conclusion of these tests indicated no definitive evidence of genotoxic potential. No untoward effects on fertility or reproduction have been observed in rats, mice and rabbits when cefepime is administered subcutaneously at 1 to 4 times the recommended maximum human dose calculated on a mg/m2 basis.

Usage in Pregnancy
Teratogenic Effects - Pregnancy Category B: Cefepime was not teratogenic or embryocidal when administered during the period of organogenesis to rats at doses up to 1000 mg/kg/day (4 times the recommended maximum human dose calculated on a mg/ m2 basis) or to mice at doses up to 1200 mg/kg (2 times the recommended maximum human dose calculated on a mg/ m2 basis) or to rabbits at a dose level of 100 mg/kg (approximately equal to the recommended maximum human dose calculated on a mg/ m2 basis).
There are, however, no adequate and well-controlled studies of cefepime use 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.
Nursing Mothers
Cefepime is excreted in human breast milk in very low concentrations. Caution should be exercised when cefepime is administered to a nursing women.
Labor and Delivery
Cefepime has not been studied for use during labor and delivery. Treatment should only be given if clearly indicated.
Pediatric Use
The safety and efficacy of cefepime in pediatric patients below the age of 2 months have not been established. This product is intended for use in paediatric patients above 2 months of age.
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. In elderly patients, dosage and administration of cefepime should be adjusted in the presence of renal insufficiency.

Dosage and administration
Cefepime should be administered intravenously over approximately 30 minutes.
The recommended adult dosages and routes of administration are:-

Site & Type Infection	Frequency	Duration (Days)
Moderate to Severe Pneumonia due to S.pneumoniae, P. aeruginosa, K.pneumoniae or Enterobactor species	1 - 2 g IV q12h	10
Empiric therapy for febrile neutropenic patients	2 g IV q8h	7
Mild to Moderate Uncomplicated or Complicated Urinary Tract Infections including pyelonephritis due to E.coli, K. pneumoniae or P. mirabilis	0.5 - 1 g IV/IM q12h	7 - 10
Severe Uncomplicated or Complicated Urinary Tract Infections including pyelonephritis due to E. coli or K.pneumoniae	2 g IV q12h	10
Moderate to Severe Uncomplicated Skin and Skin Structure Infections due to S.aureus or S. pyogenes	2 g IV q12h	10
Complicated Intra-abdominal Infections (used in combination with metronidazole) caused by E. coli, viridans group streptococci, P. aeruginosa, K.pneumoniae, Enterobacter species or B. fragilis.	2 g IV q12h	7 - 10

Impaired Hepatic Function - No adjustment is necessary for patients with impaired hepatic function. Impaired Renal Function - In patients with impaired renal function (creatinine clearance </=60 mL/min), the dose of cefepime should be adjusted to compensate for the slower rate of renal elimination.

Administration
Preparation and administration of the reconstituted solution:
Cefepime for Injection, powder for solution for injection/infusion should be dissolved in:
a) water for injections
or in one of the solutions listed in b) below for intravenous administration
b) sodium chloride 0.9% solution
sodium chloride 0.9% with glucose 5% solution
glucose 5% or 10% solution
Ringer lactate solution
Ringer lactate with glucose 5% solution
sodium lactate 1/6 M solution.
For Intravenous Injection, the volume of the solvent to be added to each vial and the resulting concentration of cefepime are presented in the following table:

Cefepime content per vial	Diluent to be added (mL)	Approximate Available Volume (mL)	Approximate Cefepime Concentration (mg/mL)
500.00 mg I.V.	5.0	5.6	100
1.00 g I.V.	10.0	10.5	100
2.00 g I.V.	10.0	12.5	160

For Intravenous Infusion, the volume of the solvent for infusion (solution listed in b)) to be used for reconstitution and the resulting concentration of cefepime are presented in the following table:

Cefepime content per vial	Diluent to be added (mL)	Approximate Available Volume (mL)	Approximate Cefepime Concentration (mg/mL)
1.0 g I.V.	50.0	51.4	19
2.0 g I.V.	50.0	52.8	38

The resulting solution should be administered over approximately 30 minutes.

For Intramuscular Injection, reconstitute the 1 g vial by using 3.0 ml of water for injections.
Note:
The reconstituted solutions, which are prepared correctly, can represent a pale yellow to amber color. This does not mean that efficacy of Cefepime for Injection may be compromised.
The content of the vial is meant for a single usage. The remaining reconstituted solution should be discarded.
Inspect the vial before using. It can only be used if the solution does not present particles.

Overdosage
Patients who receive an overdose should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis, not peritoneal dialysis, is recommended to aid in the removal of cefepime from the body. The patient exhibited seizures, encephalopathy and neuromuscular excitability.

