NUXIPIM Injection
(C e f e p i m e)

نیوکسیپم انجکشن
(سیفیپائم)

DESCRIPTION:
NUXIPIM (cefepime hydrochloride, USP) is a semi-synthetic, cephalosporin antibacterial 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-methylpyrrolidinium chloride,72 -(Z)-(Omethyloxime), monohydrochloride, monohydrate. Cefepime hydrochloride is a white to pale yellow powder. Cefepime hydrochloride contains the equivalent of not less than 825 mcg and not more than 911 mcg of cefepime ($C_{19}H_{24}N_6O_5S_2$) per mg, calculated on an anhydrous basis. And molecular weight is 480.56 g/mol., freshly constituted solutions of NUXIPIM will range in color from pale yellow to amber.

COMPOSITION:
Each Nuxipim 500mg vial contains:
Cefepime .....500mg with Sterile Arginine
as Cefepime Hydrochloride U.S.P.
(Product Specs.: U.S.P.)

Each Nuxipim 1g vial contains:
Cefepime .....1000mg with Sterile Arginine
as Cefepime Hydrochloride U.S.P.
(Product Specs.: U.S.P.)

CLINICAL PHARMACOLOGY:
Pharmacodynamic Properties:
Pharmacotherapeutic group: Antibacterials for systemic use. Other beta-lactam antibacterials. Fourth-generation cephalosporins, ATC code: J01DE01

Mechanism Of Action:
Cefepime is a broad-spectrum, bactericidal antibiotic, with activity against a wide range of Gram-positive and Gram-negative bacteria, including many strains resistant to aminoglycosides or third generation cephalosporins.
It is highly resistant to hydrolysis caused by most beta-lactamases. It has a reduced affinity for beta-lactamases changed via chromosomes and has a rapid penetration in the cells of the Gram-negative bacteria.

Microbiology:
Gram-Positive Bacteria:
- Staphylococcus aureus
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Viridans group streptococci
- Staphylococcus epidermidis
- Staphylococcus saprophyticus
- Streptococcus agalactiae

Gram-Negative Bacteria:
- Enterobacter spp.
- Escherichia coli
- Klebsiella pneumoniae
- Proteus mirabilis
- Pseudomonas aeruginosa
- Acinetobacter calcoaceticus
- Citrobacter diversus
- Citrobacter freundii
- Enterobacter agglomerans
- Haemophilus influenzae
- Hafnia alvei
- Klebsiella oxytoca
- Moraxella catarrhalis
- Morganella morganii
- Proteus vulgaris
- Providencia rettgeri
- Providencia stuartii
- Serratia marcescens

Pharmacokinetic Properties
Absorption:
Following intramuscular (IM) administration, cefepime is completely absorbed.

Distribution:
The average steady-state volume of distribution of cefepime is 18 (±2) L. The serum protein binding of cefepime is approximately 20% and is independent of its concentration in serum.

Metabolism:
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. Because renal excretion

is a significant pathway of elimination, patients with renal dysfunction and patients undergoing hemodialysis require dosage adjustment

Elimination:

The elimination average half-life of cefepime is about 2 hours, and is independent of the dose for the range of 250 mg to 2 g. The total body clearance is 120 ml/min. The average renal clearance of cefepime is 110 ml/min, suggesting an elimination almost exclusively via the kidneys, mainly by glomerular filtration.

Specific Populations

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 (±2) hours. Cefepime total body clearance decreased proportionally with creatinine clearance in patients with abnormal renal function.

Hepatic Insufficiency

The pharmacokinetics of cefepime were unaltered in patients with hepatic impairment who received a single 1 g dose.

Pediatrics:

Cefepime pharmacokinetics have been evaluated in pediatric patients from 2 months to 11 years of age following single and multiple doses on every 8 hours and every 12 hours schedules. Following a single intravenous dose, total body clearance and the steady-state volume of distribution averaged 3.3 (±1) mL/min/kg and 0.3 (±0.1) L/kg. The urinary recovery of unchanged cefepime was 60.4 (±30.4)% of the administered dose, and the average renal clearance was 2 (±1.1) mL/min/kg.

Elderly:

In elderly (65 years of age and older) whose mean (SD) creatinine clearance was 74 (±15) 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.

