

## AUSTRALIAN PRODUCT INFORMATION

# CEFEPIME ALPHAPHARM

*Cefepime (as hydrochloride) Powder for injection*



## 1 ++NAME OF THE MEDICINE

Cefepime (as hydrochloride).

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cefepime hydrochloride is a white to pale yellow powder, which is highly soluble in water.

Cefepime Alphapharm is supplied in vials containing 1 g and 2 g of cefepime (as hydrochloride). Each vial contains cefepime (as hydrochloride) and arginine as the excipient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

## 3 PHARMACEUTICAL FORM

Powder for injection.

Cefepime Alphapharm Powder for Injection is a sterile powder for injection. The 1 mg strength is available in 20 mL vials, and the 2 mg strength is available in 50 mg vials, containing cefepime (as hydrochloride).

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

#### Adult

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

#### Paediatrics

Cefepime Alphapharm 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 Alphapharm 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 Alphapharm 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 Alphapharm. In patients who are at risk of mixed aerobic-anaerobic infection, including infections in which *Bacterioides 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 Alphapharm 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 Alphapharm are provided in Table 1. The usual duration of therapy is 7-10 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 – 1g IV or IM	q12h
Mild to moderate infections other than UTI:	1 g 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 Alphapharm (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 Alphapharm infusion. The metronidazole dose should be prepared and administered in accordance with official product labelling. Due to incompatibility, Cefepime Alphapharm 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 Alphapharm followed by metronidazole should be administered 12 hours following the initial prophylactic dose.

### Paediatrics (aged 2 months up 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 7-10 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.

### Impaired Hepatic Function

No adjustment is necessary for patients with impaired hepatic function.

### 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 q12 h	500 mg q12h
30 – 50	2 g q12h	2 g q24h	1g 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
Heamodialysis*	500 mg q24h	500 mg q24h	500 mg q24h	500 mg q24h

\* Pharmacokinetic modelling 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 500mg 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, i.e.: 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 5.1 PHARMACODYNAMIC PROPERTIES, Pharmacokinetics (in 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 Alphapharm 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 Alphapharm 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 Alphapharm with 5 or 10 mL of Sterile 5% Glucose 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**).

Alternatively, constitute the 1 g or 2 g piggyback (100 mL) bottle with 50 or 100 mL of a compatible IV fluid listed in the Compatibility and Stability section. The resulting solution should be administered over a period of approximately 30 minutes.

### Intramuscular Administration

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

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

## COMPATIBILITY AND STABILITY

### Intravenous

Cefepime Alphapharm (Cefepime Hydrochloride for Injection) is compatible at concentrations between 1 and 40mg/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 40m Eq/L) and theophylline (0.8mg/mL in 5% Glucose Injection). Cefepime at a concentration of 40mg/mL in 0.9% Sodium Chloride or 5% Glucose Injection was found to be compatible with Amikin® (amikacin 6mg/mL).

### Intramuscular

Cefepime Alphapharm (Cefepime Hydrochloride 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% lidocaine (lignocaine) hydrochloride.

### For Both Routes of Administration

Cefepime Alphapharm 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 Alphapharm it should be stored at 2°C-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 Alphapharm 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**

	Amount of diluent to be added (mL)	Approximate available volume (mL)	* Approximate cefepime concentration (mg/mL)
<u>Intravenous</u>			
500 mg vial	5	5.6	88
1 g vial	10	11.3	88
2 g vial (or 77 mL bottle)	10	12.6	158
<u>Infusion (100mL)</u>			
1 g bottle	50 or 100	50 or 100	20 or 10
2 g bottle	50 or 100	50 or 100	38 or 20
<u>Intramuscular</u>			
500 mg vial	1.5	2.2	230
1 g vial	3.0	4.4	230

\*NOTE: Reconstitution of Cefepime Alphapharm 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 L-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.

#### Use in Renal Impairment

In patients with impaired renal function, such as reduction of urinary output because of renal insufficiency (creatinine clearance  $\leq$  50 mL/min) or other conditions that may compromise renal function, the dosage of

cefepime should be adjusted to compensate for the slower rate of renal elimination. Because high and prolonged serum antibiotic concentrations can occur from usual 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 postmarketing surveillance, the following serious adverse events have been reported: reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor and coma), myclonus, seizures (including nonconclusive 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 Alphapharm that exceeded recommendations. In general, symptoms of neurotoxicity resolved after discontinuation of cefepime and/or after haemodialysis 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 Alphapharm.

### **Hypersensitivity to Cefepime or cephalosporins, penicillins or other beta-lactam antibiotics**

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 Alphapharm occurs, discontinue the drug and treat the patient appropriately. Serious immediate hypersensitivity reactions may require adrenalin and other supportive therapy.

### **Clostridium difficile associated colitis**

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 broadspectrum 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.

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.

### **History of Gastrointestinal Disease**

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

### **Prolonged Use**

As with other antibiotics, prolonged use of cefepime may result in overgrowth of nonsusceptible 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.

### 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 5.1 PHARMACODYNAMIC PROPERTIES**). Serious adverse events, including 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 4.4 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 INTERACTIONS

Renal function should be monitored carefully if drugs with nephrotoxic potential, such as aminoglycosides and potent diuretics, are administered with cefepime. Nephrotoxicity has been reported following concomitant administration of other cephalosporins with aminoglycoside antibiotics or potent diuretics such as furosemide (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

Pregnancy Category: B1

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<sup>2</sup> 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.

### **Labour and Delivery**

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

### **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.

## **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

The effect of Cefepime on driving and operating machinery has not been studied.

## **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%), pruritis, 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, dyspnea, dizziness, paresthesia, genital pruritis, 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%).

