1. NAME OF THE MEDICINAL PRODUCT

[Fortsporine Injection] 1 g powder for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 g cefepime as cefepime dihydrochloride monohydrate

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefepime is indicated for the treatment of the severe infections listed below caused by cefepime-susceptible pathogens (see sections 4.4 and 5.1).

In adults and children over 12 years of age and with a body weight of ≥ 40 kg:

- Pneumonia
- Complicated urinary tract infections (including pyelonephritis)
- Complicated intra-abdominal infections
- Peritonitis associated with dialysis in patients on CAPD

In adults:

- Acute biliary tract infections

In children aged 2 months up to 12 years and with a body weight of ≤ 40 kg:

- Pneumonia

- Complicated urinary tract infections (including pyelonephritis)
- Bacterial meningitis (see section 4.4)

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.
Cefepime may be used in the empirical treatment of adults, adolescents and children aged 2 months to 12 years 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, hypotension at presentation, underlying haematological malignancy, or severe or prolonged neutropenia), antimicrobial monotherapy may be inappropriate. No sufficient data exist to support the efficacy of cefepime monotherapy in such patients. A combination therapy with an aminoglycoside or glycopeptide antibiotic may be advisable, taking into consideration the patient's individual risk profile.
Cefepime should be co-administered with other antibacterial agents whenever the possible range of causative bacteria would not fall within its spectrum of activity.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.**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.**

4.2 Posology and method of administration

After reconstitution cefepime can be administered intravenously as a slow injection over a period of 3 to 5 minutes or as a short infusion over a period of about 30 min or via deep intramuscular injection into a large muscle mass.

A single dose of 2 g cefepime should not be administered via the IM route.

Posology and method of administration are guided by the nature and severity of infection, pathogen susceptibility, renal function and the patient’s overall constitution.

Normal renal function:

Adults and adolescents over 40 kg body weight (approximately over 12 years):

Single doses and dosage interval

Severe infections: • Bacteraemia • Pneumonia • Complicated urinary tract infections (including pyelonephritis) • Acute biliary tract infections	*Very severe infections:* • Complicated intra-abdominal infections • Empirical treatment of patients with febrile neutropenia
2.0 g every 12 hours	2.0 g every 8 hours

Infants and children (aged from 1 month to 12 years and/or weighing ≤ 40 kg, with normal renal function):

Single doses (mg/kg body weight), dosage interval and treatment duration		
	Severe infections: • Pneumonia • Complicated urinary tract infections (including pyelonephritis)	*Very severe infections:* • Bacteraemia • Bacterial meningitis • Empirical treatment of patients with febrile neutropenia
Children from 2 months, body weight ≤ 40 kg:	50 mg/kg every 12 hours *More severe infections*: 50 mg/kg every 8 hours for 10 days	50 mg/kg every 8 hours for 7-10 days
Infants 1 to less than 2 months:	30 mg/kg every 12 hours *More severe infections*: 30 mg/kg every 8 hours for 10 days	30 mg/kg every 8 hours for 7-10 days

Experience in infants younger than 2 months is limited. Dosage recommendations of 30 mg/kg every 12 or 8 hours were derived from pharmacokinetic data of children older than 2 months and are considered appropriate for infants from 1 to less than 2 months.

For children weighing > 40 kg dosage recommendations for adults are applicable.
For patients older than 12 years with a body weight < 40 kg, dosage recommendations for younger patients with a body weight of < 40 kg are applicable.
The maximum recommended daily dose of 2 g every 8 h as for adults should not be exceeded.
There is only limited experience with regard to intramuscular injection in children. Data on

absorption of cefepime administered intramuscularly are limited in children.

Renal impairment:
In patients with impaired renal function, the maintenance dose of cefepime should be adjusted to compensate for the slower rate of renal elimination.

Adults and adolescents (>12 years and body weight over 40 kg):
For patients with mild to moderate renal impairment an initial dose of 2.0 g cefepime is recommended.

The following table gives the subsequent maintenance dose:

Creatinine clearance [ml/min]	**Recommended maintenance dosage:** Single doses and interval of administration	
	Severe infections: • Bacteraemia • Pneumonia • Complicated urinary tract infections (including pyelonephritis) • Acute biliary tract infections	*Very severe infections:* • Complicated intra-abdominal infections • Empirical treatment of patients with febrile neutropenia
> 50 (usual dose, no adjustment required)	2 g every 12 h	2 g every 8 h
30-50	2 g every 24 h	2 g every 12 h
11-29	1 g every 24 h	2 g every 24 h
≤ 10	0.5 g every 24 h	1 g every 24 h

Dialysis patients:
In patients undergoing haemodialysis, approximately 68% of the total amount of cefepime present in the body at the start of dialysis will be eliminated during a 3 hour dialysis period. Pharmacokinetic modelling indicates that dose reduction is necessary in these patients. The following dosage is recommended:
Loading dose of 1 g on the first day of treatment with cefepime followed by 500 mg per day thereafter except for febrile neutropenia, for which indication the recommended dose is 1 g per day.

