AUSTRALIAN PRODUCT INFORMATION

CEFEPIME KABI Cefepime (as hydrochloride) 1g and 2g Powder for Injection

1 NAME OF MEDICINE

Cefepime hydrochloride monohydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cefepime Kabi Powder for Injection is a sterile powder for injection available in 20 mL vials containing cefepime hydrochloride monohydrate equivalent to 1 g or 2 g cefepime.

For the list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder for Injection.

Cefepime hydrochloride monohydrate is a white to pale yellow powder. It is highly soluble in water.

Following reconstitution with Water for Injections, it is a pale yellow to amber coloured solution with a pH between 4.0 and 6.0.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adults

Cefepime Kabi is indicated in the treatment of the infections listed below when caused by susceptible bacteria.

- Lower respiratory tract infections, including pneumonia and bronchitis.
- Urinary tract infections, both complicated, including pyelonephritis, and uncomplicated infections.
- Skin and skin structure infections.
- Intra-abdominal infections, including peritonitis and biliary tract infections.
- Gynaecological infections.
- Septicaemia.

- Empiric treatment in febrile neutropenic patients (See Section 4.4 Special Warnings and Precautions for Use).

Cefepime Kabi is also indicated for surgical prophylaxis in patients undergoing intra-abdominal surgery. In this indication it is essential that metronidazole also be administered.

Paediatrics

Cefepime Kabi is indicated in paediatric patients over 2 months of age for the treatment of the infections listed below when caused by susceptible bacteria:

- Pneumonia
- Urinary tract infections, both complicated, including pyelonephritis, and uncomplicated infections
- Skin and skin structure infections
- Septicaemia
- Empiric treatment in febrile neutropenic patients (See Section 4.4 Special Warnings and Precautions for Use)

Culture and susceptibility studies should be performed when appropriate to determine susceptibility of the causative organism(s) to cefepime. Empiric therapy with Cefepime Kabi may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

Because of its broad spectrum of bactericidal activity against gram-positive and gram-negative bacteria, Cefepime Kabi can be used appropriately as monotherapy prior to identification of the causative organisms(s). In the treatment of febrile neutropenia, consideration should be given to the need for other antibiotics in combination with Cefepime Kabi. In patients who are at risk of mixed aerobic-anaerobic infection, including infections in which *Bacteroides fragilis* may be present, concurrent initial therapy with an anti-anaerobic agent is recommended before the causative organism(s) is known.

4.2 DOSE AND METHOD OF ADMINISTRATION

ADULTS

The usual adult dosage and route of administration of Cefepime Kabi is 1 g administered intravenously or intramuscularly every 12 hours. However, the dosage and route vary according to the susceptibility of the causative organisms, the severity of the infection, and the condition and renal function of the patient. Guidelines for dosage of Cefepime Kabi are provided in Table 1. The usual duration of therapy is 7 to 10 days; however, more severe infections may require longer treatment.

Table 1
Recommended dosage schedule for adults with normal renal function
(aged 12 years and over)

Severity of Infection	Dose & route of administration	Dosing Interval
Mild to moderate urinary tract infections	500 mg to 1 g IV or IM	q12h
Mild to moderate infections other than UTI	1g IV or IM	q12h
Severe infections	2 g IV	q12h
Very severe or life-threatening infections	2 g IV	q8h

Surgical Prophylaxis

The dose recommendation for prophylaxis to prevent infection in adults undergoing intra-abdominal surgery is as follows:

A single 2 g IV dose of Cefepime Kabi (as a 30-minute infusion, see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION)** starting 60 minutes before initial surgical incision. A single 500 mg IV dose of metronidazole should be administered immediately following completion of the cefepime infusion. The metronidazole dose should be prepared and administered in accordance with official product labelling. Due to incompatibility, Cefepime Kabi and metronidazole should not be mixed together in the same container (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Compatibility and Stability**); flushing of the intravenous line with a compatible fluid before infusion of the metronidazole is recommended.

