NEW ZEALAND DATA SHEET

1. CEFEPIME-AFT Powder for Injection

Cefepime-AFT 500 mg powder for injection.
Cefepime-AFT 1 g powder for injection.
Cefepime-AFT 2 g powder for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cefepime-AFT 500 mg: each vial contains 500 mg cefepime (as dihydrochloride monohydrate).
Cefepime-AFT 1 g: each vial contains 1 g cefepime (as dihydrochloride monohydrate).
Cefepime-AFT 2g: each vial contains 2 g cefepime (as dihydrochloride monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for injection.
White to pale yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
Cefepime-AFT 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.
- Septicaemia
- Empiric treatment in febrile neutropenic patients (see section 4.4).

Culture and susceptibility studies should be performed when appropriate to determine susceptibility of the causative organism(s) to cefepime. Empiric therapy with Cefepime-AFT 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-AFT 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-AFT. 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

Dose

Cefepime-AFT does not contain any anti-microbial preservative. It should be used in one patient on one occasion only.

Adults

The usual adult dosage and route of administration of cefepime 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-AFT 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 – 1 g I.V. or I.M.	q12h
Mild to moderate infections other than UTI:	1 g I.V. or I.M.	q12h
Severe infections:	2 g I.V.	q12h
Very severe or life-threatening infections:	2 g I.V.	q8h

Special populations

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 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, i.e. 500 mg, 1 g or 2 g, depending on infection severity, at a dosage interval of every 48 hours.

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, 'Impaired renal function').

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 4.4, 4.8 and 5.2). Serious adverse events, including encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor and coma), myclonus, seizures (including nonconclusive status epileticus), and/or renal failure have occurred in geriatric patients with renal insufficiency given the usual dose of cefepime (see sections 4.4 and 4.8).

Paediatric population

Although studies in paediatric patients are ongoing, the safety and effectiveness of cefepime in children have not been established.

Method of administration

Cefepime-AFT may be given intravenously or by deep intramuscular injection into a large muscle mass (such as the upper 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 the overall condition of the patient.

Intravenous administration

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

For direct I.V. administration, reconstitute Cefepime-AFT with 5 or 10 mL of sterile 5% Glucose Injection or 0.9% Sodium Chloride as directed in Table 5 (see section 6.6). 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 I.V. fluid (see section 6.6).

For intravenous infusion, reconstitute the 500 mg, 1 g or 2 g vial as noted above for direct I.V. administration, and add an appropriate quantity of the resulting solution to an I.V. container with one of the compatible I.V. fluids (see section 6.6). The resulting solution should be administered over a period of approximately 30 minutes.

Intramuscular administration

Cefepime-AFT should be reconstituted with one of the following diluents: Sterile Water for Injections, 0.9% Sodium chloride or 5% Glucose Injection (refer Table 5 of section 6.6). Although Cefepime-AFT can be reconstituted with 0.5% or 1.0% lignocaine, it is usually not required because cefepime causes little or no pain upon I.M. administration.

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

Cefepime-AFT powder for injection is for single use in one patient only.

For instructions on reconstitution of the medicine before administration, see section 6.6.

4.3 Contraindications

Cefepime is contraindicated in patients who have had previous experience of a major allergy or anaphylaxis to a cephalosporin or penicillin.

Cefepime is also contraindicated in patients who have experienced hypersensitivity to any component of the formulation, including L-arginine (see section 6.1).

4.4 Special warnings and precautions for use

Cefepime-AFT should be given with caution to patients who have experienced symptoms of allergy associated with a cephalosporin or penicillin.

Pseudomembranous colitis and delaying peristalsis

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It is important to consider this diagnosis in patients who develop diarrhoea in association with the use of cefepime. Drugs which delay peristalsis may prolong and/or worsen the condition and should not be used.

Prothrombin time

Prolonged prothrombin time may occur in patients receiving protracted antimicrobial therapy.

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 sections 4.2, 5.1 and 5.2).

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 nonconclusive 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.

There have been reports of neurotoxicity associated with cephalosporin treatment. Symptoms of neurotoxicity include encephalopathy, seizures and/or myoclonus. Risk factors for developing neurotoxicity with cephalosporin treatment include being elderly, renal impairment, central nervous system disorders and intravenous administration. Withdrawal of the medicine should be considered if there are signs of neurotoxicity. 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.

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 adrenalin and other supportive therapy.

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.

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.

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

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

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

4.5 Interaction with other medicines and other forms of interaction

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 frusemide.

4.6 Fertility, pregnancy and lactation

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^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.

Labour and delivery

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

clearly indicated.

Breastfeeding

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

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.

4.7 Effects on ability to drive and use machines

During treatment with cefepime undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines. Patients should be cautious when driving or operating machinery.

4.8 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, diarrhoea (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, paraesthesia, genital pruritis, taste perversion, chills and unspecified moniliasis.

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

Phlebitis at the site of injection and cutaneous vasculitis may occur. Local reactions at the site of I.V. 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 leucopenia and neutropenia were also seen (< 0.5%).