### **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.

### **Postmarketing Experience**

During postmarketing 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 leucopenia, 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, hemolytic anaemia, haemorrhage, hepatic dysfunction including cholestasis, and false positive tests for urinary glucose.

### **Paediatrics**

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

### **Reporting Suspected Adverse Effects**

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 [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## **4.9 OVERDOSE**

In case of severe overdosage, 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 **Section 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 overdosage 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 13 11 26 (Australia).

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 PHARMACODYNAMIC PROPERTIES**

#### **Mechanism of Action**

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

#### **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 colo-rectal 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 intrabdominal 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)
<b>1) Success</b>	<b>231 (75)</b>	<b>232 (75)</b>	<b>463 (75)</b>
<b>2) Failure</b>	<b>50 (16)</b>	<b>46 (15)</b>	<b>96 (16)</b>
- primary site infection	22	22	44
- unexplained use of antibiotics	23	20	43
- septicaemia and bacteraemia	5	4	9
<b>3) Unable to determine</b>	<b>26 (8)</b>	<b>30 (10)</b>	<b>56 (9)</b>
- distant site infection	20	23	43
- other	6	7	13

## 5.2 PHARMACOKINETIC PROPERTIES

### Pharmacokinetics (in adults)

Average plasma concentrations of cefepime observed in normal adult males at various times following single 30-minute infusions of 1 g and 2 g are summarised in Table 5. Following intramuscular 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
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
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 tissue (microgram/g)**

Tissue or fluid	Dose (IV)	Average time of sample post-dose (hr)	Mean concentration
Urine	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 aged 65 years old or older, who received a single 1g 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 (in 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 50mg/kg q12 h (n=13), while C<sub>max</sub>, AUC, and t<sub>2</sub>, were increased approximately 15% at steady state after 50mg/kg q 8h. Clinically relevant changes in the pharmacokinetics of cefepime have not been observed in cystic fibrosis patients.

### **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 betalactamases 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)

**Susceptibility:**

<b>Susceptible</b>	<b>% Acquired Resistance*</b>
<i>Enterobacter aerogenes</i> *	0%
<i>Enterobacter cloacae</i> *	0%
<i>Escherichia coli</i> *	0%
<i>Haemophilus influenzae</i>	0%
<i>Klebsiella pneumoniae</i> *	0%
<i>Proteus mirabilis</i> *	0%
<i>Pseudomonas aeruginosa</i> *	3%
<i>Staphylococcus aureus</i> (methicillin susceptible)	0.2%
<i>Streptococcus pneumoniae</i> *	3%
<i>Streptococcus pyogenes</i> *	0%
<b>Intermediate</b>	
<b>Insusceptible</b>	
<i>Staphylococcus aureus</i> (methicillin resistant)	

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

Note: 1-20% of Enterobacteriaceae have an acquired resistance mechanism (depressed synthesis of ampC beta lactamase or production of an ESBL) which decreases susceptibility to cefepime resulting in MICs in the 1-16 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. lwoffii*  
*Citrobacter diversus*  
*Citrobacter freundii*  
*Enterobacter agglomerans*  
*Haemophilus 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*.

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 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.

## **5.3 PRECLINICAL SAFETY DATA**

### **Genotoxicity**

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**

Although no long-term studies in animals have been performed to evaluate carcinogenic potential.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

Arginine.

### **6.2 INCOMPATIBILITIES**

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### 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 Alphapharm in the dry state in original cartons should be stored at less than 25°C. Protect from light.

To avoid the risk of microbial contamination, reconstituted Cefepime Alphapharm should be administered as soon as possible after reconstitution. If storage is necessary, hold at 2-8°C for a maximum of 24 hours.

### 6.5 NATURE AND CONTENTS OF CONTAINER

Cefepime Alphapharm is a sterile dry mixture of cefepime hydrochloride and L-Arginine.

Container Type: Glass Type 1 clear vial

Pack sizes:

Cefepime Alphapharm 1 g (20 mL vial) in packs of 1

Cefepime Alphapharm 2 g (50 mL vial) in packs of 1

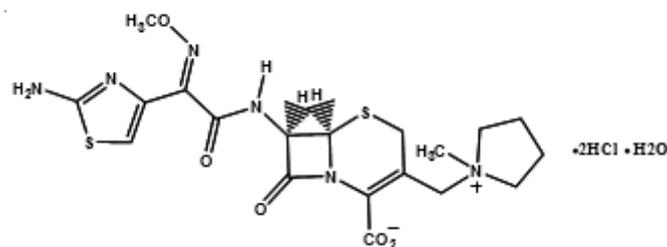
Some strengths, pack sizes and/or pack types may not be marketed.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

### 6.7 PHYSICOCHEMICAL PROPERTIES

#### Chemical Structure



#### Molecular Formula

$C_{19}H_{25}N_6O_5S_2 \cdot Cl \cdot HCl \cdot H_2O$

#### Molecular Name

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-[6 $\alpha$ ,7 $\beta$ (Z)]]

#### CAS Number

123171-59-5.

**Molecular Weight**

571.5

**7 MEDICINE SCHEDULE (POISONS STANDARD)**

S4 (Prescription Only Medicine)

**8 SPONSOR****Alphapharm Pty Limited**

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Millers Point NSW 2000

[www.mylan.com.au](http://www.mylan.com.au)**9 DATE OF FIRST APPROVAL**

08/01/2014

**10 DATE OF REVISION**

23/1/2020

**Summary Table of Changes**

<b>Section Changed</b>	<b>Summary of New Information</b>
<b>4.4 &amp; 4.8</b>	Updated sections to include reference to severe cutaneous adverse reactions (SCAR) as per the Signal Investigation Unit, Pharmacovigilance and Special Access Branch, TGA request.

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