On days of dialysis, cefepime should be administered after the course of dialysis. If possible, cefepime should be administered at the same time each day.

In patients undergoing continuous ambulatory peritoneal dialysis (CAPD) the following dosage is recommended:

- 1 g cefepime every 48 hours in case of severe infections (bacteraemia, pneumonia, complicated urinary tract infections (including pyelonephritis), acute biliary tract infections)
- 2 g cefepime every 48 hours in case of very severe infections (abdominal infections, peritonitis, empirical treatment of patients with febrile neutropenia)

Infants from 1 month and children up to 12 years with a body weight of ≤ 40 kg:
A dose of 50 mg/kg for patients between 2 months and 12 years (see section 5.2) and a dose of 30 mg/kg for infants aged 1 to 2 months is comparable to a dose of 2 g in adults including the same prolongation of dosing intervals as shown in the table below.

Children from 2 months up to 40 kg bodyweight (approx. 12 years):

Single doses (mg/kg body weight) and dosage interval		
Creatinine clearance [ml/min]	*Severe infections:* • Pneumonia • Complicated urinary tract infections (including pyelonephritis)	*Very severe infections:* • Bacteraemia • Bacterial meningitis • Empirical treatment of patients with febrile neutropenia
> 50 (usual dose, no adjustment required)	50 mg/kg every 12 h	50 mg/kg every 8 h
30-50	50 mg/kg every 24 h	50 mg/kg every 12 h
11-29	25 mg/kg every 24 h	50 mg/kg every 24 h
≤ 10	12.5 mg/kg every 24 h	25 mg/kg every 24 h

Infants from 1 to less than 2 months

Single doses (mg/kg body weight) and dosage interval		
Creatinine clearance [ml/min]	*Severe infections:* • Pneumonia • Complicated urinary tract infections (including pyelonephritis)	*Very severe infections:* • Bacteraemia • Bacterial meningitis • Empirical treatment of patients with febrile neutropenia
> 50 (usual dose, no adjustment required)	30 mg/kg every 12 h	30 mg/kg every 8 h

30-50	30 mg/kg every 24 h	30 mg/kg every 12 h
11-29	15 mg/kg every 24 h	30 mg/kg every 24 h
≤ 10	7.5 mg/kg every 24 h	15 mg/kg every 24 h

Hepatic impairment:
No dose adjustment is required in patients with impaired hepatic function (see section 5.2).

Elderly:
Since elderly are at increased risk for reduced renal function, the dosage should be chosen with caution and the patient's renal function should be monitored. Dosage adjustment is recommended if renal function is reduced (see section 4.4).

Duration of treatment:
The usual duration of therapy is 7 to 10 days. In general, cefepime should be administered not less than 7 days and not longer than 14 days per treatment. For empirical treatment of febrile neutropenia, usual duration of therapy is 7 days or until resolution of neutropenia.

Method of administration:
After appropriate reconstitution, cefepime can be administered via **direct intravenous injection** over a period of 3 to 5 minutes or injected into the tubing of an administration set while the patient is receiving a compatible i.v. fluid or via **intravenous infusion** over 30 minutes or via deep **intramuscular injection** into a large muscle mass. For incompatibility and instructions on reconstitution of the medicinal product before administration, see sections 6.2 and 6.6.

4.3 Contraindications

Cefepime is contraindicated in patients who have had previous hypersensitivity reactions to cefepime, to any of the excipients listed in section 6.1, to any other cephalosporin or to any other beta-lactam antibiotics agent (e.g. penicillins, monobactams and carbapenems). Due to its L-arginine content, this product is further contraindicated in patients with L-arginine hypersensitivity and acidosis. Caution is therefore advised in cases of hyperkalemia.

4.4 Special warnings and precautions for use

Warnings

Hypersensitivity reactions
As with all beta-lactam antibacterial agents, serious 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, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefepime, beta-lactams or other medicinal products. In 10 % of the cases there is cross-reactivity between hypersensitivity to penicillin and cephalosporins.
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.

Adequate emergency measures must be initiated."

