

Data Sheet

Name Of Medicine

Maxipime® (**Cefepime hydrochloride**).

Presentation

Maxipime is a sterile dry mixture of **cefepime hydrochloride** and L-arginine. The L-arginine, at an approximate concentration of 725 mg/g of **cefepime**, is added to control the pH of the constituted solution at 4.0-6.0.

Cefepime hydrochloride is a white to pale yellow powder with a molecular formula of $C_{19}H_{25}N_6O_5S_2.Cl.HCl.H_2O$ and a molecular weight of 571.5. It is highly soluble in water. Constituted solutions of Maxipime will vary in colour from colourless to amber.

Maxipime is available in:

1g (15mL vial)

2g (77mL vial)

Uses

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

Actions

Cefepime is a bactericidal agent that acts by inhibition of bacterial wall synthesis. It has a broad spectrum of activity against a wide range of gram-positive and gram-negative bacteria including most strains resistant to aminoglycosides or third-generation cephalosporins such as ceftazidime. Cefepime is highly resistant to hydrolysis by most beta-lactamases, has a low affinity for chromosomally-encoded beta-lactamases, and exhibits rapid penetration into gram-negative bacterial cells.

In studies using *Escherichia coli* and *Enterobacter cloacae*, **cefepime** bound with highest affinity to penicillin binding protein (PBP) 3 followed by PBP 2, then PBPs 1a and 1b. Binding to PBP 2 occurs with significantly higher affinity than that of other parenteral cephalosporins. This may enhance its antibacterial activity. The moderate affinity of **cefepime** for PBPs 1a and 1b probably also contributes to its overall bactericidal activity.

Cefepime has been shown to be bactericidal by time-kill analysis (killing-curves) and by determination of minimum bactericidal concentrations (MBC) for a wide variety of bacteria. The **cefepime** MBC/MIC ratio was 2 for more than 80% of isolates of all gram-positive and gram-negative species tested. Synergy with aminoglycosides has been demonstrated *in vitro*, primarily with *Pseudomonas aeruginosa* isolates. **Cefepime** has been shown to be active against most strains of the following organisms:

Gram-positive Aerobes:

Staphylococcus aureus (including beta-lactamase-producing strains)

Staphylococcus epidermidis (including beta-lactamase-producing strains)

Other staphylococci including *S. hominis*, *S. saprophyticus*

Streptococcus pyogenes (Group A streptococci)

Streptococcus agalactiae (Group B streptococci)

Streptococcus pneumoniae (including intermediate penicillin resistant strains with penicillin MIC of 0.1 to 1 mcg/mL)

Other -haemolytic streptococci (Groups C, G, F), *S. bovis* (Group D), Viridans streptococci.

NB: Most strains of enterococci, eg: *Enterococcus faecalis*, and methicillin-resistant staphylococci are resistant to most cephalosporins including **cefepime**.

Gram-negative Aerobes:

Pseudomonas sp. including *P. aeruginosa*, *P. putida*, *P. stutzeri*

Escherichia coli

Klebsiella sp. including *K. pneumoniae*, *K. oxytoca*, *K. ozaenae*

Enterobacter sp. including *E. cloacae*, *E. aerogenes*, *E. agglomerans*, *E. sakazakii*

Proteus sp. including *P. mirabilis*, *P. vulgaris*

Acinetobacter calcoaceticus (subsp. *anitratus*, *lwoffii*)

Aeromonas hydrophila

Capnocytophaga sp.

Citrobacter sp. including *C. diversus*, *C. freundii*

Campylobacter jejuni

Gardnerella vaginalis

Haemophilus ducreyi

Haemophilus influenzae (including beta-lactamase-producing strains)

Haemophilus parainfluenzae

Hafnia alvei

Legionella sp.

Morganella morganii

Moraxella catarrhalis (*Branhamella catarrhalis*) (including beta-lactamase-producing strains)

Neisseria gonorrhoeae (including beta-lactamase-producing strains)

Neisseria meningitidis

Providencia sp. including *P. rettgeri*, *P. stuartii*

Salmonella sp.

Serratia including *S. marcescens*, *S. liquefaciens*

Shigella sp.