If the surgical procedure lasts longer than 12 hours from the initial prophylactic dose, a second dose of Cefepime Kabi followed by metronidazole should be administered 12 hours following the initial prophylactic dose.

PAEDIATRICS (aged 2 months to 12 years with normal renal function)

Usual recommended dosages:
Pneumonia, urinary tract infections, and skin and skin structure infections: Patients > 2 months of age with body weight ≤ 40 kg: 50 mg/kg q12h. For more severe infections, a dosage schedule of q8h can be used.

Empiric treatment of febrile neutropenia: Patients > 2 months of age with body weight ≤ 40 kg: 50 mg/kg q8h.

The usual duration of therapy is 7 to 10 days; however, more severe infections may require longer treatment.

For paediatric patients with body weights > 40kg, 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 q8h). Experience with intramuscular administration in paediatric patients is limited and this route is not recommended.

Use in Patients with Impaired Hepatic Function:
No adjustment is necessary for patients with impaired hepatic function.

Use in Patients with Impaired Renal Function:

Adults with Impaired Renal Function
In patients with impaired renal function, the dose of cefepime should be adjusted to compensate for the slower renal elimination. The recommended initial dose of cefepime 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 in patients with renal insufficiency 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:

$$\text{Males: Creatinine clearance (mL/min)} = \frac{\text{weight (kg)} \times (140 - \text{age})}{814 \times \text{serum creatinine (mmol/L)}}$$

Females: 0.85 x value calculated using formula for males

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 q8h	2 g q12h	1 g q12h	500 mg q12h
30 - 50	2 g q12h	2 g q24h	1 g q24h	500 mg q24h
11 - 29	2 g q24h	1 g q24h	500 mg q24h	500 mg q24h
≤10	1 g q24h	500 mg q24h	250 mg q24h	250 mg q24h
Haemodialysis*	500 mg q24h	500 mg q24h	500 mg q24h	500 mg q24h

* Pharmacokinetic modeling indicates that reduced dosing for these patients is necessary. Patients receiving cefepime who are undergoing concomitant haemodialysis should be dosed as follows: 1 gram loading dose on the first day of cefepime therapy and 500 mg per day thereafter. On dialysis days, cefepime should be administered following dialysis. Whenever possible cefepime should be administered at the same time each day.

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 removed during a 3 hour dialysis period. In patients undergoing continuous ambulatory peritoneal dialysis, cefepime may be administered at normally recommended doses, ie: 500 mg, 1 g or 2 g, depending on infection severity, at a dosage interval of every 48 hours.

Children with Impaired Renal Function

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

A dose of 50 mg/kg in patients aged 2 months up to 12 years, and a dose of 30 mg/kg in patients aged 1 month up to 2 months, are comparable to a dose of 2 g in an adult. As recommended in Table 2 above, the same increase in interval between doses and/or reduction in dose should be used.

ADMINISTRATION

Cefepime Kabi may be given intravenously or by deep intramuscular injection into a large muscle mass (such as the upper outer quadrant of the gluteus maximus). The dosage and route vary according to the susceptibility of the causative organisms, the severity of the infection, renal function, and overall condition of the patient.

When using Cefepime Kabi for Surgical Prophylaxis it is essential that metronidazole also be administered.

Intravenous Administration

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

For direct IV administration, reconstitute Cefepime Kabi with 5 or 10 mL of Sterile Glucose 5% Injection or 0.9% Sodium Chloride, as directed in Table 3. Slowly inject directly into the vein over a period of three to five minutes or inject into the tubing of an administration set while the patient is receiving a compatible IV fluid (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Compatibility and Stability).

For intravenous infusion, reconstitute the 1 g, or 2 g vial, as noted above for direct IV administration, and add an appropriate quantity of the resulting solution to an IV container with one of the compatible IV fluids (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Compatibility and Stability).