Renal impairment
In patients with impaired renal function, (creatinine clearance ≤ 50 ml/min) or other conditions that may compromise renal function, the dosage of cefepime should be adjusted to compensate for the slower rate of renal elimination. Because high and prolonged serum antibiotic concentrations can occur from usual dosages in patients with renal insufficiency or other conditions that may compromise renal function, the maintenance dosage should be reduced when cefepime is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms (see sections 4.2 and 5.1).

During postmarketing surveillance, the following serious adverse events have been 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 that exceeded recommendations.
In general, symptoms of neurotoxicity resolved after discontinuation of cefepime and/or after hemodialysis, however, some cases included a fatal outcome.
Renal function should be monitored carefully if drugs with nephrotoxic potential, such as aminoglycosides and potent diuretics are administered with cefepime.

Special precautions for use

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including cefepime, and may range in severity from mild diarrhoea to fatal colitis. CDAD must be considered in all patients who present with diarrhoea following antibiotic 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 antibiotic use not directed against C. difficile may need to be discontinued.

As with other antibiotics, use of cefepime may result in overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Geriatric use
Of the more than 6400 adults treated with cefepime e in clinical studies, 35 % were 65 years or older while 16% were 75 years or older. For geriatric patients in clinical studies, who received the usual recommended adult dose, clinical efficacy and safety were comparable to clinical efficacy and safety in non-geriatric adult patients, unless the patients had renal insufficiency. There was a modest prolongation in elimination half-life and lower renal clearance values compared to those seen in younger persons. Dosage adjustments are recommended if renal function is compromised (see section 4.2 - Posology and administration and 5.2- Pharmacokinetic properties).
Cefepime is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and renal function should be monitored (see sections 4.8 Undesirable effects and 5.2 - Pharmacokinetic properties). Serious adverse events, including reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures (including nonconvulsive status epilepticus), and/or renal failure have occurred in geriatric patients with renal insufficiency given the usual dose of cefepime (see section 4.8 - Undesirable effects).

Antibacterial activity of cefepime
Due to the relatively limited spectrum of antibacterial activity of cefepime it is not suitable for 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).

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

No interaction studies have been performed.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Reproductive studies in mice, rats, and rabbits showed no evidence of fetal damage, however there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation
Cefepime is excreted in human breast milk in very low concentrations. Caution should be used when cefepime is administered to a nursing woman, then the infant should be monitored closely.

Fertility
No impairment of fertility has been seen in rats. There are no data on the use of cefepime in human fertility.

4.7 Effects on ability to drive and use machines

The effects of medicinal product on 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 and 4.9).

4.8 Undesirable effects

Undesirable effects are classified into the following categories, according to system organ class, MedDRA terminology and MedDRA frequencies: 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 (frequency cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table: Adverse drug events reported during clinical or postmarketing experience

System Organ Class	Frequency	MedDRA Term
Infections and infestations	Uncommon	Oral candidiasis, vaginal infection

	Rare	Candidiasis
Blood and lymphatic system disorders	Very common	Coombs test positive
	Common	Prothrombin time prolonged, partial thromboplastin time prolonged, anaemia, eosinophilia
	Uncommon	Thrombocytopenia, leukopenia, neutropenia
	Not known	Aplastic anaemiaa, haemolytic anaemiaa, agranulocytosis
Immune system disorders	Rare	Anaphylactic reaction, angioedema
	Not known	Anaphylactic shock
Metabolism and nutrition disorders	Not known	Urine glucose false positive
Psychiatric disorders	Not known	Confusional state, hallucination
Nervous system disorders	Uncommon	Headache
	Rare	Convulsion, paraesthesia, dysgeusia, dizziness
	Not known	Coma, stupor, encephalopathy, altered state of consciousness, myoclonus
Vascular disorders	Common	Infusion site phlebitis
	Rare	Vasodilation
	Not known	Haemorrhagea
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
Hepatobiliary disorders	Common	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased
Skin and subcutaneous tissue disorders	Common Uncommon Not known	Rash Erythema, urticaria, pruritus Toxic epidermal necrolysisa , Stevens-Johnson syndromea, erythema multiformea
Renal and urinary disorders	Uncommon Not known	Blood urea increased, blood creatinine increased Renal failure, nephropathy toxica
Reproductive system and breast disorders	Rare	Pruritus genital
General disorders and administration site condition	Common Uncommon Rare	Infusion site reaction, injection site pain, injection site inflammation Pyrexia, infusion site inflammation Chills
Investigations	Common	Alkaline phosphatase increased

- [a] Adverse reactions that are generally accepted as being attributable to other compounds in the class.

Paediatric population
The safety profile of cefepime in infants and children is similar to that seen in adults. The most frequently reported adverse event considered related to cefepime in clinical trials was rash

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 national reporting system listed in Appendix V*.