Yersinia enterocolitica

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

Anaerobes:

Bacteroides sp.

Clostridium perfringens

Fusobacterium sp.

Mobiluncus sp.

Peptostreptococcus sp.

Prevotella melaninogenica (formerly known as *Bacteroides melaninogenicus*).

Veillonella sp.

Note: **Cefepime** is inactive against *Bacteroides fragilis* and *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

Diffusion Techniques:

Laboratory reports with standardized single-disk susceptibility results using a 30mcg **cefepime** disk should be interpreted according to the following criteria:

<i>Zone Diameter (mm)</i>	<i>Interpretation</i>
18	(S) Susceptible
15-17	(I) Intermediate
14	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood concentrations. A report of "Intermediate" indicates that the organism would be susceptible when high dosage is used or when the infection is confined to tissues and fluids (eg: interstitial fluid and urine) in which high antibiotic levels are attained. A report of "Resistant" indicates that the achievable concentration of the antibiotic is unlikely to be inhibitory and other therapy should be selected.

Organisms should be tested with the **cefepime** disk because **cefepime** has been shown to be active *in vitro* against certain strains found to be resistant with other beta-lactam disks. The **cefepime** disk should not be used for testing susceptibility to other cephalosporins. Standardized quality control procedures require the use of control organisms.

Dilution Techniques:

Using standardized dilution methods, the MIC values obtained should be interpreted according to the following criteria:

<i>MIC (mcg/mL)</i>	<i>Interpretation</i>
8	(S) Susceptible
16	(I) Intermediate
32	(R) Resistant

As with diffusion techniques, dilution techniques require the use of laboratory control organisms.

Pharmacokinetics

Adults:

Average plasma concentrations of **cefepime** observed in normal adult males at various times following single 30-minute infusions or intramuscular injections of 500mg, 1g and 2g are summarized in Table 1. Following intramuscular administration, **cefepime** is completely absorbed.

Table 1
Mean plasma concentrations of cefepime (mcg/mL)

Cefepime dose	<i>0.5 hr</i>	<i>1 hr</i>	<i>2 hr</i>	<i>4 hr</i>	<i>8 hr</i>	<i>12 hr</i>
500mg IV	38.2	21.6	11.6	5.0	1.4	0.2
1g IV	78.7	44.5	24.3	10.5	2.4	0.6
2g IV	163.1	85.8	44.8	19.2	3.9	1.1
500mg IM	8.2	12.5	12.0	6.9	1.9	0.7
1g IM	14.8	25.9	26.3	16.0	4.5	1.4
2g 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 2.

Table 2
Mean concentrations of cefepime in various
Body fluids (mcg/mL) and tissues (mcg/g)

<i>Tissue or fluid</i>	<i>Dose (IV)</i>	<i>Average time of sample post-dose (hr)</i>	<i>Mean concentration</i>
Urine	500mg	0-4	292
	1g	0-4	926
	2g	0-4	3120
Bile	2g	9.4	17.8
Peritoneal fluid	2g	4.4	18.3
Blister fluid	2g	1.5	81.4
Bronchial mucosa	2g	4.8	24.1
Sputum	2g	4.0	7.4
Prostate	2g	1.0	31.5
Appendix	2g	5.7	5.2
Gallbladder	2g	8.9	11.9

Cefepime is metabolised to N-methylpyrrolidine which is rapidly converted to the N-oxide. Urinary recovery of unchanged **cefepime** accounts for approximately 85% of the administered dose; high concentrations of unchanged **cefepime** are found in the urine. Less than 1% of the administered dose is recovered from urine as N-methylpyrrolidine, 6.8% as the N-oxide, and 2.5% as an epimer of **cefepime**. Serum protein binding of **cefepime** averages 16.4% and is independent of concentration in the serum.

The average elimination half-life of **cefepime** is approximately 2 hours, and does not vary with respect to dose over the range of 250mg to 2g. There was no accumulation in healthy subjects receiving doses up to 2g intravenously every 8 hours for a period of 9 days. Total body clearance averages 120mL/min. The average renal clearance of **cefepime** is 110mL/min, suggesting that **cefepime** is eliminated almost exclusively by renal mechanisms, primarily glomerular filtration.