NOTE: PARENTERAL DRUGS SHOULD BE INSPECTED VISUALLY FOR PARTICULATE MATTER BEFORE ADMINISTRATION.
As with other cephalosporins, the color of cefepime powder, as well as its solutions, tend to darken depending on storage conditions; however, when stored as recommended, the product potency is not adversely affected.

Storage
Store below 30°C, protected from light.

Presentation
IVIPIME 1g is available in a vial in a carton.
IVIPIME 500mg is available in a vial in a carton.

® Registered Trademark

Manufactured in India by :
VHB MEDI SCIENCES LIMITED
Plot No. 20-22 and 49-51, IIE, Sector-5, Sidcul, Pantnagar, Udhamsingh Nagar - 263 145, Uttarakhand, INDIA.

VP338.1.AA

For the use of a Registered Medical Practitioner or Hospital or Laboratory only

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CEFEPIME FOR INJECTION USP

IVIPIME®

Composition
IVIPIME 1g
Each vial contains:
Cefepime Hydrochloride USP equivalent to Cefepime ..... 1 g
Excipient: L-Arginine

IVIPIME 500 mg
Each vial contains:
Cefepime Hydrochloride USP equivalent to Cefepime ..... 500 mg
Excipient: L-Arginine

Description
Cefepime hydrochloride is a semi-synthetic, broad spectrum, cephalosporin antibiotic for parenteral administration. The chemical name is 1-[[(6R, 7R)- 7 -[2-(2-amino-4-thiazolyl) -glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0] oct-2-en-3-yl]methyl]- 1-mathylpyrrolidinium chloride, 72-(Z)-(O- methyloxime), monohydrochloride monohydrale.
Cefepime is a sterile, dry mixture of cefepime hydrochloride and L-arginine. The L-arginine, at an approximate concentration of 725mg/g of cefepime is added to control the pH of the constituted solution at 4.0-6.0.

Pharmacokinetics
The average plasma concentrations of cefepime observed in healthy adult male volunteers at various times following single 30-minute infusion (IV) of cefepime 500mg and 1g are summarized as: -

Parameters (Time in hr. after administration)	Cefepime 500 mg I.V.	Cefepime 1g I.V.
0.5 hr.	38.2	78.7
1 hr.	21.6	44.5
2 hr.	11.6	24.3
4 hr.	5.0	10.5
8 hr.	1.4	2.4
12 hr.	0.2	0.6
C max (mcg/ml)	39.1	81.7
AUC (mcg/hr/ml)	70.8	148.5

Absorption
Following intramuscular (IM) administration, cefepime is completely absorbed. The average plasma concentrations of cefepime at various times following a single IM injection are summarized as: -

Parameters (Time in hr. after administration)	Cefepime 500 mg I.M.	Cefepime 1g I.M.
0.5 hr.	8.2	14.8
1 hr.	12.5	25.9
2 hr.	12.0	26.3
4 hr.	6.9	16.0
8 hr.	1.9	4.5
12 hr.	0.7	1.4
C max (mcg/ml)	13.9	29.6
T max (hr.)	1.4	1.6
AUC (mcg/hr/ml)	60.0	137.0

Distribution
The average steady state volume of distribution of cefepime is 18.0(+_2.0) L.
The serum protein binding of cefepime is approximately 20% & is independent of its conc. in serum.
Average concentrations of cefepime in specific body fluids (mcg /ml) and in specific tissues (mcg/ g)

Metabolism and Excretion
Cefepime is metabolized to N-methylpyrrolidine (NMP) which is rapidly converted to the N-oxide (NMP-N-oxide). Urinary recovery of unchanged cefepime accounts for approximately 85% of the administered dose. Less than 1% of the administered dose is recovered from urine as NMP, 6.8% as NMP-N-oxide and 2.5% as an epimer of cefepime. Since renal excretion is a significant pathway of elimination, patients with renal dysfunction and patients undergoing hemodialysis require dosage adjustment.

Pharmacokinetics in special population
Geriatric patients
Cefepime pharmacokinetics have been investigated in elderly (65 years of age and older) men and women whose creatinine clearance was 74.0 (15.0) mL/ min. There appeared to be a decrease in cefepime total body clearance as a function of creatinine clearance. Therefore, dosage administration of cefepime in the elderly should be adjusted as appropriate if the patient's creatinine clearance is 60 mL/min or less.
Renal insufficiency: Cefepime pharmacokinetics have been investigated in patients with various degrees of renal insufficiency. The average half-life in patients requiring hemodialysis was 13.5 (2.7) hours and in patients requiring continuous peritoneal dialysis was 19.0 (2.0) hours. Cefepime total body clearance decreased proportionally with creatinine clearance in patients with abnormal renal function which serves as the basis for dosage adjustment recommendations in this group of patients.