4.9 Overdose

In case of severe overdose, 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 - Posology and administration and 4.4 - Special warnings and precautions for use). Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures (see section 4.8).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fourth-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.

Pharmacokinetic/pharmacodynamic relationship
Efficacy is largely dependent on the length of time during which drug levels exceed the minimal inhibitory concentration (MIC) of the pathogen concerned.

Mechanisms of resistance
Cefepime has a low affinity for chromosomally-encoded beta-lactamases and is highly resistant to hydrolysis by most beta-lactamases.
Bacterial resistance to cefepime may be due to one or more of the following mechanisms:
- reduced affinity of penicillin-binding proteins for cefepime,
- production of β-lactamases which are able to hydrolyse cefepime efficiently (e.g, several of the extended-spectrum and chromosomally-mediated β-lactamases),
- outer membrane impermeability, which restricts access of cefepime to penicillin binding proteins in gram-negative organisms,

efflux pumps for active substances.

There is partial or complete cross resistance between cefepime and other cephalosporins and penicillins.

Cefepime testing is performed using the standard dilution series. The following minimum inhibitory concentrations have been determined for susceptible and resistant germs:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints (2014-01-01)

Pathogen	**susceptible**	**resistant**
Enterobacteriaceae	≤ 1 mg/l	> 4 mg/l
Pseudomonas spp.	≤ 8 mg/l [1]	> 8 mg/l
Staphylococcus spp.	note [2]	note [2]
Streptococcus groups A, B, C and G	note [3]	note [3]
Streptococcus pneumoniae	≤ 1 mg/l [4]	> 2 mg/l
Viridans group streptococci	≤ 0.5 mg/l	> 0.5 mg/l
Haemophilus influenzae	≤ 0.25 mg/l [4]	> 0.25 mg/l
Moraxella catarrhalis	≤ 4 mg/l	> 4 mg/l
PK/PD (non-species related) breakpoints [5]	≤ 4 mg/l	> 8 mg/l

1. Breakpoints relate to high dose therapy.
2. 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.
3. The susceptibility of streptococcus groups A, B, C and G to cephalosporins is inferred from the benzylpenicillin susceptibility.
4. 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.
5. Breakpoints apply to a daily intravenous dose of 2 g x 2 and a high dose of at least 2 g x 3.

Susceptibility

The prevalence of resistance in individualized bacterial strains may vary according to the region and time, so it is recommended to obtain local information about the susceptibility of the strains before initiating the treatment.

Cefepime is usually active against the following microorganisms *in vitro* (status: January 2016).

Commonly susceptible species
Aerobic Gram-positive microorganisms
Staphylococcus aureus (Methicillin-susceptible)
Streptococcus pneumoniae (incl. penicillin-resistant strains)°
Streptococcus pyogenes°
Aerobic Gram-negative microorganisms
Acinetobacter pittii
Citrobacter freundii
Enterobacter aerogenes

Haemophilus influenzae
Moraxella catarrhalis°
Morganella morganii
Proteus mirabilis[%]
Proteus vulgaris°
Serratia liquefaciens°
Serratia marcescens
Species in which acquired resistance may pose a problem during use
Aerobic Gram-positive microorganisms
Staphylococcus aureus[3]
Staphylococcus epidermidis[+]
Staphylococcus haemolyticus[+]
Staphylococcus hominis[+]
Aerobic Gram-negative microorganisms
Acinetobacter baumannii
Enterobacter cloacae
Escherichia coli[%]
Klebsiella oxytoca[%]
Klebsiella pneumoniae[%]
Pseudomonas aeruginosa
Naturally resistant species
Aerobic Gram-positive microorganisms
Enterococcus spp.
Listeria monocytogenes
Staphylococcus aureus (methicillin-resistant)
Aerobic Gram-negative microorganisms
Legionella spp.
Stenotrophomonas maltophilia
Anaerobic microorganisms
Bacteroides fragilis
Clostridium difficile
Other microorganisms
Chlamydia spp.
Chlamydophila 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%.

5.2 Pharmacokinetic properties

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

Absorption:
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 bodily 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.

Biotransformation:
Cefepime is metabolised 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.

Elderly:
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 *"Renal impairment in adults"* and 4.4. Special warnings and precautions for use *"Elderly").*
With single-dose administration of 1 g, the kinetics of cefepime is unchanged in patients with cystic fibrosis and hepatic dysfunction. Thus, no dose adjustment is required.