Intramuscular Administration

Cefepime Kabi should be reconstituted with one of the following diluents: Sterile Water for Injections, 0.9% Sodium Chloride or Glucose 5% Injection (refer to Table 3). Although Cefepime Kabi can be constituted with 0.5% or 1.0% lignocaine hydrochloride, it is usually not required because cefepime causes little or no pain upon intramuscular administration.

Experience with intramuscular administration in paediatric patients is limited and this route is not recommended.

COMPATIBILITY AND STABILITY

Intravenous:

Cefepime Kabi Powder for Injection is compatible at concentrations between 1 and 40 mg/mL with the following IV infusion fluids: 0.9% Sodium Chloride, 5% Glucose Injection, M/6 Sodium Lactate Injection, 5% Glucose and 0.9% Sodium Chloride Injection, Lactated Ringers and 5% Glucose Injection.

Cefepime in 0.9% Sodium Chloride or 5% Glucose Injection is compatible when admixed with heparin (10 or 50 units/mL), potassium chloride (10 or 40 mEq/L) and theophylline (0.8mg/mL in 5% Glucose Injection). Cefepime at a concentration of 40 mg/mL in 0.9% Sodium Chloride or 5% Glucose Injection was found to be compatible with amikacin 6 mg/mL.

Intramuscular:

Cefepime Kabi Powder for Injection should be reconstituted with the following diluents: Sterile Water for Injections, 0.9% Sodium Chloride, 5% Glucose Injection, or 0.5% or 1% lignocaine hydrochloride.

For Both Routes of Administration:

Cefepime Kabi should be reconstituted immediately before use and used as soon as practicable after reconstitution, any residue being discarded. If there is any delay in use of the reconstituted Cefepime Kabi it should be stored at 2˚C to 8˚C for a maximum of 24 hours.

Solutions of cefepime, like those of most beta-lactam antibiotics, should not be added to solutions of gentamicin, metronidazole, vancomycin, tobramycin sulphate or netilmicin sulphate because of physical or chemical incompatibility. However, if concurrent therapy with cefepime and gentamicin is indicated, each of these antibiotics can be administered separately to the same patient.

Note: Parenteral drugs should be inspected visually for particulate matter before administration and not used if particulate matter is present.

As with other cephalosporins, the colour of reconstituted Cefepime Kabi may darken on storage, however, product potency is not adversely affected.

Reconstituted solutions should be protected from light.

Table 3
Preparations of solutions of Cefepime Kabi

	Amount of diluent to be added (mL)	*Approximate available volume (mL)*	**Approximate cefepime concentration (mg/mL)*
Intravenous			
1g vial	10	11.3	88
2g vial	10	12.6	158
Intramuscular			
1g vial	3.0	4.4	230

*NOTE: Reconstitution of Cefepime Kabi Powder for Injection in a volume of diluent other than those included in this table will not produce a linear change in concentration.

4.3 CONTRAINDICATIONS

Cefepime is contraindicated in patients who have shown immediate hypersensitivity reactions to any component of the formulation (including Arginine), the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, cefepime should be discontinued immediately and an alternative treatment should be considered.

Hypersensitivity Reactions

Before therapy with cefepime is instituted, careful inquiry should be made to determine whether the patient has had previous immediate hypersensitivity reactions to cefepime, cephalosporins, penicillins, or other beta-lactam antibiotics. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to cefepime occurs, discontinue the drug and treat the patient appropriately. Serious immediate hypersensitivity reactions may require adrenaline and other supportive therapy.

Use in Renal Impairment

In patients with impaired renal function, such as reduction of urinary output because of renal insufficiency (creatinine clearance ≤ 50 mL/min) or other conditions that may compromise renal function, the dosage of cefepime should be adjusted to compensate for the slower rate of renal elimination. Because high and prolonged serum antibiotic concentrations can occur from usual doses 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.1 PHARMACODYNAMIC PROPERTIES).