THERAPEUTIC INDICATIONS:

NUXIPIM is indicated in the treatment of infections caused by bacteria that are cefepime-sensitive:

- Lower respiratory tract infections, including nosocomial pneumonia and community acquired pneumonia, acute bacterial exacerbation of chronic bronchitis and secondary bacterial infection of acute bronchitis;
- Uncomplicated and complicated urinary tract infections, including pyelonephritis;
- Skin and subcutaneous infections;
- Intra-abdominal infections, including peritonitis and biliary tract infections;
- Gynaecological infections;
- Bacterial meningitis in infants and children;
- In combination with other antibacterial agents in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection;
- Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

DOSAGE AND ADMINISTRATION:

Adults and children weighing > 40 kg with normal renal function:

Severity of the infection	Dosage and route of administration	Interval between the doses
Mild to moderate urinary tract infections (UTI)	500 mg to 1 g IV or IM	every 12 h
Other mild to moderate infections (non UTI)	1 g IV or IM	every 12 h
Severe infections	2 g IV	every 12 h
Very severe or life-threatening infections	2 g IV	every 8 h

In patients weighing ≤ 40 kg, the posology indicated for the children is recommended.

Adults with renal insufficiency:

The cefepime dose should be adjusted to compensate the slower renal elimination rate. In adult patients with mild to moderate renal insufficiency, the initial dose of cefepime recommended should be the same as for patients with normal renal function.

Creatinine clearance (ml/min)	Recommended maintenance dose			
> 50	Usual dose, no dose adjustment is required			
	2 g, 3x day 2x day	2 g, 2x day	1 g, 2x day	500 mg,
30 to 50	2 g, 2x day	2 g, 1x day	1 g, 1x day	500 mg, 1xday
11 to 29	2 g, 1x day	1 g, 1x day	500 mg, 1xday	500 mg, 1xday
< 10	1 g, 1x day	500 mg, 1xday	250 mg, 1xday	250 mg, 1xday
Haemodialysis	500 mg, 1xday	500 mg, 1xday	500 mg, 1xday	500 mg, 1xday

Patients on dialysis:

About 68% of the total quantity of cefepime present in the body in the beginning of the dialysis will be removed during a 3 hour dialysis. In the patient doing continuous ambulatory peritoneal dialysis, cefepime can be administered in the same dosages that are recommended for the patients with normal renal function, i.e. 500 mg, 1 g or 2 g, depending on the severity of the infection, but with an interval of 48 hours between doses.

Elderly:

No dose adjustment is required in patients with normal renal function; the dose adjustment is recommended in patients with impaired renal function.

Children with normal renal function

- *Pneumonia, urinary tract infection, skin and subcutaneous tissue infection:*
  Children aged more than 2 months and weighing ≤ 40 kg: 50 mg/kg every 12 hours in more severe infections, 8 hours interval between the intakes should be done.
- *Bacteraemia that occurs in association with infections, bacterial meningitis and empirical treatment of febrile neutropenia:*
  Children aged more than 2 months and weighing ≤ 40 kg: 50 mg/kg every 8 hours.
  The experience in children aged less than 2 months is limited. In children from 1 month to 2 months old, a dose of 30 mg/kg every 12 or 8 hours can be considered. The administration of NUXIPIM in these patients should be carefully monitored.

In the child weighing > 40 kg, it is recommended to use the dose indicated for adults. The maximum recommended dose for adults (2 g every 8 hours) should not be exceeded. The experience with the intramuscular use in children is limited.

Children with renal insufficiency:
The dose should be adjusted in children with renal insufficiency. A dose of 50 mg/kg in children from 2 months to 12 year old and a dose 30 mg/kg in children 1 month to 2 months are comparable to a 2 g dose in the adult.

Method of Administration:
NUXIPIM can be administered via intravenous use or intramuscular use. The usual dose and the route of administration vary in accordance with the severity of the infection, the renal function and the general conditions of the patient. The IV route of administration is preferable in the patients with severe infections or in a life-threatening situation, particularly if there is the possibility of shock.

CONTRAINDICATIONS:
NUXIPIM is contraindicated in patients who have shown immediate hypersensitivity reactions to cefepime or the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics.

WARNINGS AND PRECAUTIONS:
Hypersensitivity Reactions
Before therapy with NUXIPIM 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 NUXIPIM occurs, discontinue the drug and institute appropriate supportive measures.

Neurotoxicity
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 nonconvulsive status epilepticus. Most cases occurred in patients with renal impairment who did not receive appropriate dosage adjustment. 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
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including NUXIPIM, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. 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 antibacterial drug 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, discontinue cefepime and appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

Development of Drug-Resistant Bacteria
Prescribing NUXIPIM in the absence of a proven or strongly suspected bacterial infection increases the risk of the development of drug-resistant bacteria. As with other antimicrobials, prolonged use of NUXIPIM may result in overgrowth of nonsusceptible microorganisms. Repeated evaluation of the patient's condition is essential. If super infection occur during therapy, appropriate measures should be taken.

