**DBL™ CEFEPIME POWDER FOR INJECTION**

**NAME OF THE MEDICINE**

Cefepime (as hydrochloride monohydrate) powder for solution for injection

**PRESENTATIONS**

Cefepime hydrochloride is a semi-synthetic broad spectrum cephalosporin antibiotic for parenteral administration. The chemical name is: Pyrrolidinium, 1-[[7-[[2-amino-4-thiazolyl](methoxyimino)acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-,chloride, monohydrochloride, monohydrate, [6R- [6α, 7β(Z)]].

Cefepime hydrochloride is a white to pale yellow powder. It is highly soluble in water. It has a pH of between 4.0 and 6.0.

DBL™ Cefepime Powder for Injection is a sterile lyophilised powder for injection containing the inactive ingredient L-arginine to control the pH of the reconstituted solution at 4.0 to 6.0. Following reconstitution with Water for Injection as directed in labelling, it results in a pale yellow to amber coloured, clear solution.

Each 20 mL vial contains either 1.914 g or 3.828 g of sterile cefepime – L-arginine powder, which is equivalent to 1 g or 2 g of cefepime and approximately 725 mg of arginine per gram of cefepime. It contains no antimicrobial preservative and is for use in one patient only.

**USES**

**Actions**

Cephalosporins act by interfering with bacterial cell-wall synthesis, leading to lysis of the infectious organism.

**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 1. Following intramuscular (IM) administration, cefepime is completely absorbed. The average plasma concentrations of cefepime at various times following a single IM injection are summarised in Table 1.

**Table 1: Mean plasma concentrations of cefepime (microgram/mL)**

<table>
<thead>
<tr>
<th>Cefepime doses</th>
<th>0.5 hr</th>
<th>1 hr</th>
<th>2 hr</th>
<th>4 hr</th>
<th>8 hr</th>
<th>12 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 g IV</td>
<td>66.9</td>
<td>41.8</td>
<td>25.3</td>
<td>11.0</td>
<td>2.8</td>
<td>0.8</td>
</tr>
<tr>
<td>2 g IV</td>
<td>127.6</td>
<td>81.7</td>
<td>45.4</td>
<td>20.1</td>
<td>4.6</td>
<td>1.2</td>
</tr>
<tr>
<td>1 g IM</td>
<td>14.8</td>
<td>25.9</td>
<td>26.3</td>
<td>16.0</td>
<td>4.5</td>
<td>1.4</td>
</tr>
<tr>
<td>2 g IM</td>
<td>36.1</td>
<td>49.9</td>
<td>51.3</td>
<td>31.5</td>
<td>8.7</td>
<td>2.3</td>
</tr>
</tbody>
</table>

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 (microgram/mL) and tissues (microgram/g)**

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<table>
<thead>
<tr>
<th>Tissue or fluid</th>
<th>Dose (IV)</th>
<th>Average time of sample post-dose (hr)</th>
<th>Mean concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>1 g</td>
<td>0-4</td>
<td>926</td>
</tr>
<tr>
<td></td>
<td>2 g</td>
<td>0-4</td>
<td>3120</td>
</tr>
<tr>
<td>Bile</td>
<td>2 g</td>
<td>9.4</td>
<td>7.7</td>
</tr>
<tr>
<td>Peritoneal fluid</td>
<td>2 g</td>
<td>4.4</td>
<td>16.4</td>
</tr>
<tr>
<td>Blister fluid</td>
<td>2 g</td>
<td>1.5</td>
<td>24.5</td>
</tr>
<tr>
<td>Bronchial mucosa</td>
<td>2 g</td>
<td>4.8</td>
<td>24.1</td>
</tr>
<tr>
<td>Sputum</td>
<td>2 g</td>
<td>4.0</td>
<td>7.4</td>
</tr>
<tr>
<td>Prostate</td>
<td>2 g</td>
<td>1.0</td>
<td>31.5</td>
</tr>
<tr>
<td>Appendix</td>
<td>2 g</td>
<td>5.7</td>
<td>5.2</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>2 g</td>
<td>8.9</td>
<td>11.9</td>
</tr>
</tbody>
</table>

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

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

Healthy volunteers 65 years old or older, who received a single 1g intravenous (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 WARNINGS AND PRECAUTIONS and DOSAGE AND 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 1g 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 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.