Neurotoxicity

During post-marketing surveillance, the following serious adverse events have been reported including life threatening or fatal occurrences of the following: reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor and coma), myoclonus, seizures (including non-convulsive status epilepticus), and/or renal failure (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). 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 haemodialysis however, some cases included a fatal outcome.

If neurotoxicity associated with cefepime therapy occurs, consider discontinuing cefepime or making appropriate dosage adjustments in patients with renal impairment.

Renal function should be monitored carefully if drugs with nephrotoxic potential, such as aminoglycosides and potent diuretics, are administered with Cefepime Kabi.

Clostridium Difficile-associated Diarrhoea

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics including cefepime; therefore, it is important to consider this diagnosis in patients who develop diarrhoea in association with the use of antibiotics. Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of antibiotic-associated colitis. Mild cases of pseudomembranous colitis may respond to drug discontinuation alone. In moderate to severe cases, management should include fluid, electrolyte and protein supplementation. When colitis does not improve after drug discontinuation or when it is severe, it should be treated with an antibiotic clinically effective against Clostridium difficile. Other causes of colitis should also be considered.

History of Gastrointestinal Disease

Cefepime should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

High Risk Patients

In patients (adult and paediatric) at high risk for severe infection (including patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying haematologic malignancy, or with severe or prolonged neutropenia), antimicrobial monotherapy may not be appropriate. Insufficient data exist to support the efficacy of cefepime monotherapy in such patients.

Prolonged Use

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

If neutropenia occurs as a result of prolonged therapy, cefepime should be discontinued and alternative antibiotic therapy used.

Patients with Meningeal Seeding/Meningitis

In those patients in whom meningeal seeding from a distant infection site or in whom meningitis is suspected or documented, an alternate agent with demonstrated clinical efficacy in this setting should be used.

Use in the elderly

Of the more than 6400 adults treated with cefepime in clinical studies, 35% were 65 years or older while 16% were 75 years or older. In clinical studies, when geriatric patients 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 DOSE AND METHOD OF ADMINISTRATION).

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS and Section 5.2 PHARMACOKINETIC PROPERTIES) Serious adverse events, including encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor and coma), myoclonus, seizures (including non-convulsive status epileticus), and/or renal failure have occurred in geriatric patients with renal insufficiency given the usual dose of cefepime (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).).

Paediatric Use

Experience with the use of cefepime in paediatric patients aged less than 2 months is limited. Safety and effectiveness in paediatric patients below the age of 2 months have not been established. Therefore, the administration of cefepime to patients less than 2 months of age is not recommended.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with Cefepime for Injection because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibiotics.

Nephrotoxicity has been reported following concomitant administration of cephalosporins with potent diuretics such as frusemide.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Standard tests to assess fertility in rats show no impairment of fertility at exposure levels nearly two-fold higher than the calculated maximal daily human exposure.

Use in Pregnancy - Category B1.

Category B1: Drugs which have been taken by only a limited number of pregnant women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

Reproduction studies performed in mice and rats showed no evidence of impaired fertility or harm to the foetus at dose levels equivalent to (mouse) or slightly greater (rat) than the maximum human daily dose when the daily doses are compared to those in man on a mg/m^2 basis. There are, however, 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.

Use in Lactation

Cefepime is excreted in human breast milk in very low concentrations. Although less than 0.01% of a 1 g IV dose is excreted in milk, caution should be used when cefepime is administered to a nursing woman.

Labour and Delivery

Cefepime has not been studied for use during labour and delivery. Treatment should only be given if clearly indicated.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of Cefepime Kabi include altered state of consciousness, dizziness, confusion and hallucinations which could affect the ability to drive or use machines (see Sections 4.4 Special warnings and precautions and 4.8 Adverse effects (Undesirable effects)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Cefepime is generally well tolerated. In clinical trials (n= 5598) the most common adverse events were gastrointestinal symptoms and hypersensitivity reactions. Adverse events considered to be of definite, probable or possible relationship to cefepime are listed below.

