CEFMEX POWDER FOR INJECTION

DESCRIPTIONS:
CEFMEX 500MG and 1G POWDER FOR INJECTION:
Before reconstitution: A white to pale yellow powder, After reconstitution: From colorless to amber solution

COMPOSITION:
Cefmex (Cefepime Hydrochloride for injection) is a cephalosporin antibiotic intended for intramuscular or intravenous administration.
Each Cefmex vial contains 500mg or 1g of cefepime activity in the form of 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.

PHARMACODYNAMICS:
Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Cefepime is a bactericidal agent that has a spectrum of activity against a range of Gram-positive and Gram-negative bacteria.
Cefepime is highly resistant to hydrolysis by a number of beta-lactamases, has a low affinity for chromosomally encoded beta-lactamases, and exhibits rapid penetration into Gram-negative bacteria cells.
Cefepime minimum bactericidal concentrations were ≤2 times the minimum inhibitory concentration for the majority of organisms tested.
Cefepime has been shown to be active against most strains tested of the following organisms both in vitro and in clinical infections.

Gram-positive aerobes:Staphylococcus aureus (including penicillinase-producing strains but excluding methicillin-resistant staphylo-cocci), Streptococcus agalactiae (Group B streptococci), Streptococcus pnemoniae (formerly Diplococcuspnemoniae), Streptococcus pyogenes (Group A streptococci), other beta-haemolytic streptococci (Group C, G, F).

Gram-negative aerobes: Acinetobacter calcoaceticus (subsp.anitratus,lwoffi), Enterobacter spp.(including E. aerogenes, E. agglomerans, E.cloacae, E. sakazakii), Escherichia coli, Haemophilus influenzae, (including strains of beta-lactamase producing H. influenzae), Haemophilus parainfluzae, Klebsiella spp.(including K. oxytoca, K. ozaenae, K. pneumoniae), Moraxella catarrhalis (formerly Branhamella catarrhalis), Morganella morganii, Proteus mirabilis, Pseudomonas aeruginosa (not all strains), Serratia marcescens.
Cefepime exhibits in vitro minimum inhibitory concentrations (MIC's) of 8 mcg/mL or less against 90% or more of the strains of the following micro-organisms: however, in vitro activity does not necessarily imply clinical efficacy.

Gram-positive aerobes: Enterococci like Enterococcus faecalis and methicilin-resistant staphylococci, are resistant to cefepime. Staphylococcus aureus (including beta-lactamase-producing strains but excluding methicillin-resistant staphylococci), Staphylococcus epidermidis (including beta-lactamase-producing strains), Staphylococcus horminis, Staphylococcus saprophyticus, Group D streptococci (Streptococcus bovis), Viridans streptococci.

Gram-negative aerobes: Pseudomonas putida, P.stutzeri, Proteus vulgaris, Aeromonas hydrophila, Capnocytophaga spp., Citrobacter spp. including C. freundii, Campylobacter jejuni, Gardnerella vaginalis,Haemophilus ducreyi, Hafnia alvei, Neisseria gonorrhoeae (including beta-lactamase-producing strains), Shigella spp., Yersinia enterocolitica.
Cefepime is inactive against most strains of Xanthomonas maltophilia (Pseudomonas maltophilia). Not all pseudomonas strains are susceptible.

PHARMACOKINETICS:
Adults
Following intramuscular injection, cefepime is completely absorbed. Therapeutic concentrations are found in various body fluids such as urine, bile, peritoneal fluid, blister fluid and sputum, and tissues such as bronchial mucosa, prostate, appendix and gallbladder, following intravenous administration of a single dose of cefepime. The average elimination half-life of cefepime is approximately two hours. There is no evidence of accumulation in healthy subjects receiving doses up to 2g intravenously every 8 hours for a period of 9 days. Total body clearance average 120mL/min.
The average renal clearance of cefepime is 110mL/min, demonstrating that cefepime is eliminated almost exclusively by renal mechanisms, primarily glomerular filtration.
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 concentration in the serum.
Healthy volunteers 65 years old or older, who received a single 1g intravenous dose of cefepime had higher area under the concentration-time curve and lower renal clearance values compared to younger healthy adults. Dosage adjustments in the elderly are recommended if renal function is compromised (see WARNING and RECOMMENDED DOSAGE).
The pharmacokinetics of cefepime was unaltered in patients with impaired hepatic function who received a single 1g dose.
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 RECOMMENDED DOSAGE AND ROUTE OF ADMINISTRATION).
Average half-life in severely impaired patients requiring dialysis therapy is 13 hours for haemodialysis and 19 hours for continuous ambulatory peritoneal dialysis.