**MICROBIOLOGY**

Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Cefepime has a broad spectrum of *in vitro* activity that encompasses a wide range of gram-positive and gram-negative bacteria. Cefepime has a low affinity for chromosomally-encoded beta-lactamases. Cefepime is highly resistant to hydrolysis by most beta-lactamases and exhibits rapid penetration into gram-negative bacterial cells. Within bacterial cells, the molecular targets of cefepime are the penicillin binding proteins (PBP).
Cefepime has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the INDICATIONS section.

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

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

The presence 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** (With % acquired resistance* for susceptible organisms as follows).

**Susceptible:**
- 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:**
No organisms listed

**Insusceptible:**
- Staphylococcus aureus (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 entrococci, eg Enterococcus faecalis, and methicillin-resistant staphylococci are resistant to cefepime.

Aerobic Gram-Negative Microorganisms
Acinetobacter calcoaceticus subsp. Iwoffi
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.

Susceptibility testing
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.

INDICATIONS

Adults
DBL™ Cefepime Powder for Injection 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 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 DBL™ Cefepime Powder for Injection 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, DBL™ Cefepime Powder for Injection 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 DBL™ Cefepime Powder for Injection. 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.

**DOSAGE AND ADMINISTRATION**

**Adults**
The usual adult dosage and route of administration of cefepime is 1g 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 are provided in Table 3. The usual duration of therapy is 7-10 days; however, more severe infections may require longer treatment.

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

<table>
<thead>
<tr>
<th>Severity of Infection</th>
<th>Dose and Route of Administration</th>
<th>Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate urinary tract infection</td>
<td>500 mg – 1 g IV or IM</td>
<td>q12 hours</td>
</tr>
<tr>
<td>Mild to moderate infections other than UTI</td>
<td>1 g IV or IM</td>
<td>q12 hours</td>
</tr>
<tr>
<td>Severe infections</td>
<td>2 g IV</td>
<td>q12 hours</td>
</tr>
<tr>
<td>Very severe or life threatening infections</td>
<td>2 g IV</td>
<td>q8 hours</td>
</tr>
</tbody>
</table>

**Impaired Hepatic Function**
No adjustment is necessary for patients with impaired hepatic function.

**Impaired Renal Function - Adults**
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 4.

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:

\[
\text{Males: Creatinine clearance (mL/min)} = \frac{\text{weight (kg)} \times (140 - \text{age})}{72}
\]
Females: 0.85 x value calculated using formula for males

Table 4: Maintenance Dosing Schedule in Adult Patients With Renal Impairment

<table>
<thead>
<tr>
<th>Creatine Clearance (mL/min)</th>
<th>Recommended Maintenance dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>2 g q8h 2 g q12h 1 g q12h 500 mg q12h</td>
</tr>
<tr>
<td>30 - 50</td>
<td>2 g q12h 2 g q24h 1 g q24h 500 mg q24h</td>
</tr>
<tr>
<td>11 - 29</td>
<td>2 g q24h 1 g q24h 500 mg q24h 500 mg q24h</td>
</tr>
<tr>
<td>≤ 10</td>
<td>1 g q24h 500 mg q24h 250 mg q24h 250 mg q24h</td>
</tr>
<tr>
<td>Haemodialysis*</td>
<td>500 mg q24h 500 mg q24h 500 mg q24h 500 mg q24h</td>
</tr>
</tbody>
</table>

* 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, ie: 1g or 2g, depending on infection severity, at a dosage interval of every 48 hours.

Administration
DBL™ Cefepime Powder for Injection 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.

Product is for single use in one patient only.

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 DBL™ Cefepime Powder for Injection with 10mL of Sterile 5% Glucose Injection or 0.9% Sodium Chloride, as directed in Table 5. 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 Compatibility).

For IV infusion, reconstitute the 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). The resulting solution should be administered over a period of approximately 30 minutes.

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

Intravenous

DBL™ Cefepime Powder 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.

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

Intramuscular

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

NOTE: 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.

Stability

Cefepime 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 it should be stored at 2°C-8°C for a maximum of 24 hours. Reconstituted solutions should be protected from light.

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 DBL™ Cefepime Powder for Injection may darken on storage, however, product potency is not adversely affected.

