Maxum™
(Cefepime)

Highnoon

COMPOSITION
Maxum 500mg IM/IV injection: Each pack contains:
Vial: Cefepime (as Hydrochloride) 500mg
(with L-Arginine)
Ampoule: Sterile water for injection USP 5mL
Maxum 1g IM/IV injection: Each pack contains:
Vial: Cefepime (as Hydrochloride) 1g
(with L-Arginine)
Ampoule: Sterile water for injection USP 10mL
Maxum 2g IV injection: Each pack contains:
Vial: Cefepime (as Hydrochloride) 2g
(with L-Arginine)
Ampoule: Sterile water for injection USP 10mL

DESCRIPTION
Maxum (Cefepime) Injection is sterile, injectable product consisting of Cefepime Hydrochloride, a semi-synthetic, broad spectrum, cephalosporin antibiotic for parenteral administration.

PHARMACOLOGY
Maxum (Cefepime) is an antibacterial agent belonging to the cephalosporin class of antibacterials with in vitro antibacterial activity against facultative Gram-positive andGram-negative bacteria.
Mechanism of action
Maxum (Cefepime) is an antibacterial drug similar to other beta-lactam antimicrobial agents, the time that the unbound plasma concentration of cefepime exceeds the MIC of the infecting organism has been shown to best correlate with efficacy in animal models of infection.
However, the pharmacokinetic/pharmacodynamic relationship for cefepime has not been evaluated in patients.

PHARMACOKINETICS
Cefepime is given by injection as the hydrochloride. It is rapidly and almost completely absorbed on intramuscular injection and mean plasma concentration of about 14 and 30 micrograms/mL occur about 1.5 hours after doses of 500mg and 1gm respectively. Within 30 minutes of similar intravenous doses, peak plasma concentrations are 40 and 80 microgram/mL respectively. The plasma half-life of Cefepime is about 2 hours and prolonged in patients with renal impairment. About 20% of Cefepime is bound to plasma proteins.
Cefepime is widely distributed in the body tissues and fluids. High concentrations occur in bile. Low concentrations have been detected in plasma breast milk. Cefepime is eliminated principally by the kidneys and about 85% of dose is recovered unchanged in the urine. Cefepime is substantially removed by hemodialysis.

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 isolates of the following microorganisms;

Gram-Negative Bacteria:
Enterobacter
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

Gram-Positive Bacteria:
Staphylococcus aureus (methicillin-susceptible isolates only)
Streptococcus pneumoniae
Streptococcus pyogenes (Lancefield's Group A streptococci)
Viridans group streptococci
The Cefepime has been shown to have in vitro activity against most isolates of the following microorganisms; however, the safety and effectiveness of cefepime in treating clinical infections due to these microorganisms have not been established.

Gram-Positive Bacteria:
Staphylococcus epidermidis (methicillin-susceptible isolates only)
Staphylococcus saprophyticus
Streptococcus agalactiae (Lancefield's Group B streptococci)

NOTE: Most isolates of enterococci, e.g., Enterococcus faecalis, and methicillin- resistant staphylococci are resistant to cefepime.

Gram-Negative Bacteria:
Acinetobacter calcoaceticus subsp. lwoffii
Citrobacter diversus
Citrobacter freundii
Enterobacter agglomerans
Haemophilus influenzae (including beta-lactamase producing isolates)
Hafnia alvei
Klebsiella oxytoca Moraxella catarrhalis (including beta-lactamase producing isolates)
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

NOTE: Cefepime is inactive against many isolates of Stenotrophomonas malyophilia.