Paediatrics
Single and multiple-dose pharmacokinetics of cefepime were evaluated in patients ranging in age from 2 months to 16 years who received 50 mg/kg doses administered by IV infusion or IM injection: multiple doses were administered every 8 or 12 hours for at least 48 hours. Mean plasma concentrations of cefepime after the first dose were similar to those at steady state, with only slight accumulation seen upon repeated dosing.
Following IM injection under steady state conditions, mean peak cefepime plasma concentrations of 68 mcg/mL were achieved at a median time of 0, 75 hours, compared to 185, 6 mcg/mL after IV. The mean trough concentration after IM injection at steady state was 6, 0 mcg/mL at 8 hours. Bioavailability averaged 82% after IM injection.

Other pharmacokinetic parameters in infants and children were not different between first-dose and steady-state determinations, regardless of dosing schedule (q12h or q8h). There were also no differences in pharmacokinetics among various patients' ages or between males and female patients.
Following a single IV dose, total body clearance (in children over 6 months) averaged 3,4 mL/min/kg and average of unchanged cefepime was 60,4% of the administered dose, and renal clearance was the primary pathway of elimination, averaging 2,0 mL/min/kg. Concentrations of cefepime in cerebrospinal fluid relative to those in plasma are shown in Table 1.

TABLE 1 : Mean (SD) Plasma (PL) and CSF Concentrations, and CSF/PL Ratios of Cefepime in Infants and Children*

Sampling Time (hr)	N	Plasma concentration mcg/mL)	CSF concentration (mcg/mL)	Ratios CSF/PL
0,5	6	70,4 (55,4)	5,7 (8)	0,12 (0,14)
1	4	44,1 (7,8)	4,3 (1,5)	0,10 (0,04)
2	5	23,9 (12,9)	3,6 (2,0)	0,17 (0,09)
4	5	11,7 (15,7)	4,2 (1,1)	0,87 (0,56)
8	5	4,9 (5,9)	3,3 (2,8)	1,02 (0,64)

*Patients ranged in ages from 3,1 months to 14,7 years, with a mean (SD) age of 2,9 (3,9) years. Patients with suspected central nervous system infection were treated with cefepime at a dose of 50mg/kg administered as an IV infusion over 5 to 20 minutes every 8 hours. Single plasma and CSF samples were collected from selected patients at the sampling times shown relatives to the end of infusion on day 2 or 3 of cefepime treatment.

INDICATIONS:
Adult:
Cefmex is indicated in adults for the treatment of the following infections when caused by susceptible strains of 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)
Gynecological infections.
Septicemia.
Empiric treatment in febrile neutropenic patients

Pediatrics:
Cefmex is indicated in pediatric patients for treatment of infections when caused by susceptible bacteria:
Pneumonia
Urinary tract infections (both complicated and uncomplicated, including pyelonephritis)
Skin and skin structure infections
Septicemia
Empiric treatment in febrile neutropenia.
Culture and susceptibility studies should be performed when appropriate to determine susceptibility of the causative organism(s) to cefepime. Empiric therapy with Cefmex 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, Cefmex can be used as monotherapy prior to identification of the causative organism(s). In patients who are at risk of mixed aerobic-anaerobic infection, particularly if bacteria not susceptible to cefepime may be present, concurrent initial therapy with anti-anaerobic agent is recommended before the causative agents may or may not be necessary, depending on the susceptibility profile.

RECOMMENDED DOSAGE:
Cefepime 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, and the overall condition and renal function of the patient.

Adults
Guidelines for dosage of cefepime for adults with normal renal function are provided in Table 2. Table 2 Recommended dosage schedule for Adults with Normal Renal Function (aged 12 years and older)*

SITE AND TYPE OF INFECTION	DOSE	FREQUENCY
Mild to moderate urinary tract infections (uncomplicated and complicated)	500 mg to 1g IV or IM	q12h
Mild to moderate infections including bronchitis, skin and skin-structure infections	1g IV or IM	q12h
Severe infections including pneumonia, urinary tract infections, complicated intra- abdominal infections, including cases with an associated bacteremia	2g IV	q12h
Empiric treatment of fever in neutropenic patients	2g IV	q8h

* Usual duration of therapy is 7-10 days; more severe infections may require longer treatment. In the treatment of beta-hemolytic streptococcal infections a therapeutic dose must be administered for at least 10 days. For empirical treatment of Febrile neutropenia, usual duration of therapy is 7 days or until resolution of neutropenia.

