inhibition of bacterial cell wall synthesis (in the growth phase), due to inhibition of penicillin-binding proteins (PBPs) e.g. transpeptidases. This results in a bactericidal action.

Mechanism of Resistance

Resistance to cefepime can be based on the following mechanisms:

- Inactivation by beta-lactamases. Cefepime can be hydrolysed by certain beta-lactamases, particularly by extended-spectrum beta-lactamases (ESBLs), occurring for example in strains of *Escherichia coli* or *Klebsiella pneumoniae*.
- Reduced affinity of PBPs to cefepime: acquired resistance in pneumococci and other streptococci is due to modifications of existing PBPs as a result of mutation. On the other hand, formation of an additional PBP, with reduced affinity to cefepime, is responsible for resistance in the case of methicillin (oxacillin)-resistant staphylococci.
- In Gram-negative bacteria, inadequate penetration of cefepime through the external cell wall may result in insufficient PBP inhibition.
- Cefepime can be actively transported from the cell by 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.

Breakpoints

European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing are presented below.

EUCAST clinical MIC breakpoints for Cefepime (2014-01-01)

Organism	**Susceptible (S) (mg/l)**	**Resistant (R) (mg/l)**
Enterobacteriaceae	≤ 1	> 4
Pseudomonas aeruginosa	≤ 8[a]	> 8
Staphylococcus spp. *	note [b]	note [b]
Streptococcus groups A, B, C and G	note [c]	note [c]
Streptococcus pneumoniae[1]	≤ 1[d]	> 2
Viridans group *streptococci*[2]	≤ 0.5	> 0.5
Haemophilus influenzae	≤ 0.25[d]	> 0.25
Moraxella catarrhalis	≤ 4	> 4
Non-species related breakpoints[5]	≤ 4	> 8[e]

a. Breakpoints relate to high dose therapy (2 g x 3).

b. Susceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility except for ceftazidime, cefixime and ceftibuten, which do not have breakpoints and should not be used for staphylococcal infections. Some methicillin-resistant *S. aureus* are susceptible to ceftaroline.

c. The beta-lactam susceptibility of beta-hemolytic streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.

d. Isolates with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence

regarding clinical response for confirmed isolates with MIC values above the current resistant breakpoint they should be reported resistant.
e. Breakpoints apply to a daily intravenous dose of 2 g x 2 and a high dose of at least 2 g x 3.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, 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. Particularly in the case of serious infections or treatment failure, a microbiological diagnosis - with detection of the pathogen and its susceptibility to cefepime - should be sought.

Lists of Microorganisms

Commonly susceptible species

Gram-positive aerobes:

Staphylococcus aureus (methicillin-susceptible)

*Streptococcus pneumoniae (*incl. penicillin-resistant strains*)*°

Streptococcus pyogenes°

Gram-negative aerobes:

Acinetobacter pittii

Citrobacter freundii

Enterobacter aerogenes

Haemophilus influenzae

Hafnia alvei

Moraxella catarrhalis°

Morganella morganii

Proteus mirabilis[%]

Proteus vulgaris°

Providencia rettgeri

Providencia stuartii

Serratia liquefaciens°

Serratia marcescens

Species for which acquired resistance may be a problem

Gram-positive aerobes

Staphylococcus aureus[3]

Staphylococcus epidermidis[+]

Staphylococcus haemolyticus[+]

Staphylococcus hominis[+]

Gram-negative aerobes

Acinetobacter baumannii

Enterobacter cloacae

Escherichia coli[%]

Klebsiella oxytoca[%]

Klebsiella pneumoniae[%]

Pseudomonas aeruginosa

Inherently resistant organisms

Gram-positive aerobes

Enterococcus spp.

Listeria monocytogenes

Staphylococcus aureus (methicillin-resistant)

Gram-negative aerobes

Stenotrophomonas maltophilia

Anaerobes

Bacteroides fragilis

Clostridium difficile

Other micro-organisms

Chlamydia spp.