INDICATIONS AND USAGE
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Maxum (Cefepime) Injection and other antibacterial drugs, Cefepime Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. It is used in the following conditions;

- It is indicated for pneumonia (moderate to severe) caused by Streptococcus pneumoniae, including cases associated with concurrent bacteremia, Pseudomonas aeruginosa, Klebsiella pneumoniae, or Enterobacter species
- 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.
- It is indicated for 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 bacteremia with these bacteria.
- It is indicated for uncomplicated skin and skin structure infections caused by Staphylococcus aureus (methicillin-susceptible isolates only) or Streptococcus pyogenes.
- It is indicated for complicated intra-abdominal infections (used in combination with metronidazole) caused by Escherichia coli, viridans group streptococci, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter species, or Bacteroides fragilis.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefepime and other antibacterial drugs, it should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

DOSAGE AND ADMINISTRATION
Adults and Pediatric Population:
The recommended adult and pediatric dosages and routes of administration are outlined below. It should be administered intravenously over approximately 30 minutes.
Recommended Dosage Schedule for Cefepime Injection in Patients with CrCL Greater Than 60 mL/min

Site and Type of Infection	Dose	Frequency	Duration (days)
Adults Moderate to Severe Pneumonia	1-2 g I.V.	Every 12 hours	10
Empiric therapy for febrile neutropenic patients	2 g I.V.	Every 8 hours	7
Mild to Moderate Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis	0.5-1 g I.V. / I.M.	Every 12 hours	7-10
Severe Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis	2 g I.V.	Every 12 hours	10
Moderate to Severe Uncomplicated Skin and Skin Structure Infections	2 g I.V.	Every 12 hours	10
Complicated Intra-abdominal Infections (used in combination with metronidazole)	2 g I.V.	Every 12 hours	7-10

Pediatric Patients (2 months up to 16 years):
The maximum dose for pediatric patients should not exceed the recommended adult dose. The usual recommended adult dose. The usual recommended dosage in pediatric patients up to 40 kg in weight for durations as given above for adults is:

- 50 mg per kg per dose, administered every 12 hours for uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, and pneumonia (see below).
- For moderate to severe pneumonia due to P. aeruginosa give 50 mg per kg per dose, every 8 hours.
- 50 mg per kg per dose, every 8 hours for febrile neutropenic patients.

Patients with Hepatic Impairment:
No adjustment is necessary for patients with hepatic impairment.

Patients with Renal Impairment:
In patients with creatinine clearance less than or equal to 60 mL/min, the dose of Cefepime Injection should be adjusted to compensate for the slower rate of renal elimination. The recommended initial dose of Cefepime Injection should be the same as in patients with CrCL greater than 60 mL/Min except in patients undergoing hemodialysis. The recommended doses of Maxum Injection in patients with renal impairment are;
Recommended Dosing Schedule for Cefepime Injection in Adult Patients (Normal Renal Function, Renal Impairment, and Hemodialysis)

Creatinine Clearance (Ml/min)	Recommended Maintenance Schedule			
Greater than 60	500 mg every 12 hours	1 g every 12 hours	2 g every 12 hours	2 g every 8 hours
30–60	500 mg every 24 hours	1 g every 24 hours	2 g every 24 hours	2 g every 12 hours
11–29	500 mg every 24 hours	500 mg every 24 hours	1 g every 24 hours	2 g every 24 hours
Less than 11	250 mg every 24 hours	250 mg every 24 hours	500 mg every 24 hours	1 g every 24 hours
Continuous Ambulatory Peritoneal Dialysis (CAPD)	500 mg every 48 hours	1 g every 48 hours	2 g every 48 hours	2 g every 48 hours
Hemodialysis	1 g on day 1	500 mg every 24 hours		1 g every 24 hours

In patients undergoing continuous ambulatory peritoneal dialysis, it may be administered at normally recommended doses at a dosage interval of every 48 hours.
The dosage for hemodialysis patients is 1 g on Day 1 followed by 500 mg every 24 hours for the treatment of all infections except febrile neutropenia, which is 1 g every 24 hours.
It should be administered intravenously over approximately 30 minutes.
Intermittent intravenous infusion with a Y-type administration set can be accomplished with compatible solutions. However, during infusion of Cefepime injection, it is desirable to discontinue the other solution. Solutions of cefepime, like those of most beta-lactam antibiotics, should not be added to solutions of ampicillin at a concentration greater than 40 mg per mL, and should not be added to metronidazole, vancomycin, gentamicin, tobramycin, netilmicin sulfate or aminophylline because of potential interaction. However, if concurrent therapy with cefepime is indicated, each of these antibiotics can be administered separately.