Pediatrics (aged 1 month up to 12 years with normal renal function)
Pneumonia, urinary tract infections, and skin structure infections: Patients 2 months of age with body weight ≤40 kg: 50 mg/kg q12h for 10 days. For more severe infections, a dosage schedule of q8h can be used.
Empiric treatment of febrile neutropenia: Patients ≥2 months of age with body weight ≤40 kg: 50 mg/kg q8h for 7-10 days.
Experience with the use of cefepime in pediatric patients, 2 months of age is limited. While this experience has been attained using the 50 mg/kg dose, modeling of pharmacokinetic data obtained in patients >2 months of age suggest that a dosage of 30 mg/kg q12h or q8h may be considered for patients aged 1 month up to 2 months. Administration of cefepime in these patients should be carefully monitored.
For pediatric patients with body weight .40 kg, adults dosing recommendations apply (see Table 2). For patients older than 12 years who are ≤40 kg, the dosage recommendations for younger patients ≤40 kg should be used. Dosage in pediatric patients should not exceed the maximum recommended dosage in adults (2g q8h). Experience with intramuscular administration in pediatric patients is limited.

Children with Impaired Renal Function
Since urinary excretion is the primary route of elimination of cefepime in pediatric patients (see PHARMACOKINETICS), an adjustment of the dosage of cefepime should also be considered in patients<12 years of age with renal impairment.

Elderly
Dose adjustment is not required, unless there is concurrent renal impairment.
Impaired Hepatic Function: No adjustment is necessary for patients with impaired hepatic function.
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 3.

TABLE 3 Maintenance dosing schedule in Adults patients with renal impairment*

Creatinine clearance (mL/min)	Recommended Maintenance Dosage			
	Usual dose, no adjustment necessary			
>50	2g q8h	2g q12h	1g q12h	500 mg q12h
30-50	2g q12h	2g q24h	1g q24h	500 mg q24h
11-29	2g q24h	1g q24h	500 mg q24h	500 mg q24h
≤10	1g q24h	500 mg q24h	250 mg q24h	250 mg q24h

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

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

Females: 0,85 x value calculated using the formula for males.

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 time doses recommended for patients with normal renal function, i.e., 500 mg, 1g or 2g depending on infection severity, but at a dosage interval of every 48 hours.

ROUTE OF ADMINISTRATION:
Preparation of solution and Administration
Cefepime powder is to be constituted using the volumes of diluent shown in Table 4; the diluents to be used are identified following this table.

TABLE 4 Preparations of solutions of cefepime.

	Amount of diluent to be added (mL)	Approximate available volume (mL)	Approx. Cefepime concentration (mg/mL)
Intravenous			
500 mg vial	5	5,7	90
1g vial	10	11,4	90
Intra-muscular			
500 mg vial	1,5	2,2	230
1g vial	3,0	4,4	230

Intravenous (IV) 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, constitute cefepime with Sterile Water for Injection, 5% Dextrose Injection or 0.9% Sodium Chloride, using the diluents volumes shown in Table 4. 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 patients is receiving a compatible IV fluid (see Compatibility and Stability).
For intravenous infusion, constitute the 500mg and 1g vial, as noted above for direct IV administration then, add the appropriate quantity of the resulting solution to an IV container with one of the compatible IV fluids identified under.
Compatibility and Stability.
IV infusions of a volume between 50 mL and 100 mL should be administered over a period of approximately 30 minutes.

Intramuscular (IM) administration:
Cefepime should be constituted with one of the following diluents using the volumes shown in Table 4: Sterile Water for Injection, 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or then administered by deep IM injection into a large muscle mass (such as the upper outer quadrant of the gluteus maximus). Although cefepime can be constituted with 0.5% or 1.0% Lidocaine hydrochloride, it is usually not necessary because cefepime causes little or no pain upon IM administration.
Compatibility and Stability
Intravenous: Cefepime is compatible at concentrations between 1 and 40 mg/mL with one of the following IV infusion fluids: Sterile Water for Injection, 5% Dextrose Injection or 0.9% Sodium Chloride. These solutions are stable for 48 hours under refrigeration (2°C to 8°C). Intramuscular: Cefepime constituted as directed (in Table 4) is stable for 48 hours under refrigeration (2°C to 8°C) when using the following diluents: Sterile Water for Injection, 5% Dextrose Injection or 0.9% Sodium Chloride

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 cefepime powder and solution may darken on storage, however, product potency is not adversely affected.