Healthy volunteers 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 subjects. Dosage adjustments in the elderly are recommended if renal function is compromised (see **Precautions and Dosage And Administration**).

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

Elimination half-life is prolonged in patients with various degrees of renal insufficiency, with a linear relationship between total body clearance and creatinine clearance. This serves as the basis for dosage adjustment recommendations in this group of patients (see **Dosage And 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.

Clinical Trial Information

Indications

Adults:

Maxipime is indicated in adults for 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.
- Septicaemia.
- Intra-abdominal infections, including peritonitis and biliary tract infections
- Empiric treatment of febrile neutropenia (**SEE WARNINGS AND PRECAUTIONS**)

Culture and susceptibility studies should be performed when appropriate to determine susceptibility of the causative organism(s) to **cefepime**. Empiric therapy with Maxipime 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, Maxipime can be used as monotherapy prior to identification of the causative organisms(s). In patients who are at risk of mixed aerobic-anaerobic infection, particularly if bacteria not susceptible to **cefepime** may be present (see **Actions**), concurrent initial therapy with an anti-anaerobic agent is recommended before the causative organism(s) is known. Once these results become available, combination therapy with Maxipime and other anti-infective agents may or may not be necessary, depending on the susceptibility profile.

Dosage And Administration

Maxipime can be administered either intravenously or intramuscularly. 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.

Adults:

Guidelines for dosage of Maxipime for adults with normal renal function are provided in Table 3.

Table 3
Recommended dosage schedule for adults with normal renal function
(aged 12 years and older)*

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

* The usual duration of therapy is 7-10 days; however, more severe infections may require longer treatment. For empirical treatment of febrile neutropenia, usual duration of therapy is 7 days or until resolution of neutropenia.

Patients with Impaired Renal Function:

The initial dose of **cefepime** is the same as in patients with normal renal function. The recommended maintenance doses of **cefepime** in patients with renal insufficiency are presented in Table 4.

Table 4
Maintenance dosing schedule in adult patients with renal impairment

Creatinine Clearance (mL/min)	Recommended Maintenance Dosage			
	Usual dose, no adjustment necessary			
> 50	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‡	500mg q24h	500mg q24h	500mg q24h	500mg q24

* The initial dose is the same as in patients with normal renal function

‡ 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 500mg per day thereafter for all infections except febrile neutropenia, which is 1 gram per day. On dialysis days, cefepime should be administered following dialysis. Whenever possible, cefepime

should be administered at the same time each day.

When only serum creatinine 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:

$$\text{Males} \quad \text{Creatinine clearance (mL/min)} = \frac{\text{weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females 0.85 x above value

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. A repeat dose, equivalent to the initial dose, should be given at the completion of each dialysis session. In patients undergoing continuous ambulatory peritoneal dialysis, **cefepime** may be administered at the same doses recommended for patients with normal renal function, ie: 500mg, 1g or 2g, depending on infection severity, at a dosage interval of every 48 hours.

Impaired Hepatic Function:

No adjustment is necessary for patients with impaired hepatic function.

Preparation of Solutions and Administration:

Maxipime may be given intravenously or by deep intramuscular injection into a large muscle mass (such as the upper outer quadrant of the gluteus maximus).

Maxipime powder is to be reconstituted using the volumes of diluent shown in Table 5; the diluents to be used are identified following the table.

Table 5
Preparations of solutions of Maxipime

	<i>Amount of diluent to be added (mL)</i>	<i>Approximate available volume (mL)</i>	<i>Approximate cefepime concentration (mg/mL)</i>
<u>Intravenous</u>			
500mg vial	5	5.7	90
1g vial	10	11.4	90
2g vial	10	12.8	160
<u>Intramuscular</u>			
500mg vial	1.5	2.2	230
1g vial	3.0	4.4	230

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 **Maxipime** with 5 or 10mL of Sterile Water for Injection, 5% Dextrose Injection or 0.9% Sodium Chloride, as directed in Table 5. The resulting solution should be injected directly into the vein over a period of three to five minutes or injected into the tubing of an administration set while the patient is receiving a compatible IV fluid (see Compatibility and Stability).

