TVAXIPIM

Instructions for the medicinal product

Trade name: Tvaxipim.
International Nonproprietary Name: Cefepime.
Dosage form: Powder for Injection + SWFI.
Composition: Each combipack contains:
One Vial of Cefepime Hydrochloride USP eq. to Cefepime 1 gm.
(Sterile Mixture of Cefepime Hydrochloride USP and L-Arginine USP)
One 10 ml Ampoule of Sterile water for Injection USP.
Pharmacotherapeutic group: Cephalosporin Antibiotics.
ATC Code: J01DE01.
Pharmacologic property:
Pharmacodynamics:
Cefepime is a fourth-generation cephalosporin antibiotic. Cefepime has an extended spectrum of activity against Gram-positive and Gram-negative bacteria, with greater activity against both Gram-negative and Gram-positive organisms than third-generation agents.
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 bacterial 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 staphylococci), Streptococcus agalactiae (Group B streptococci), Streptococcus pneumoniae (formerly Diplococcus pneumoniae), Streptococcus pyogenes(Group A streptococci), other beta-haemolytic streptococci (Groups C, G, F).
Gram-negative aerobes:
Acinetobacter calcoaceticus (subsp. anitratus, Iwoffi), Enterobacter spp.(including E. aerogenes, E. agglomerans, E. cloacae, E. sakazakii), Escherichia coli, Haemophilus influenzae, (including strains of beta-lactamase producing H. influenzae), Haemophilus parainfluenzae, 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:
Note: Enterococci like Enterococcus faecalis and methicillin-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 hominis, 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), Neisseria meningitidis, Providencia sp. including P. rettgeri, P. stuartii, Salmonella spp., Serratia liquefaciens, Shigella spp., Yersinia enterocolitica.
Note: Cefepime is inactive against most strains of Xanthomonas maltophilia (Pseudomonas maltophilia). Not all pseudomonas strains are susceptible.
Anaerobes: Clostridium perfringens, Mobiluncus spp. Note: Cefepime is inactive against Bacteroides fragilis and Clostridium difficile.
Pharmacokinetics:
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 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.
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.
The pharmacokinetics of cefepime were 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.
Average half-life in severely impaired patients requiring dialysis therapy is 13 hours for haemodialysis and 19 hours for continuous ambulatory peritoneal dialysis.
Indications for use:
Adults
Tvaxipim is indicated in the treatment of the infections listed below when caused by susceptible bacteria. Culture and susceptibility studies should be performed to determine susceptibility of the causative organism(s) to cefepime:
• *Lower respiratory tract infections:* Nosocomial and Community-Acquired Pneumonia caused by Staphylococcus aureus (methicillin-susceptible strains), Pseudomonas aeruginosa, Klebsiella species (including Klebsiella pneumoniae), Enterobacter species, Escherichia coli, Proteus mirabilis, Streptococcus pneumoniae (including intermediate penicillin resistant strains), Haemophilus influenzae (including beta-lactamase producing strains), Haemophilus parainfluenzae and Moraxella (Branhamella) catarrhalis (including beta-lactamase producing strains), including cases associated with Bacteremia. When P. aeruginosa is isolated or suspected, combination therapy with an aminoglycoside should be used.
Acute Bacterial Exacerbation of Chronic Bronchitis and Acute Bronchitis due to Streptococcus pneumoniae (including intermediate penicillin resistant strains), Haemophilus influenzae (including beta-lactamase producing strains), Moraxella (Branhamella) catarrhalis (including beta-lactamase producing strains).
• *Urinary tract infections:* Complicated Urinary Tract Infections caused by Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus mirabilis and Enterobacter species, including cases associated with Bacteremia. When P. aeruginosa is isolated or suspected, combination therapy with an aminoglycoside should be used. Uncomplicated Urinary Tract Infections due to Escherichia coli, Proteus mirabilis, Klebsiella species and Enterobacter species.