Drug/Laboratory Test Interactions
Urinary Glucose
The administration of cefepime may result in a false-positive reaction for glucose in the urine when using some methods. It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

Coombs' Tests
Positive direct Coombs' tests have been reported during treatment with NUXIPIM. 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.

DRUG INTERACTIONS:
Aminoglycosides
Monitor renal function if aminoglycosides are to be administered with NUXIPIM 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.

ADVERSE EFFECTS:
Very Common: Positive Coombs test

Uncommon: Oral candidiasis, vaginal infection, thrombocytopenia, leukopenia, neutropenia, headaches, pseudomembranous colitis, colitis, nausea, vomiting, erythema, urticaria, pruritus, blood urea increased, blood creatinine increased, pyrexia, infusion site inflammation.

Common: Anaemia, eosinophilia, phlebitis at the infusion site, diarrhoea, skin rash, infusion site reaction, injection site inflammation and pain, alkaline phosphatase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, prothrombin time prolonged, partial thromboplastin time prolonged

Rare: Candidiasis, anaphylactic reaction, angioedema, convulsions, paraesthesia, digeusia, dizziness, vasodilatation, dyspnoea, abdominal pain, constipation, genital pruritus, chills

Not Known: Aplastic anaemia, haemolytic anaemia, agranulocytosis, anaphylactic shock, state of confusion, hallucination, coma, stupor, encephalopathy, altered state of conscience, myoclonus, haemorrhage, gastrointestinal disorder, toxic epidermal necrolysis, stevens-johnson syndrome, erythema multiforme, renal failure, toxic nephropathy, false positive glycosuria

USE IN PREGNANCY AND LACTATION:
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.

Lactation:
Cefepime is excreted in human breast milk. Caution should be exercised when cefepime is administered to a nursing woman.

OVERDOSE:
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.

RECONSTITUTION:
For Intravenous injection:
For 0.5 g Intravenous Injection 5 ml of the volume of the solvent to be added to each vial of cefepime.
For 1 g Intravenous Injection 10 ml of the volume of the solvent to be added to each vial of cefepime.

For Intravenous infusion:
For 1 g Intravenous Infusion 50 ml of the volume of the solvent for infusion to be used for reconstitution.
The resulting solution should be administered over approximately 30 minutes.

For Intramuscular injection:
For 0.5 g Intramuscular Injection 1.5 ml of the volume of the solvent to be added to each vial of cefepime.
For 1 g Intramuscular Injection 3 ml of the volume of the solvent to be added to each vial of cefepime.

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.

NUXIPIM, powder for solution for injection/infusion should be dissolved in:
- Water for injections
- 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.

INCOMPATIBILITIES:
Cefepime must not be mixed with other medicinal products. There is a physical-chemical incompatibility with metronidazole, vancomycin, gentamicin, tobramycin, netilmicin and aminophylline. In the cases where a concomitant intravenous administration is indicated, these active substances should not be administered together with cefepime or through the same intravenous route.

SHELF LIFE:
3 years.

STABILITY:
The in-use physical and chemical stability was demonstrated for 18 hours at room temperature (15 - 25°C) and for 7 days in a refrigerator (2 - 8°C). The medicinal product should be used immediately. If not used immediately, in-use time and storage conditions prior to administration are users' responsibility and, usually, should not exceed 24 hours at 2-8°C, unless reconstitution has occurred under validated aseptic controlled conditions.
Do not refrigerate.

STORAGE AND INSTRUCTIONS
Protect from heat, sunlight & moisture. Dry powder store below 25°C.
The expiration date refer to the product correctly stored at the required condition.
Use freshly preprared solution immediately.
Keep out of the reach of children.
Patients and healthcare professionals can also report suspected adverse drug reaction at ade@bosch-pharma.com.
To be sold on prescription of a registered medical practitioner only.

PRESENTATION:
NUXIPIM 500mg Injection: pack of 1 vial + 1 ampoule of 5ml sterile water for injection as a solvent.
NUXIPIM 1g Injection: pack of 1 vial + 1 ampoule of 10ml sterile water for injection as a solvent.

پٹھوں/وریدی استعمال کے لئے۔

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
غیر تیار شدہ دوا کو دھوپ، گرمی اور نمی سے محفوظ ۲۵ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
محلول تیار کرنے کے بعد فوراً استعمال کریں۔
بچوں کی پہنچ سے دُور رکھیں۔ صرف مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔

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ISO 9001:2015 Certified Company