CONTRAINDICATIONS
It is contraindicated in patients who have shown immediate hypersensitivity reactions to cefepime or the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics.
Solutions containing dextrose may be contraindicated in patients with known allergy to corn or corn products.

WARNINGS AND PRECAUTIONS

- 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 beta- lactams. Exercise caution if this product is to be given to penicillin-sensitive patients because cross-hypersensitivity among beta-lactam antibacterial drugs 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 and institute appropriate supportive measures.
- Serious adverse reactions have been reported including life-threatening or fatal occurrences of the following: encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), aphasia, myoclonus, seizures, and non-convulsive status epilepticus. Most cases occurred in patients with renal impairment who did not receive appropriate dosage adjustment. However, some cases of neurotoxicity occurred in patients receiving a dosage adjustment appropriate for their degree of renal impairment. In the majority of cases, symptoms of neurotoxicity were reversible and resolved after discontinuation of cefepime and/or after hemodialysis. If neurotoxicity associated with cefepime therapy occurs, discontinue cefepime and institute appropriate supportive measures.
- Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Cefepime Injection, and may range in severity from mild diarrhea to fatal colitis. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. 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. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.
  Prescribing cefepime in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
- As with other antimicrobials, prolonged use of it 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.
- *Urinary Glucose:* The administration of cefepime may result in a false-positive reaction for glucose in the urine when using some methods (e.g. Clinitest tablets). Coombs' Test: Positive direct Coombs' tests have been reported during treatment with Cefepime. In patients who develop hemolytic anemia, discontinue the drug and institute appropriate therapy. Positive Coombs' test may be observed in newborns whose mothers have received cephalosporin antibiotics before parturition
- *Prothrombin Time:* Many cephalosporins, including cefepime, have been associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, 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.

ADVERSE REACTIONS
The reported adverse events are; hypersensitivity reaction, neurotoxicity, clostridium difficile associated diarrhea, rash, local reactions including phlebitis, pain, inflammation, Colitis (including pseudomembranous colitis), diarrhea, fever, headache, nausea, oral moniliasis, pruritus, urticaria, vomiting, vaginitis, positive Coombs' test, decreased phosphorus, increased ALT/SGPT, AST/SGOT, eosinophils, abnormal PTT, Increased alkaline phosphatase, BUN, calcium, creatinine, phosphorus, potassium, total bilirubin; decreased calcium, hematocrit, neutrophils, platelets, WBC and hypocalcemia
The additional reported adverse events are Encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor and coma), aphasia, myoclonus, seizures, nonconvulsive status epilepticus, If neurotoxicity associated with cefepime therapy occurs, consider discontinuing it or making appropriate dosage adjustments in patients with renal impairment. As with other cephalosporins, anaphylaxis including anaphylactic shock, transient leukopenia, neutropenia, agranulocytosis, thrombocytopenia, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal impairment, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic impairmentincludingcholestasis, andpancytopenia have been reported.

DRUG INTERACTIONS

- Drug/Laboratory Test Interactions; The administration of cefepime may result in a false-positive reaction for glucose in the urine with certain methods, It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.
- Aminoglycosides; Monitor renal function if aminoglycosides are to be administered with Cefepime because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibacterial drugs.
- Diuretics; Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide. Monitor renal function when cefepime is concomitantly administered with potent diuretics.

USE IN SPECIFIC POPULATIONS
Pregnancy (Pregnancy Category B):
There are no adequate and well-controlled studies of cefepime use in pregnant women. this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:
Cefepime is excreted in human breast milk. Caution should be exercised when Cefepime Injection is administered to a nursing woman.

Pediatric Use:
The safety and effectiveness of cefepime in the treatment of uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, pneumonia, and as empiric therapy for febrile neutropenic patients have been established in the age groups 2 months up to 16 years. Safety and effectiveness in pediatric patients below the age of 2 months have not been established.