Events that occurred at an incidence of > 0.1% - 1% (except where noted) were:

- Hypersensitivity: rash (1.8%), pruritus, urticaria
- Gastrointestinal: nausea, vomiting, oral moniliasis, diarrhea (1.2%), colitis (including pseudomembranous colitis)
- Central nervous system: headache
- Other: fever, vaginitis, erythema

Events that occurred at an incidence of 0.05% - 0.1% were abdominal pain, constipation, vasodilation, dyspnoea, dizziness, paresthesia, genital pruritus, taste perversion, chills and unspecified moniliasis.

Events that occurred at an incidence of < 0.05% included anaphylaxis and seizures.

Local reactions at the site of IV infusions occurred in 5.2% of patients; these included phlebitis (2.9%) and inflammation (0.1%). Intramuscular administration of cefepime was very well tolerated with 2.6% of patients experiencing pain or inflammation at the injection site.

Laboratory test abnormalities that developed during clinical trials in patients with normal baseline values were transient. Those that occurred at a frequency between 1% and 2% (unless noted) were: elevations in alanine aminotransferase (3.6%), aspartate aminotransferase (2.5%), alkaline phosphatase, total bilirubin, anaemia, eosinophilia, prolonged prothrombin time, partial prothrombin time (2.8%), and positive Coombs' test without haemolysis (18.7%). Transient elevations of serum urea, and/or serum creatinine and transient thrombocytopenia were observed in 0.5% to 1% of patients. Transient leukopenia and neutropenia were also seen (< 0.5%).

Post marketing Experience

Skin and Other Subcutaneous Tissue Disorders

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in beta-lactam antibiotics.

During post-marketing experience, encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor and coma), seizures, myoclonus and/or renal failure have been reported. Most cases occurred in patients with renal impairment who received doses of cefepime that exceeded recommendations (see also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Anaphylaxis including anaphylactic shock, transient leukopoenia, neutropenia, agranulocytosis and thrombocytopenia have been reported rarely.

Because of the uncontrolled nature of these spontaneous reports, a causal relationship to cefepime has not been determined.

The following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics: Urticaria, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, aplastic anaemia, haemolytic anaemia, haemorrhage, hepatic dysfunction including cholestasis, and false positive tests for urinary glucose.

Paediatrics

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 registration 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 at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In case of severe over dosage, especially in patients with compromised renal function, dialysis 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 DOSE AND METHOD OF ADMINISTRATION, Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Symptoms of over dosage include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures and neuromuscular excitability.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia) or 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Cefepime hydrochloride is a semi-synthetic broad spectrum cephalosporin antibiotic for parenteral administration.

Microbiology

Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Cefepime has a broad spectrum of in vitro activity that encompasses a wide range of gram-positive and gram-negative bacteria. Cefepime has a low affinity for chromosomally-encoded beta-lactamases. Cefepime is highly resistant to hydrolysis by most beta-lactamases and exhibits rapid penetration into gram-negative bacterial cells.

Within bacterial cells, the molecular targets of cefepime are the penicillin binding proteins (PBP).

Cefepime has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in Section 4.1 THERAPEUTIC INDICATIONS.

Aerobic Gram-Negative Microorganisms:
Enterobacter
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus (methicillin-susceptible strains only)
Streptococcus pneumoniae
Streptococcus pyogenes (Lancefield's Group A streptococci)

The prevalence of acquired resistance may vary geographically and with time for selected species. Information about the local resistance pattern should be obtained from a local bacteriological laboratory and taken into account in the choice of empiric therapy.