For intravenous **infusion**, reconstitute the 500mg, 1g, or 2g 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 Compatibility and Stability). The resulting solution should be administered over a period of approximately 30 minutes.

Intramuscular Administration:

Maxipime should be reconstituted with one of the following diluents at the volumes shown in Table 5: Sterile water for Injection, 0.9% Sodium Chloride, 5% Dextrose Injection, or Bacteriostatic Water for Injection with Parabens or Benzyl Alcohol then administered by deep intramuscular injection into a large muscle mass (such as the upper outer quadrant of the gluteus maximus). In a pharmacokinetic study, doses up to 1g (volumes <3.1 mL) were administered at single injection sites; the maximum dose (2g/6.2 mL) was administered at two injection sites. Although **MAXIPIME** can be constituted with 0.5% or 1.0% Lidocaine hydrochloride, it is usually not required because **Maxipime** causes little or no pain upon IM administration.

Compatibility and Stability:***Intravenous:***

Maxipime (Cefepime Hydrochloride for Injection) is compatible at concentrations between 1 and 40mg/mL with the following IV infusion fluids: 0.9% Sodium Chloride, 5% or 10% Dextrose Injection, M/6 Sodium Lactate Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, Lactated Ringers and 5% Dextrose Injection. These solutions are stable up to 24 hours at room temperature or 7 days under refrigeration.

Maxipime admixture compatibility and stability information is summarised in Table 6.

**Table 6
Cefepime Admixture Stability**

Maxipime concentration	Admixture and concentration	IV infusions solutions	Stability time for	
			RT/L	Refrigeration
40 mg/mL	amikacin 6 mg/mL	NS or D5W	24 hours	7 days
40 mg/mL	ampicillin 1 mg/mL	D5W	8 hours	8 hours
40 mg/mL	ampicillin 10 mg/mL	D5W	2 hours	8 hours
40 mg/mL	ampicillin 1 mg/mL	NS	24 hours	48 hours
40 mg/mL	ampicillin 10 mg/mL	NS	8 hours	48 hours
4 mg/mL	ampicillin 40 mg/mL	NS	8 hours	8 hours
4-40 mg/mL	clindamycin 0.25-6 mg/mL	NS or D5W	24 hours	7 days
4 mg/mL	heparin 10-50 units/mL	NS or D5W	24 hours	7 days
4 mg/mL	potassium chloride 10-40 mEq/L	NS or D5W	24 hours	7 days
4 mg/mL	theophylline 0.8 mg/mL	D5W	24 hours	7 days
1-4 mg/mL	NA	Parenteral nutrition solution ^a	8 hours	3 days
0.125-0.25 mg/mL	NA	Peritoneal dialysis solution ^b	24 hours at RT/L or 37°C	7 days

^a Aminosyn® II 4.25% in dextrose 25% with electrolytes and calcium

^b Inpersol® with 4.25% dextrose

NS 0.9% Sodium Chloride Injection

D5W 5% Dextrose Injection

NA not applicable

RT/L room temperature and light

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

Intramuscular:

Maxipime (**Cefepime Hydrochloride** for Injection) constituted as directed (in Table 5) is stable for 24 hours at room temperature or for 7 days under refrigeration with the following diluents: Sterile Water for Injection, 0.9% Sodium Chloride, 5% Dextrose Injection, Bacteriostatic Water for Injection with Parabens or Benzyl Alcohol, or 0.5% or 1% Lidocaine hydrochloride.

Note:

Parenteral drugs should be inspected visually for particulate matter before administration.

As with other cephalosporins, the colour of Maxipime may darken on storage, however, product potency is unaffected.

Contraindications

Maxipime is contraindicated in patients who have had previous hypersensitivity reactions to any component of the formulation, the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics.

Warnings And Precautions

Before therapy with Maxipime 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 Maxipime occurs, discontinue the drug and treat the patient appropriately. Serious hypersensitivity reactions may require epinephrine and other supportive therapy.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including cefepime, and may range in severity from mild diarrhea to fatal colitis. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C.difficile* may need to be discontinued.