Hepatic insufficiency: The pharmacokinetics of cefepime were unaltered in patients with impaired hepatic function who received a single 1 g dose.

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: -
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)
NOTE: Most strains of enterococci, e,g. Enterococcus faecalis and methicillin-resistant Staphylococci are resistant to cefepime. Cefepime is inactive against most strains of Clostridium difficile.

Indications
Cefepime is indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms: -
Pneumonia (moderate to severe) caused by Streptococcus pneumoniae, including cases associated with concurrent bacteremia, Pseudomonas aeruginosa, Klebsiella pneumoniae or Enterobacter species.
Empiric Therapy for Febrile Neutropenic Patients: Cefepime as monotherapy is indicated for empiric treatment of febrile neutropenic patients. 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 hematologic 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.
Uncomplicated and Complicated Urinary Tract Infections (including pyelonephritis) caused by Escherichia coli or Klebsiella pneumoniae when the infection is severe or caused by Escherichia coli, Klebsiella pneumoniae or Proteus mirabilis when the infection is mild to moderate; including cases associated with concurrent becteremia with these microorganisms.
Uncomplicated Skin and Skin Structure Infections caused by Staphylococcus aureus (methicillin-susceptible strains only) or Streptococcus pyogenes.
Complicated Intra-abdominal Infections (used in combination with metronidazole) caused by Escherichia coli, Streptococcus viridans, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter species or Bacteroides fragilis.

Contraindications
Cefepime is contraindicated in patients who have shown immediate hypersensitivity reactions to cefepime or the cephalosporin class of antibiotics, penicillins or other betalactam antibiotics.

Adverse Reactions
Dose 1 g 12 hrly

Adverse Reactions	Incidence
Local Reactions	3.0%
Phlebitis	1.3%
Rash	1.1%
Pain & Inflammation	0.6%
Colitis, Diarrhea, Fever, Nausea, Headache, Oral moniliasis, Pruritus, Urticaria, Vaginitis, Vomiting	> 0.1% to less than 1%

Dose 2 g 12 hrly

Adverse Reactions	Incidence
Rash	4%
Diarrhea	3%
Nausea	2%
Vomiting, Pruritus, Fever, Headache	1% Each

Adverse Laboratory Changes Cefepime Multiple-Dose Dosing

Laboratory Changes	Incidence
Positive Coombs' test (without hemolysis)	16.2%
Decreased phosphorous	2.8%
Increased ALT (SGPT)	2.8%
Increased AST (SGOT)	2.4%
Eosinophilia	1.7%
Abnormal PTT	1.6%
PT	1.4%
Increased alkaline phosphatase, BUN, calcium, creatinine, phosphorous, potassium, total bilirubin, decreased calcium, hematocrit, neutrophils, platelets, WBC	>0.1% to <1.0%

Cephalosporin-class adverse reactions
In addition to the adverse reactions listed above that have been observed in patients treated with cefepime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics: -
Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic dysfunction including cholestasis and pancytopenia.

Drug-drug/ Drug-Laboratory Test Interactions
Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with cefepime because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide.
The administration of cefepime may result in a false-positive reaction for glucose in the urine when using Clinitest® tablets. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes-Tape®) be used.

WARNINGS
BEFORE THERAPY WITH CEFEPIME FOR INJECTION IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS IMMEDIATE HYPERSENSITIVITY REACTIONS TO CEFEPIME, CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFEPIME OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES INCLUDING OXYGEN, CORTICOSTEROIDS, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, PRESSOR AMINES AND AIRWAY MANAGEMENT AS CLINICALLY INDICATED.
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefepime and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Precautions
General
As with other antimicrobials, prolonged use of cefepime may result in overgrowth of nonsusceptible microorganisms. Repeated evaluation of the patient's condition is essential. Should superinfection occur during therapy, appropriate measures should be taken.

Many cephalosporins, including cefepime, have been associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.
Positive direct Coombs' test have been reported during treatment with cefepime. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.
Cefepime should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
In patients with impaired renal function (creatinine clearance </=60 mL/min), the dose 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 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. Serious adverse events including encephalopathy, myoclonus, seizures, and/or renal failure have been reported postmarketing in patients with renal impairment treated with unadjusted doses of cefepime. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms.

Carcinogenesis, Mutagenesis and Impairment of Fertility
No long-term animal carcinogenicity studies have been conducted with cefepime. A battery of in vivo and in vitro genetic toxicity tests, including the Ames Salmonella reverse mutation assay, CHO/HGPRT mammalian cell forward gene mutation assay, chromosomal aberration and sister chromatid exchange assays in human lymphocytes, CHO fibroblast clastogenesis assay and cytogenetic and micronucleus assays in mice were conducted. The overall