Susceptibility

Susceptibility	% Acquired Resistance*
*Enterobacter aerogenes**	0 %
*Enterobacter cloacae**	0 %
*Escherichia coli **	0 %
Haemophilus influenza	0 %
*Klebsiella pneumoniae**	0 %
*Proteus mirabilis**	0 %
*Pseudomonas aeruginosa**	3 %
Staphylococcus aureus (methicillin susceptible)	0.2 %
*Streptococcus pneumoniae**	3 %
*Streptococcus pyogenes**	0 %

Intermediate
No organisms listed

Insusceptible
Staphylococcus aureus (methicillin resistant)

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications.

Note: 1 to 20% of Enterobacteriaceae have an acquired resistance mechanism (depressed synthesis of ampC beta lactamase or production of an ESBL (extended spectrum beta lactamase)) which decreases susceptibility to cefepime resulting in MICs in the 1 to 16 microgram/mL range.

The following in vitro data are available, but the clinical significance is unknown. Cefepime has been shown to have in vitro activity against most strains of the following microorganisms; however, the safety and effectiveness of cefepime in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-Positive Microorganisms:
Staphylococcus epidermidis (methicillin-susceptible strains only)
Staphylococcus saprophyticus
Streptococcus agalactiae (Lancefield's Group B streptococci)
Viridans group streptococci

NOTE: Most strains of enterococci, e.g. *Enterococcus faecalis*, and methicillin-resistant *staphylococci* are resistant to cefepime.

Aerobic Gram-Negative Microorganisms:
Acinetobacter calcoaceticus subsp. *lwoffi*
Citrobacter diversus
Citrobacter freundii
Enterobacter agglomerans
Haemophilius influenzae (including beta-lactamase producing strains)
Hafnia alvei
Klebsiella oxytoca
Moraxella catarrhalis (including beta-lactamase producing strains)
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

NOTE: Cefepime is inactive against many strains of *Stenotrophomonas* (formally *Xanthomonas maltophilia* and *Pseudomonas maltophilia*).

Anaerobic Microorganisms:

NOTE: Cefepime is inactive against most strains of *Clostridium difficile*.

SUSCEPTIBILITY TESTS:

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of 'Susceptible' indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of 'Intermediate' indicates the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of 'Resistant' indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Clinical trials

SURGICAL PROPHYLAXIS

Cefepime has been studied in a clinical trial of surgical prophylaxis. A multi-centre, randomised, open-label study enrolled a total of 615 adult subjects who were to be treated by elective colorectal surgery. A single dose of 2 g of either cefepime or ceftriaxone was administered intravenously to subjects followed by a single dose of metronidazole 500 mg IV, starting approximately 1 hour prior to surgery. The primary study endpoint was the absence of infection at the operative site and of intra-abdominal infection.

Clinical outcomes are shown in Table 4 below.

Table 4: Clinical Response AI411-230

	Number (%) of subjects		
	Cefepime (N= 307)	Ceftriaxone (N= 308)	Total (N= 615)
1) Success	231 (75)	232 (75)	463 (75)
2) Failure	50 (16)	46 (15)	96 (16)
- primary site infection	22	22	44
- unexplained use of antibiotics	23	20	43
- septicaemia and bacteraemia	5	4	9
3) Unable to determine	26 (8)	30 (10)	56 (9)
- distant site infection	20	23	43
- other	6	7	13

5.2 PHARMACOKINETIC PROPERTIES

Adults

Average plasma concentrations of cefepime observed in normal adult males at various times following single 30-minute infusions of 500 mg, 1 g and 2 g are summarised in Table 5. Following intramuscular (IM) administration, cefepime is completely absorbed. The average plasma concentrations of cefepime at various times following a single IM injection are summarised in Table 5.