Chlamydophila spp.

Legionella spp.

Mycoplasma spp

° There were no current data available at the time of publishing this table. Susceptibility is assumed in the primary literature, standard works and therapeutic recommendations.

[+] Rate of resistance is over 50% in at least one region.

[%] Extended-spectrum beta-lactamase (ESBL)-producing strains are always resistant.

[3] In an outpatient setting, the rate of resistance is <10%.

PK/PD relationship

Similar to other beta-lactam antibacterial agents, the time that Cefepime concentrations exceed the MIC of the pathogen (T>MIC) has been shown to best correlate with efficacy.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of cefepime are linear within the range of 250 mg to 2 g IV and 500 mg to 2 g IM; they do not differ with regard to duration of treatment.

Absorption: For the most part, cefepime is completely absorbed following IM administration. After IV administration of 2 g over 30 minutes to healthy volunteers, peak plasma concentrations (C_{max}) were 126 - 193 µg/ml and - following IM administration of this same dose - 57.5 µg/ml.

Distribution: Cefepime is well distributed in body fluids and tissues. Within the range of 250 mg to 2 g, the relative tissue distribution of cefepime does not vary in relation to the administered dose. The mean steady-state volume of distribution is 18 l. There is no evidence of any accumulation in healthy subjects given doses of up to 2 g IV at 8-hourly intervals over a 9-day period. Serum protein binding of cefepime is < 19% and is not dependent on serum concentrations. The mean elimination half-life is approximately 2 hours.

Metabolism: Cefepime is metabolized to a minor extent. The primary urinary metabolite is N-methylpyrrolidine oxide, a tertiary amine, accounting for only around 7% of the dose.

Elimination: Mean total body clearance is 120 ml/min. The mean renal clearance of cefepime is 110 ml/min; this shows that cefepime is almost exclusively eliminated via renal mechanisms, mainly by glomerular filtration. Urine recovery of unchanged cefepime is approximately 85% of the dose, leading to high urinary concentrations of cefepime. Following IV administration of 500 mg cefepime, cefepime was no longer detectable after 12 hours in plasma and after 16 hours in urine.

Special populations

Elderly patients: Distribution of cefepime has been tested in elderly male and female patients (> 65 years). Safety and efficacy in elderly patients is comparable with adults, whilst a slight prolongation of the elimination half-life and lower renal clearance values were observed in elderly patients. Dose adjustment is required when there is concomitant impairment of renal function (see section 4.2. Posology and method of administration ”Impaired renal function in adults”).

Children: The pharmacokinetics of cefepime has been studied in patients between 2 months and 16 years of age. A single dose of 50 mg/kg body weight (IV infusion or IM injection) - or multiple doses of 50 mg/kg every 8 or 12 hours over at least 48 hours - were administered. Absorption: The mean bioavailability of cefepime was 82% after IM injection. Distribution: Mean cefepime plasma concentrations after the initial dose were similar to those at steady state. Slight accumulation was only observed with multiple dosing. At steady state following

IM injection, mean peak plasma levels of 68 µg/ml were reached, on average, after 0.75 hours. Following IM injection, the mean trough steady-state concentration was 6.0 µg/ml after 8 hours. Elimination: After a single dose (IV), mean body clearance was 3.3 ml/min./kg and the mean volume of distribution was 0.3 l/kg. The mean elimination half-life was 1.7 hours. In the urine, 60.4% of the administered dose was recovered unchanged. Cefepime is mainly excreted via the kidneys and mean renal clearance is 2.0 ml/min./kg.
Other pharmacokinetic parameters were the same in infants and children after the initial dose and at steady state with a dosing interval of 12 or 8 hours. There were no pharmacokinetic differences in children of varying ages (2 months - 12 years) or between boys and girls.
Impaired renal function: Studies in patients with varying degrees of renal dysfunction have shown that the elimination half-life is significantly prolonged in the presence of renal dysfunction. In patients with impaired renal function, there is a linear relationship between total body clearance and creatinine clearance. In dialysis patients - either hemodialysis or continuous ambulatory peritoneal dialysis - the half-life is 13 to 19 hours.
Other: With single-dose administration of 1 g, the kinetics of cefepime is unchanged in patients with *cystic fibrosis and hepatic dysfuncti*on. Thus, no dose adjustment is required.