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

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

In patients with impaired renal function, such as reduction of urinary output because of renal insufficiency (creatinine clearance \leq 50mL/min) or other conditions that may compromise renal function, the dosage of **Maxipime** should be adjusted to compensate for a slower rate of renal elimination (see **Dosage And Administration** and **Actions**).

In patients at high risk of severe infection (including patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying 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.

Because high and prolonged serum antibiotic concentrations can occur from usual dosages in patients with renal insufficiency or other conditions that may compromise renal function, the maintenance dosage should be reduced when cefepime is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms.

Serious adverse events, including encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), seizures (including nonconvulsive status epilepticus), myoclonus, and/or renal failure, have been reported in postmarketing experience in patients with renal impairment who receive unadjusted doses of **Maxipime** (see **Adverse Events**). In general, symptoms of neurotoxicity resolved after discontinuation of cefepime and/or 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 **Maxipime**.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

No long-term studies in animals have been performed to evaluate carcinogenic potential. *In vitro* and *in vivo* tests for genotoxicity have shown that **cefepime** is not genotoxic. No impairment of fertility has been seen in rats.

Usage in Pregnancy-Category B1:

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

Lactation:

Cefepime is excreted in human breast milk in very low concentrations. Caution should be used when **cefepime** is administered to a nursing woman.

Labour and Delivery:

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

Paediatric Use:

Although studies in paediatric patients are ongoing, the safety and effectiveness of **Maxipime** in children has not been established.

Geriatric Use:

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. 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 **Dosage And 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.

Serious adverse events, including reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor and, coma), myoclonus, seizures (including nonconvulsive status epilepticus), and/or renal failure have occurred in geriatric patients with renal insufficiency given the usual dose of cefepime.

Driving/Operating Machinery:

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

Adverse Effects

Maxipime 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 **Maxipime** 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 between 0.05% - 0.1% were: abdominal pain, constipation, vasodilation, dyspnea, dizziness, paraesthesia, genital pruritus, taste perversion, chills and unspecified moniliasis.

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

Local reactions at the site of IV infusion occurred in 5.2% of patients; these included phlebitis (2.9%) and inflammation (0.1%). Intramuscular administration of **Maxipime** 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, eosinophilia, prolonged prothrombin time, partial thromboplastin time (2.8%), decreases in calcium and positive Coombs' test without haemolysis (18.7%). Transient elevations of blood urea nitrogen and/or serum creatinine and transient thrombocytopenia were observed in 0.5% to 1% of patients. Transient leucopenia and neutropenia were also observed (< 0.5%). During postmarketing experience, agranulocytosis has been reported rarely.

During postmarketing experience, encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), seizures, myoclonus, and/or renal failure have been reported in patients with renal impairment who received unadjusted doses of **cefepime** (see **Precautions**). Because of the uncontrolled nature of these spontaneous reports, a causal relationship to **Maxipime** has not been determined.

As with other cephalosporins, anaphylaxis including anaphylactic shock, transient leukopenia, neutropenia, agranulocytosis, and thrombocytopenia have been reported.

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

Interactions

Renal function should be carefully monitored if high doses of aminoglycosides are to be administered with **cefepime** or if aminoglycoside therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Nephrotoxicity has been reported following concomitant administration of other cephalosporins with aminoglycoside antibiotics or potent diuretics such as frusemide.

Overdosage

In case of severe overdosage, especially in patients with compromised renal function, haemodialysis will aid in the removal of **cefepime** from the body; peritoneal dialysis is of no value. Accidental overdosing can occur if large doses are given to patients with reduced renal function (see **Precautions**).

Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, and neuromuscular excitability.

Pharmaceutical Precautions

Maxipime in the dry state original cartons should be stored at less than 30° C.

Medicine Classification

Prescription Only Medicine.

Package Quantities

500mg	(15mL vial) – <u>(not marketed)</u>
1g	(15mL vial)
2g	(77mL vial)

All available as 1's.

Name And Address

Bristol-Myers Squibb (NZ) Limited
Simpson Grierson
88 Shortland Street
Auckland
New Zealand

Date Of Preparation

19th March 2012