Table 5.
Mean plasma concentrations of cefepime (microgram/mL)

Cefepime dose	*0.5 hr*	*1 hr*	*2 hr*	*4 hr*	*8 hr*	*12 hr*
500 mg IV	33.6	18.9	11.3	4.6	1.0	0.6
1 g IV	66.9	41.8	25.3	11.0	2.8	0.8
2 g IV	127.6	81.7	45.4	20.1	4.6	1.2
500 mg IM	8.2	12.5	12.0	6.9	1.9	0.7
1 g IM	14.8	25.9	26.3	16.0	4.5	1.4
2 g IM	36.1	49.9	51.3	31.5	8.7	2.3

Concentrations of cefepime achieved in specific tissues and body fluids are listed in Table 6.

Table 6
Mean concentrations of cefepime in various
body fluids (microgram/mL) and tissues (microgram/g)

Tissue or fluid	*Dose (IV)*	*Average time of sample post-dose (hr)*	*Mean concentration*
Urine	500 mg	0-4	292
	1 g	0-4	926
	2 g	0-4	3120
Bile	2 g	9.4	7.7
Peritoneal fluid	2 g	4.4	16.4
Blister fluid	2 g	1.5	24.5
Bronchial mucosa	2 g	4.8	24.1
Sputum	2 g	4.0	7.4
Prostate	2 g	1.0	31.5
Appendix	2 g	5.7	5.2
Gallbladder	2 g	8.9	11.9

The average elimination half-life of cefepime is approximately 2 hours, and the disposition of cefepime does not vary with respect to dose over the range of 250 mg to 2 g. There is no evidence of accumulation in healthy subjects 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.

Cefepime is metabolised to N-methylpyrrolidine which is rapidly converted to the N-oxide. Urinary recovery of unchanged cefepime represents approximately 85% of dose, resulting in high concentrations of cefepime in the urine. The serum protein binding of cefepime averages 16.4% and is independent of its concentration in the serum.

Healthy volunteers 65 years old or older, who received a single 1 g IV dose of cefepime had higher AUC and lower renal clearance values compared to younger healthy adults; Dosage adjustments in the elderly are recommended if renal function is compromised (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

The pharmacokinetics of cefepime do not change to a clinically significant degree in cystic fibrosis patients. The pharmacokinetics of cefepime are unaltered in patients with impaired hepatic function who received a single 1 g dose. It is not necessary to alter the dosage of cefepime in these patient populations.

Studies in patients with various degrees of renal insufficiency have demonstrated a prolongation in elimination half-life. There is a linear relationship between total body clearance and creatinine clearance in patients with abnormal renal function, which serves as the basis for dosage adjustment recommendations in this group of patients (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). The average half-life in severely impaired patients requiring dialysis therapy is 13 hours for haemodialysis or 19 hours for continuous ambulatory peritoneal dialysis.

Pharmacokinetics (paediatrics)

Single- and multiple-dose pharmacokinetics of cefepime were evaluated in patients ranging in age from 2 months to 16 years who received 50 mg/kg doses administered by IV infusion; multiple doses were administered every 8 or 12 hours for 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.

Other pharmacokinetic parameters in infants and children were not different between first-dose and steady-state determinations, regardless of dosing schedule (q12h or q8h). There were also no differences in pharmacokinetics among the various patient ages or between male and female patients.

Following a single IV dose, total body clearance averaged 3.3 mL/min/kg and average volume of distribution was 0.3 L/kg. The overall mean elimination half-life was 1.7 hours. 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.

No accumulation was seen when cefepime was given at 50 mg/kg q12h (n= 13), while C_{max}, AUC, and t_2, were increased approximately 15% at steady state after 50 mg/kg q8h. Clinically relevant changes in the pharmacokinetics of cefepime have not been observed in cystic fibrosis patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Although no long-term studies in animals have been performed to evaluate carcinogenic potential, a battery of in vitro and in vivo tests for genotoxicity have been conducted. The overall conclusion of this testing is that cefepime is not genotoxic.

Carcinogenicity

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Cefepime Kabi Powder for Injection also contains the inactive ingredient Arginine.