Paediatric population:

The pharmacokinetics with respect to single and multiple doses of cefepime has been evaluated in patients aged between 2 months and 16 years who received doses of 50 mg/kg, administered via I.V. infusion; multiple doses were administered every 8 or 12 hours for a period of at least 48 hours.
The mean plasma concentrations of cefepime after the first dose were similar to those in steady-state, and a slight accumulation was observed with the administration of additional doses.
The values of the other pharmacokinetic parameters in infants and children, determined both after the first dose and in steady-state, did not differ, regardless of the dosage schedule (every 12 hours or every 8 hours). There were no differences in the pharmacokinetic values, neither between the patients of different ages, nor between males and females.
After the administration of a single I.V. dose, the average total body clearance was 3.3 ml/min/kg and the distribution volume was 0.3 l/kg. The total average elimination half-life was 1.7 hours. The proportion of cefepime recovered unchanged in the urine was 60.4% of the administered dose and renal clearance was the main route of elimination with an average value of 2.0 ml/min/kg.

Renal impairment:
Studies in patients with various degrees of renal insufficiency have indicated a significant prolongation of the elimination half-life. There is a linear relationship between the individual body clearance and the creatinine clearance in subjects with renal impairment.
The average elimination half-life in dialysis patients is 13 hours (haemodialysis) and 19 hours for continuous ambulatory peritoneal dialysis.

Hepatic impairment:
With single-dose administration of 1 g, the kinetics of cefepime is unchanged in patients with cystic fibrosis and hepatic dysfunction. Thus, no dose adjustment is required.

5.3 Preclinical safety data

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Arginine

6.2 Incompatibilities

Solutions of [nationally completed name] must **not** be mixed with the following antibiotics: metronidazole, vancomycin, gentamicin, tobramycin sulphate and netilmicin sulphate, because physical or chemical incompatibilities may arise. Should concomitant therapy be indicated, such agents must be administered separately.
If the solution or container permits, all parenteral products should be visually inspected for particles prior to administration.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

36 months

Reconstituted product:
Chemical and physical in use stability has been demonstrated for not more than 24 hours at 20 to 25 °C or 7 days at no more than 2 to 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. Once opened, the product may be stored for a maximum of 24 hours at no more than 2 to 8 °C. Other in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Finished product:
Do not store above 30 °C.
Keep the vial in the outer carton in order to protect from light.

Reconstituted product:
For storage conditions, see section 6.3.

6.5 Nature and contents of container

0.5 g powder:
Colourless type III 20 ml glass vial closed with halogenated butyl rubber stopper and sealed with aluminium crimp cap and yellow plastic flip-off cap.

Pack sizes: 1 and 10 vials

1 g powder:
Colourless type III 20 ml glass vial closed with halogenated butyl rubber stopper and sealed with aluminium crimp cap and white plastic flip-off cap.

Pack sizes: 1 and 10 vials

2 g powder:
Colourless type II 50 ml glass bottle closed with halogenated butyl rubber stopper and sealed with aluminium crimp cap and white plastic flip-off cap.

Pack sizes: 1 and 10 bottles

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This product is for single use only.

Intravenous administration:
[nationally completed name] is compatible with the following solutions for infusion: sterile water for injection, 0.9% sodium chloride injection, 5% glucose injection, 10% glucose injection, 1/6 molar sodium lactate injection, 5% glucose and 0.9% sodium chloride injection, lactated ringer's and 5% glucose injection and lactated ringer's injection.

For IV injections
For direct IV injection, the vial/bottle contents are dissolved in 5 or 10 ml water for injections, 5% glucose solution for injection, or 0.9% sodium chloride solution for injection, as indicated in the following table.

Strength	Solvent added (ml)	Available volume (ml)	Concentration (approx., in mg/ml)
0.5 g IV	5.0	5.7	90
1 g IV	10.0	11.4	90
2 g IV	10.0	12.8	160

The prepared solution is injected slowly over a 3 to 5-minute 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 IV infusions
For IV infusions, the powder is dissolved as described for direct IV injections. An appropriate amount of the prepared solution is added to an IV infusion container with a compatible IV solution for infusion.

The prepared solution should be administered over a period of approximately 30 minutes.

Intramuscular administration:
[Nationally completed name] is compatible with 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 [Nationally completed name] can be prepared with 0.5% or 1.0% lidocaine solution, this ist generally not required, as IM administration causes no or only mild pain

For IM injections:
For IM injections, contents of vials are dissolved in 1.5 ml or 3.0 ml of solvents as indicated in the following table..

Strength	Solvent added (ml)	Available volume (ml)	Concentration (approx., in mg/ml)
1 g IM	3.0	4.4	230

See 6.2 for incompatibilities.

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

8. MARKETING AUTHORISATION NUMBER(S)

[[Zolon Healthcare Limited]]