Geriatric Use:
This drug 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.

Renal Impairment:
Adjust the dose of Cefepime in patients with creatinine clearance less than or equal to 60 mL/min to compensate for the slower rate of renal elimination.

PREPARATION OF MAXUM (CEFEPIME) FOR INTRAVENOUS INFUSION
Vials:
Constitute the 0.5 gram, 1 gram, or 2 grams vial, of Maxum (Cefepime) with the one of the following diluents:

- Sterile Water for Injection
- 0.9% Sodium Chloride Injection
- 5% Dextrose Injection
- 0.5% or 1% Lidocaine Hydrochloride Injection
- Sterile Bacteriostatic Water for Injection with Parabens or Benzyl Alcohol

Dilute the reconstituted solution with one of the following compatible infusion solutions prior to intravenous infusion (Refer to Table below for the amount of diluent to be added to each vial and the amount of the reconstituted solution to be withdrawn):

- 0.9% Sodium Chloride Injection
- 5% and 10% Dextrose Injection
- M/6 Sodium Lactate Injection
- 5% Dextrose and 0.9% sodium Chloride Injection
- Lactated Rings and 5% Dextrose Injection
- Normosol-R and Normosol-M in 5% Dextrose Injection

Parenteral drugs should be inspected visually for particulate matter before administration. If particulate matter is evident in reconstituted fluids, the drug solution should be discarded. Administer the resulting intravenous infusion over approximately 30 minutes. Intermittent intravenous infusion with a Y-type administration set can be accomplished with compatible solutions. However, during infusion of a solution containing cefepime, it is desirable to discontinue the other solution.
Constitute only with 50 mL or 100 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection in ADD-Vantage flexible diluent containers for reconstitution

Preparation for Intramuscular Administration:
Constitute Maxum (Cefepime) vials 0.5 gram, 1 gram and 2 grams with one of the following diluents:
Sterile Water for Injection,

- 0.9% Sodium Chloride,
- 5% Dextrose Injection,
- 0.5% or 1% Lidocaine Hydrochloride, or
- Sterile Bacteriostatic Water for Injection with Parabens or Benzyl Alcohol.

Refer to Table below for the amount of diluent to be added to each vial and the amount of reconstituted volume to be withdrawn. Parenteral drugs should be inspected visually for particulate matter before administration. If particulate matter is evident in reconstituted fluids, the drug solution should be discarded.
Preparation of Reconstituted Solutions of Maxum (Cefepime) for Injection:

Single-Dose Vials for Intravenous (I.V.) / Intramuscular (I.M.) Administration	Amount of Diluent to be added (mL)	Approximate Cefepime Concentration (mg/mL)	Amount of Reconstituted Volume to be Withdrawn (mL)
Cefepime vial content			
500 mg (I.V.)	5	100	5
500 mg (I.M.)	1.3	280	1.8
1 g (I.V.)	10	100	10.5
1 g (I.M.)	2.4	280	3.6
2 g (I.V.)	10	160	12.5

Do not add solutions of Maxum (Cefepime), to solutions of ampicillin at a concentration greater than 40 mg per mL, or to metronidazole, vancomycin, gentamicin, tobramycin, netilmicin sulfate, or aminophylline because of potential interaction. However, if concurrent therapy with Maxum (Cefepime) is indicated, each of these antibiotics can be administered separately.

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

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION
Maxum is supplied in the following dosage forms, strengths and pack sizes:
Maxum 500mg IM/IV Injection:
1 vial of 500mg Cefepime and 1 ampoule of 5mL sterile water for injection

Maxum 1g IM/IV Injection:
1 vial of 1g Cefepime and 1 ampoule of 10mL sterile water for injection

Maxum 2g IV Injection:
1 vial of 2g Cefepime and 1 ampoule of 10mL sterile water for injection

میکسم™
(سیفی پائم)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

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Plot No. 517, Sundar Industrial Estate,
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17.5 KM, Multan Road, Lahore, Pakistan.
www.highnoon-labs.com

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