5.3. Preclinical safety data

Animal studies indicate that Cefepime is well tolerated.
Although no long-term animal studies have been performed to evaluate carcinogenic potential, *in vivo* and *in vitro* testing has shown that cefepime is not genotoxic. Studies in animals have shown that daily doses of up to 10 times the recommended dose in humans do not have any direct or indirect harmful effects on reproduction, embryonal/foetal development, duration of gestation or peri/postnatal development.

5. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

L-Arginine

6.2. Incompatibilities

Solutions of Cefepime must not be mixed with the following antibiotics: metronidazole, vancomycin, gentamicin, tobramycin sulphate and netilmicin sulphate, because physical or chemical incompatibilities may arise. In the cases where a concomitant therapy is indicated, these active substances must be administered separately.

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”.

6.3. Shelf life

Unopened vials: 3 years.

After reconstitution:

Reconstituted solution for injection, reconstituted with water for injections:

Chemical and physical in use stability has been demonstrated for not more than 18 hours at 20 to 25°C or 7 days in a refrigerator (2 - 8°C).

From a microbiological point of view, unless the method of opening and reconstitution precludes the risk of microbial contamination, the product should be used immediately.

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 - 25°C).

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

Do not store above 30°C, keep vial in the outer carton.

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

6.5 Nature and contents of container

Cefepime 1 g powder for solution for injection/infusion

1 g powder in 20 ml glass vial with rubber stopper and aluminium or flip-off cap.

The vials are packed in boxes of 1, 5, 10, 1-50 or 50 vials.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Intravenous administration

Cefepime 1 g powder for solution for injection or 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 direct 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:

Strength	Volume of solvent added (ml)	Approximate Available volume (ml)	Approximate concentration of cefepime (mg/ml)
1.0 g I.V.	10.0	11.3	100
2.0 g I.V.	10.0	12.5	160

The prepared solution is injected slowly over a 3 to 5minute period - either directly into a vein or directly into the cannula of an infusion system whilst the patient is receiving an infusion with a compatible IV solution.

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:

Strength	Volume of solvent added (ml)	Approximate Available volume (ml)	Approximate concentration of cefepime (mg/ml)
1.0 g I.V.	50.0 100.0	51.4 101.4	19 10
2.0 g I.V.	50.0 100.0	52.8 102.8	38 19

The resulting solution should be administered over approximately 30 minutes.

Intramuscular administration:

Cefepime must be prepared with one of the following solutions: water for injections, 0.9% sodium chloride solution for injection, 5% glucose solution for injection, water for injection with parabens or benzyl alcohol. Althought Cefepime can be prepared with 0.5% or 1.0%

lidocaine solution, this is generally not required, as IM administration causes no or only mild pain.

The volume of the solvent for infusion to be used and the resulting concentration of cefepime are presented in the following table::

Strength	Volume of solvent added (ml)	Approximate Available volume (ml)	Approximate concentration of cefepime (mg/ml)
1 g IM	3.0	4.4	230

Standard aseptic techniques should be used for solution preparation and administration. Inspect the vial before use. It must only be used if the solution is free from particles.

Use only clear solutions.

Like other cephalosporins, cefepime solutions can develop a yellow to amber colour, depending on storage conditions. However, this has no negative influence on the effect of the product.

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

7. Marketing authorisation holder

“KRASPHARMA” OJSC

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8. Marketing authorisation number(s)

Cefepime 1 g powder for solution for injection / infusion _____

9. Date of first Authorisation/ renewal of the authorisation

_____

10. Date of revision of the text

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