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

WARNING AND PRECAUTIONS:
Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with Cefmex 500 mg Powder for Injection, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, Cefmex 500mg Powder for Injection must be discontinued immediately and appropriate alternative therapy instituted.
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 diarrhea in association with the use of antibiotics. Mild cases of colitis may respond to drug discontinuation alone; moderate to severe cases may require more elaborate management. Use of cefepime may result in overgrowth of non-susceptible organisms. Should super-infection occur during therapy, appropriate measures should be taken.

Renal Impairment
In patient 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 (see RECOMMENDED DOSAGE and PHARMACOKNETICS). Serious adverse events, including encephalopathy, seizures, myoclonus, and/or renal failure, have been reported in post-marketing experience in patients with renal impairment who received unadjusted doses of cefepime. Renal function should be monitored carefully if drugs with nephrotoxic potential, such as aminoglycosides and potent diuretics, are administered with cefepime.

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. Dosage adjustments are recommended if renal function is compromised (see RECOMMENDED DOSAGE AND ROUTE OF ADMINISTRATION).

INTERACTION WITH OTHER MEDICATION:
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.

USE IN PREGNANCY AND LACTATION: Safely of use in pregnancy and lactation has not been established.

SIDE EFFECTS:
Cefepime is generally well tolerated. The most common adverse events were gastrointestinal symptoms and hypersensitivity reactions. The following adverse events occurred most frequent:
Hypersensitivity: Rash, pruritus, urticaria. Gastrointestinal: Diarrhea, nausea, vomiting, oral moniliasis, diarrhea and colitis (including pseudomembranous colitis). Central Nervous System: Headache. Others: Fever, vaginitis and erythema. Events that occurred frequently were abdominal pain, constipation, vasodilation, dyspnea, dizziness, paresthesia, genital pruritus, taste perversion, chills and unspecified moniliasis. Events of clinical significance that occurred less frequent included anaphylaxis and seizure.
Injection Site Reactions: Local reactions eg, phlebitis and inflammation at the site of IV injection occurred. IM administration of Cefepime was very well tolerated: patients experienced inflammation or pain at the injection site. Laboratory Test Abnormalities: Elevations in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, eosinophilia, anemia, thromboctopenia, prolonged prothrombin time or PTT, and positive Coombs'test without hemolysis. Transient elevations of BUN, and/or serum creatinine and transient thrombocytopenia were observed in patient. Transient leukopenia, neutropenia were also seen. During post marketing experience, agranulocytosis has been reported rarely. During post-marketing experience encephalopthy, seizures, myoclonus and/or renal failure have been reported in patients with renal impairment who received unadjusted doses of cefepime. Because of 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 cephalosporins: Urticaria, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage and false-positive tests for urinary glucose.

SYMPTOMS AND TREATMENT OF OVERDOSAGE:
Treatment should be symptomatic and supportive.
In case of severe over dosage, 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 WARNINGS AND PRECAUTIONS).

INCOMPATIBILITIES: Unknown

STORAGE CONDITIONS:

Dry Powder:	Store at room temperature below 30°C and protect from light.
Reconstituted:	See Compatibility and Stability under ROUTE OF ADMINISTRATION. The solutions are stable for 2 days/48 hours under refrigeration (2°C to 8°C).

KEEP OUT OF REACH OF CHILDREN (*Jauhkan daripada kanak-kanak)*

SHELF LIFE:
Please refer to outer package

PACK SIZE:
Cefmex Injection 500 mg (Cefepime for Injection) & Cefmex Injection 1 g (Cefepime for Injection): Pack in 10 vials, 25 vials and 100 vials per box

PRODUCT REGISTRATION HOLDER & MANUFACTURER:
DUOPHARMA (M) SDN BHD
Lot 2599 Jalan Seruling 59 Kawasan 3,
Taman Klang Jaya, 41200 Klang, Selangor Darul Ehsan, MALAYSIA.

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