• *Skin and skin structure infections:* caused by Staphylococcus aureus (methicillin-susceptible strains), Streptococcus pyogenes (Group A streptococci), Streptococcus agalactiae (Group B streptococci), other beta-haemolytic Streptococcus species, Enterobacter species, Klebsiella species, Proteus mirabilis, Morganella morganii, Escherichia coli, Serratia marcescens and Acinetobacter calcoaceticus.
• *Intra-abdominal infections:* Complicated Intra-abdominal Infections Including Peritonitis and Biliary Tract Infections caused by Escherichia coli, sensitive Pseudomonas aeruginosa. Peritonitis is often polymicrobial and may include anaerobic micro-organisms such as Bacteroides species which are resistant to cefepime. When resistant anaerobes are suspected, cefepime should be combined with an antibiotic effective against these micro-organisms, including cases associated with Bacteremia. In patients who are at risk of mixed aerobic-anaerobic infection, including infections in which Bacteroides fragilis may be present, concurrent therapy with an anti-anaerobic agent is recommended.
• *Empiric treatment in febrile neutropenia:* Combination of cefepime with other appropriate antimicrobial agents should be considered in patients at high risk for severe infection (including patients with a history of recent bone marrow transplantation, hypotension at presentation, an underlying haematologic malignancy, or severe or prolonged neutropenia) or when called for by host or local epidemiological factors.
Paediatrics:
Indicated in paediatric patients (2 months and older) for the treatment of the infections listed below when caused by susceptible bacteria, (when P. aeruginosa is isolated or suspected, combination therapy with an aminoglycoside should be used):
• *Lower respiratory tract infection:* Pneumonia caused by S. aureus, S. pneumoniae, H. influenzae.
• *Urinary tract infections:* caused by E. coli.
• Skin and skin structure: Infections caused by Staphylococcus epidermidis, streptococcus, S. aureus, S. pyogenes.
• Empiric treatment in febrile neutropenia: Combination of cefepime with other appropriate antimicrobial agents should be considered in patients at high risk for severe infection (including patients with a history of recent bone marrow transplantation, hypotension at presentation, an underlying haematologic malignancy, or severe or prolonged neutropenia) or when called for by host or local epidemiological factors.
Contraindications:
• hypersensitivity reactions to any component of the formulation, the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics.
Pregnancy and lactation:
Should be used during pregnancy only if clearly needed.
Cefepime is excreted in human breast milk in very low concentrations. Caution should be exercised when cefepime is administered to a nursing woman.
Dosage and directions for use:
Tvaxipim 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.
Recommended dosage for Adults with Normal Renal Function aged 12 years and older:
Mild to moderate urinary tract infections (uncomplicated and complicated) - 500 mg - 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, q 8h.
Usual duration of therapy is 7-10 days; more severe infections may require longer treatment. In the treatment of beta-haemolytic 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.
Paediatrics (aged 1 month up to 12 years with normal renal function):
Usual Recommended dosages:
Pneumonia, urinary tract infections, and skin structure infections: Patients 2 months of age with body weight <40 kg: 50 mg/kg q 12 h for 10 days. For more severe infections, a dosage schedule of q 8 h 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 Tvaxipim in paediatric patients <2 months of age is limited. While this experience has been attained using the 50 mg/kg dose, modelling of pharmacokinetic data obtained in patients >2 months of age suggests that a dosage of 30 mg/kg q12h or q8h may be considered for patients aged 1 month up to 2 months.
Administration of Tvaxipim in these patients should be carefully monitored.
For paediatric patients with body weights > 40 kg, adult dosing recommendations apply. For patients older than 12 years who are <40 kg, the dosage recommendations for younger patients <40 kg should be used. Dosage in paediatric patients should not exceed the maximum recommended dosage in adults (2g q 8 h). Experience with intramuscular administration in paediatric patients is limited.
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 recommended maintenance doses of cefepime in patients with renal insufficiency:

Creatinine clearance (mL/min)	*Recommended Maintenance Dosage*
> 50	Usual dose, no adjustment necessary 2g q 8h, 2g q12h, 1g q 12h, 500 mg q 12h.
30 - 50	1g q 8h, 2g q 24h, 1g q 24h, 500 mg q 24h.
11 - 29	1g q 12h, 1g q 24h, 500 mg q 24h,500 mg q 24h.
<10	1g q 24h, 500 mg q 24h, 250 mg q 24h, 250 mg q 24h.

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 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.
Children with Impaired Renal Function:

Since urinary excretion is the primary route of elimination of cefepime in paediatric patients, an adjustment of the dosage of Tvaxipim should also be considered in patients <12 years of age with renal impairment.
Tvaxipim powder is to be constituted using the volumes of diluent; the diluents to be used are identified following:
Preparations of solutions of Tvaxipim:

	Amount of diluent to be added (mL)	Approx. available volume (mL)	Approx. cefepime concentration (mg/mL)
Intravenous:			
500 mg vial	5	5,7	90
1g vial	10	11,4	90
2g vial	10	12,8	160
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 Tvaxipim with Sterile Water for Injection, 5% Dextrose Injection or 0,9% Sodium Chloride using the diluent volumes as noted above. 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 patient is receiving a compatible IV fluid.
For intravenous infusion, constitute the 500 mg, 1g, or 2g 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: Tvaxipim should be constituted with one of the following diluents using the volumes as noted above: Sterile Water for Injection, 0,9% Sodium Chloride Injection, 5% Dextrose Injection, or Bacteriostatic Water for Injection with Parabens or Benzyl Alcohol then administered by deep IM injection into a large muscle mass (such as the upper outer quadrant of the gluteus maximus). Although Tvaxipim can be constituted with 0,5% or 1,0% Lidocaine hydrochloride, it is usually not necessary because Tvaxipim causes little or no pain upon IM administration.
Side-effects:
The most common side effects were gastrointestinal symptoms and sensitivity reactions. Adverse events that occurred are listed below by body system:
Hypersensitivity - anaphylaxis, rash, pruritus, urticaria, fever.
Gastrointestinal - diarrhoea, nausea, vomiting, oral moniliasis, colitis (including pseudomembranous colitis), taste perversion, constipation, abdominal pain, dyspepsia.
Cardiovascular - vasodilation.
Respiratory - dyspnea.
Central nervous system - headache, dizziness, paraesthesia, seizures have been reported.
Other - fever, vaginitis, erythema, genital pruritus, chills and unspecified moniliasis. Hepatitis and cholestatic jaundice have occurred less frequently.
Local reactions such as phlebitis and inflammation at the site of IV injection and inflammation or pain at the site of intramuscular injection occurred with some patients.
Laboratory test abnormalities that developed in patients with normal baseline values during clinical trials were: elevations in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, eosinophilia, anaemia, thrombocytopenia and prolonged prothrombin time, partial thromboplastin time, and positive Coomb's test without haemolysis. Transient elevations of blood urea nitrogen, and/or serum creatinine and transient thrombocytopenia were observed.
The following adverse events and altered laboratory tests have been reported for cephalosporin-class antibiotics: Stevens-Johnson syndrome, erythema multiformae, toxic epidermal necrolysis, toxic nephropathy, aplastic anaemia, haemolytic anaemia, haemorrhage, and false positive tests for urinary glucose.
Overdose:
Symptoms: encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, and neuromuscular excitability.
Treatment: Should be symptomatic and supportive.
In case of severe overdosage, especially in patients with compromised renal function, haemodialysis will aid in the removal of cefepime from the body; peritoneal dialysis is of no value.
Drug interactions:
Cefepime exhibits physical or chemical incompatibility when admixed with vancomycin hydrochloride, gentamycin sulfate, netilmycin sulfate and aminophylline.
In patients treated with cefepime, false positive urinary tests for glucose may result when reducing agents are employed. False positives are not seen with glucose-oxidase methods.
Cautions:
Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to Tvaxipim occurs, discontinue the drug and treat the patient appropriately. Serious immediate hypersensitivity reactions may require epinephrine 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. Mild cases of colitis may respond to drug discontinuation alone; moderate to severe cases may require more elaborate management.
Use of Tvaxipim may result in overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.
Renal function should be monitored carefully if drugs with nephrotoxic potential, such as aminoglycosides and potent diuretics, are administered with Tvaxipim.
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. Serious adverse events, including reversible 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.
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 Tvaxipim 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. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms.
Presentation:
1x1, 20 ml glass vial +10 ml plastic ampoule sterile water in a monocarton, with instruction for use.
Storage:
Keep in dry place, protected from light at a temperature below 30°C. Keep out of reach of children.
Shelf life:
Labeled. Do not use after expiry date.
Distribution Condition:
Prescribed medicine.