6.2 INCOMPATIBILITIES

Solutions of cefepime, like those of most beta-lactam antibiotics, should not be added to solutions of gentamicin, metronidazole, vancomycin, tobramycin sulphate or netilmicin sulphate because of physical or chemical incompatibility. However, if concurrent therapy with cefepime and gentamicin is indicated, each of these antibiotics can be administered separately to the same patient. (See section 4.2 Dose and method of administration – compatibility and stability.)

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Cefepime Kabi should be stored in the dry state in the original container at or below 25˚C. Protect from light.

To avoid the risk of microbial contamination, reconstituted Cefepime Kabi should be administered as soon as possible after reconstitution.

6.5 NATURE AND CONTENTS OF CONTAINER

Cefepime Kabi 1 g (Cefepime Powder for Injection 1 g) is presented in single dose 20 mL vial and is intended for IV or IM administration.

Cefepime Kabi 2 g (Cefepime Powder for Injection 2 g) is presented in single dose 20 mL vial and is intended for IV or IM administration.

Vials are clear glass with halobutyl rubber stoppers (latex free), flip-off aluminium cap with a plastic cap.

Cefepime Kabi Powder for Injection vials are for single use in one patient only.

Cefepime Kabi is available in:

- 1 g (20mL vial) in packs of 1, 10 and 50
- 2 g (20mL vial) in packs of 1, 10 and 50

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

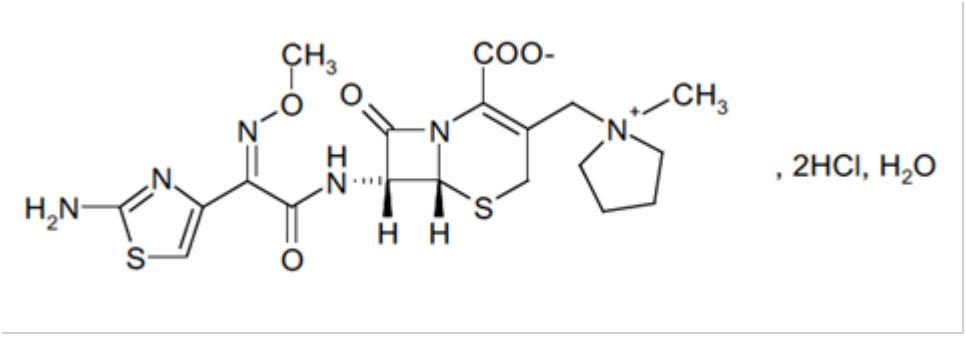
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Cefepime hydrochloride monohydrate is a semi-synthetic broad spectrum cephalosporin antibiotic for parenteral administration.

Cefepime hydrochloride monohydrate has a partition coefficient (n-octanol/water) of 2.49 – 2.52 at pH 5, and 2.62 – 2.65 at pH 9.

Chemical structure



Molecular Formula

$C_{19}H_{25}N_6O_5S_2Cl.HCl.H_2O$

Molecular Name

The chemical name is Pyrrolidinium, 1-[[7-[[(2-amino-4-thiazolyl) (methoxyimino) acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-,chloride, monohydrochloride, monohydrate, [6R-[6α,7β(Z)]].

CAS number

123171-59-5

Molecular Weight

571.5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Australia: Schedule 4 (Prescription Medicine)
New Zealand: General sales Medicine

8 SPONSOR

Fresenius Kabi Australia Pty Limited
Level 2, 2 Woodland Way
Mount Kuring-gai, NSW 2080
Australia
Telephone: (02) 9391 5555

Fresenius Kabi New Zealand Limited
60 Pavilion Drive
Airport Oaks, Auckland 2022
New Zealand
Freecall: 0800 144 892

9 DATE OF FIRST APPROVAL

07 Sep 2015

10 DATE OF REVISION

29 November 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All new format	New format
Section 4.4	Information added to Special Warnings and Precautions for Use
Section 4.8	Information added to Adverse Effects
Sections 5.1 & 5.3	Information added to Pharmacological Properties