Post-marketing experience

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).

Anaphylaxis including anaphylactic shock, transient leucopoenia, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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 sections 4.2, 4.4 and 4.8). Symptoms of overdosage include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures and neuromuscular excitability.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Fourth-generation cephalosporins, ATC code: J01D01.

Cefepime hydrochloride monohydrate is a semi-synthetic, broad spectrum cephalosporin antibiotic for

parenteral administration. The chemical name is (6R,7R)-7-[[(2Z)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino]-3[(1-methylpyrrolidinio)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate dihydrochloride, monohydrate. The CAS number is 123171-59-5. The empirical formula is $C_{19}H_{24}N_6O_5S_2.2HCl.H_2O$. The molecular weight is 571.5.

Mechanism of action

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 both gram-positive and gram-negative bacteria. Cefepime has a low affinity for chromosomally-encoded β-lactamases. Cefepime is highly resistant to hydrolysis by most β-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 micro-organisms, both *in vitro* and in clinical infections as described in section 4.1.

Aerobic Gram-Negative Micro-organisms
Enterobacter
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

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

Susceptibility

Susceptible Organism	**% Acquired Resistance***
*Enterobacter aerogenes**	0%
*Enterobacter cloacae**	0%
*Escherichia coli **	0%
Haemophilus influenzae	0%
*Klebsiella pneumoniae**	0%
*Proteus mirabilis**	0%
*Pseudomonas aeruginosa**	3%
Staphylococcus aureus (methicillin susceptible)	0.2%
*Streptococcus pneumoniae**	3%
*Streptococcus pyogenes**	0%
Intermediate	
Not Susceptible	
Staphylococcus aureus (methicillin resistant)	

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

Note: 1-20% of Enterobacteriacae 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 μg/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 micro-organisms however the safety and effectiveness of cefepime in treating clinical infections due to these micro-organisms have not been established in adequate and well-controlled trials.

Aerobic Gram-Positive Micro-organisms:
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. Entercoccus faecalis, and methicillin-resistant staphylococci are resistant to cefepime.

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

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

Anaerobic Micro-organisms
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 micro-organisms 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 micro-organism 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.

5.2 Pharmacokinetic properties

Adults

Absorption

Average plasma concentrations of cefepime observed in normal adult males following single 30-minute infusions of 500 mg, 1 g and 2 g are summarised in Table 3. Following intramuscular administration, cefepime is completely absorbed. The average plasma concentrations of cefepime at various times following a single I.M. injection are summarised in Table 3.

Table 3: mean plasma concentrations of Cefepime (µg/mL)

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

Concentrations of cefepime achieved in specific tissues are listed in the Table 4.

Table 4: mean concentrations of Cefepime in various body fluids (µg/mL) and tissues (µg/mL)

Tissue or fluid	*Dose (I.V.)*	*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

Elimination

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 250 mg to 2 g. There is no evidence of accumulation in healthy subjects receiving doses of 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.

Metabolism

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 1 g I.V. dose of cefepime had higher AUC and lower renal clearance values compared to younger healthy adults. Dosage adjustments in the elderly recommended if renal function is compromised (see sections 4.2 and 4.4).

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 varying degrees of renal insufficiency have indicated 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). The average half-life in severely impaired patients undergoing dialysis therapy is 13 hours for haemodialysis or 19 hours for continuous

ambulatory peritoneal dialysis.

5.3 Preclinical safety data

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-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 sulfate or netilmicin sulfate 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.

6.3 Shelf life

Powder: 24 months.
Reconstituted solution: To avoid the risk of microbial contamination, reconstituted Cefepime-AFT should be administered as soon as possible after reconstitution. If there is any delay in the use of reconstituted Cefepime-AFT it should be stored at 2 – 8 ºC for a maximum of 24 hours.

6.4 Special precautions for storage

Store at or below 25°C. Protect from light.

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

6.5 Nature and contents of container

Glass vials with rubber stoppers, in packs of 1, 5 and 10 vials.

6.6 Special precautions for disposal and other handling

Cefepime-AFT should be reconstituted immediately before use and used as soon as practicable after reconstitution, any residue being discarded.

Intravenous

Cefepime-AFT is compatible at concentration between 1 and 40 mg/mL with the following I.V. 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 (0.8 mg/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-AFT 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.

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-AFT may darken on storage. However product potency is not adversely affected.
Reconstituted solutions should be protected from light.

Table 5: Preparations of Solutions of Cefepime-AFT

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

* Note: Reconstitution of Cefepime-AFT in a volume of diluent other than those included in this table will not produce a linear change in concentration

** Requires intravenous container

7. MEDICINE SCHEDULE

Prescription Only Medicine.

8. SPONSOR

AFT Pharmaceuticals Ltd
PO Box 33-203
Takapuna
Auckland 0740

9. DATE OF FIRST APPROVAL

22 May 2014

10. DATE OF REVISION OF THE TEXT

16 February 2023

Summary table of changes:

Section changed	Summary of new information
4.4	Addition of a new warning statement