Table 5: Preparations of solutions of DBL™ Cefepime Powder for Injection

<table>
<thead>
<tr>
<th></th>
<th>Amount of diluent to be added (mL)</th>
<th>Approximate available volume (mL)</th>
<th>*Approximate cefepime concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1g vial</td>
<td>10.0</td>
<td>11.3</td>
<td>88</td>
</tr>
<tr>
<td>2g vial</td>
<td>10.0</td>
<td>12.6</td>
<td>158</td>
</tr>
<tr>
<td>Intramuscular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1g vial</td>
<td>3.0</td>
<td>4.4</td>
<td>230</td>
</tr>
</tbody>
</table>

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

WARNINGS AND PRECAUTIONS
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. Drugs which delay peristalsis may prolong and/or worsen the condition and should not be used.

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

In patients 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 nonsusceptible organisms. Should superinfection 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.

Impaired Renal Function
In patients with impaired renal function, such as reduction of urinary output because of renal insufficiency (creatinine clearance < 50 mL/min) or other conditions that may compromise renal function, the dosage of cefepime should be adjusted to compensate for the slower rate of renal elimination. Because high and prolonged serum antibiotic concentrations can occur from usual doses in patients with renal insufficiency or other conditions that may compromise renal function, the maintenance dosage should be reduced when cefepime is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms (see DOSAGE AND ADMINISTRATION and USES). During postmarketing surveillance, the
following serious adverse events have been reported: reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor and coma), myoclonus, seizures (including nonconvulsive status epilepticus), and/or renal failure (see ADVERSE EFFECTS). Most cases occurred in patients with renal impairment who received doses of cefepime that exceeded recommendations. In general, symptoms of neurotoxicity resolved after discontinuation of cefepime and/or after haemodialysis however, some cases included a fatal outcome.

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

**Carcinogenicity, mutagenicity, impairment of fertility**

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

**Use in pregnancy (Category B1)**

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 humans on a mg/m² basis. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Use in lactation**

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

**Use in labour and delivery**

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

**Use in paediatrics**

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

**Effect on ability to drive or operate machinery**

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.

**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

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† Category B1

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

Studies in animals have not shown evidence of an increased occurrence of foetal damage.
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 (see WARNINGS AND PRECAUTIONS, ADVERSE EFFECTS and USES). 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 WARNINGS AND PRECAUTIONS and ADVERSE EFFECTS).

ADVERSE 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, cutaneous vasculitis may occur
- 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 may occur. 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%).

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 WARNINGS AND PRECAUTIONS).

Anaphylaxis including anaphylactic shock, transient leukopenia, 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 effects and altered laboratory tests have been reported for cephalosporin-class antibiotics: Urticaria, Stevens-Johnson syndrome, erythema multiforme,
toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, aplastic anaemia, haemolytic anaemia, haemorrhage, hepatic dysfunction including cholestasis, and false positive tests for urinary glucose.

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

**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 frusemide.

**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 DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS and ADVERSE EFFECTS). Symptoms of overdosage include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures and neuromuscular excitability.

In case of overdose, immediately contact the Poison Information Centre for advice (In New Zealand, call 0800 764 766).

**PHARMACEUTICAL PRECAUTIONS**
DBL™ Cefepime Powder for Injection is a 20 mL vial containing a powder for solution for injection providing 1 g or 2 g cefepime. Following reconstitution with Water for Injection as directed in DOSAGE AND ADMINISTRATION, it results in pale yellow to amber coloured, clear solution.

DBL™ Cefepime Powder for Injection in original cartons should be stored at below 25°C. Protect from light.

To avoid the risk of microbial contamination, reconstituted DBL™ Cefepime Powder for Injection should be administered as soon as possible after reconstitution.

**PACKAGE QUANTITIES**
DBL™ Cefepime Powder for Injection is available in packs containing 1 vial:
- 1g (20 mL vial)
- 2g (20 mL vial)

**MEDICINE CLASSIFICATION**
Prescription Medicine
FURTHER INFORMATION

Molecular Formula: $\text{C}_{19}\text{H}_{25}\text{N}_{6}\text{O}_{5}\text{S}_{2}\text{Cl.HCl.H}_2\text{O}$
Molecular Weight: 571.5
CAS Registry No.: 123171-59-5
ATC code: J01DE01

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