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MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS

Patient Information Leaflet

CEFEPIME-TF (ЦЕФЕПИМ-ТФ) Powder for solution for intramuscular injection/ intravenous infusion 500 mg, 1 g.

Invented trade name: Cefepime-TF

International Non-proprietary Name: Cefepime

Pharmaceutical form: powder for solution for intramuscular injection/ intravenous infusion

Description: White to pale yellow powder.

Qualitative and quantitative composition:

1 vial contains:
Cefepime – 500 mg or 1 g
(as cefepime hydrochloride and L- arginine)

Pharmacotherapeutic group: Antibacterials for systemic use. Fourth-generation cephalosporins.

ATC-code: J01DE01.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Fourth-generation cephalosporin antibiotic. It has a broad spectrum of activity against a wide range of Gram-positive and Gram-negative bacteria, the strains resistant to aminoglycosides or the third generation cephalosporins. Cefepime-TF is highly resistant to hydrolysis by most beta-lactamases, has a low affinity for chromosomally-encoded beta-lactamases. The antibiotic inhibits the bacterial cell wall peptidoglycan synthesis causing the death of microorganisms.

Cefepime-TF is active against the following *Gram-positive aerobic bacteria*: *Staphylococcus aureus* (including β -lactamase-producing strains), *Staphylococcus epidermidis* (including β -lactamase-producing strains), *Staphylococcus saprophyticus*, *Streptococcus pyogenes* (Group A streptococci), *Streptococcus agalactiae* (Group B streptococci), *Streptococcus pneumoniae*, *Streptococcus viridans*; the following *Gram-negative aerobic bacteria*: *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella* spp. (including *Klebsiella pneumoniae*, *Klebsiella oxytoca*), *Enterobacter* spp., *Proteus* spp. (including *Proteus mirabilis*, *Proteus vulgaris*), *Acinetobacter calcoaceticus* (subtype *Acinetobacter lwoffii*), *Citrobacter diversus*, *Citrobacter freundii*, *Haemophilus influenzae* (including β -lactamase-producing strains), *Hafnia alvei*, *Morganella morganii*, *Moraxella catarrhalis* (including β -lactamase-producing strains), *Providencia* spp. (including *Providencia rettgeri*, *Providencia stuartii*), *Serratia marcescens*.

The strains of *Xanthomonas maltophilia*, *Pseudomonas maltophilia*, *Stenotrophomonas maltophilia*, *Bacteroides fragilis*, *Clostridium difficile* are resistant to Cefepime-TF.

Most of the methicillin-resistant strains of enterococci (including *Enterococcus faecalis*) and staphylococci are resistant to most of the cephalosporin antibiotics, including Cefepime-TF.

Pharmacokinetics

Absorption

The maximum plasma concentration of Cefepime-TF after the intravenous administration of 500 mg, 1 g and 2 g, equals 39.1 \pm 3.5 mcg/ ml, 81.7 \pm 5.1 mcg/ ml and 163.9 \pm 25.3 mcg/ ml, respectively.

Following intramuscular administration, cefepime is completely absorbed. After the administration of 500 mg, 1 g and 2 g of the drug product, the maximum plasma concentration of Cefepime-TF equals 13.9 \pm 3.4 mcg/ ml, 29.6 \pm 4.4 mcg/ ml, 57.5 \pm 9.5 mcg/ ml, respectively. The time to maximum concentration equals 1.4 \pm 0.9 h, 1.6 \pm 0.4 h, 1.5 \pm 0.4 h, respectively.

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Distribution

Serum protein binding of cefepime is less than 19% and is independent of its concentration in the serum. There was no accumulation in healthy subjects receiving doses of 2 g intravenously every 8 hours for a period of 9 days. Therapeutic concentrations of Cefepime-TF are found in the urine, bile, peritoneal fluid, the contents of burn blisters, mucous secretion of the bronchi, tissues of the prostate, appendix and gallbladder.

Metabolism and elimination

Cefepime-TF is metabolized to N-methylpyrrolidine which is rapidly converted to the N-methylpyrrolidine oxide. Average elimination half-life of Cefepime-TF is approximately 2 hours. Total body clearance averages 120 ml/min. Average renal clearance of cefepime is 110 ml/min, suggesting that cefepime is eliminated almost exclusively by renal mechanisms, primarily glomerular filtration. 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 N-methylpyrrolidine, 6.8% as N-methylpyrrolidine oxide, and 2.5% as an epimer of cefepime.

Pharmacokinetics in special populations

Elimination half-life is prolonged in patients with various degrees of renal insufficiency, so they require dose adjustment. The kinetics of cefepime is unchanged in patients with impaired hepatic function or cystic fibrosis. Thus, no dose adjustment is required.

There were no significant effects of age or gender on total body clearance or volume of distribution, corrected for body weight. The exposure to cefepime following a 50 mg per kg intravenous dose in a pediatric patient is comparable to that in an adult treated with a 2 g intravenous dose.

The absolute bioavailability of Cefepime-TF after an intramuscular dose of 50 mg/kg was 82%

Therapeutic indications

Cefepime-TF is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms: pneumonia (moderate to severe), urinary tract infections (both complicated, including pyelonephritis, and uncomplicated), uncomplicated skin and soft tissue infections, complicated intra-abdominal infections (with metronidazole), neutropenic fever (as empiric therapy).

Contraindications

Cefepime-TF is contraindicated in patients who have had previous hypersensitivity reactions to cefepime or any component of the formulation or the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics. Cefepime-TF is contraindicated in children under 2 months of age.

Special warnings and precautions for use

Use in pregnancy and lactation

The drug should be used during pregnancy only if the potential benefit justifies the potential risk. In each case, the drug must be used under the direct supervision of a physician. Cefepime is excreted in human breast milk in very low concentrations. If Cefepime-TF is to be administered to a nursing woman, the breastfeeding discontinuation should be considered.

Special warnings

Before therapy with cefepime is instituted, careful inquiry should be made to determine whether the patient has had previous immediate hypersensitivity reactions to cefepime, cephalosporins, penicillins, or other drug products.

If this product is to be given to sensitive patients, caution should be exercised because cross-hypersensitivity among betalactam antibiotics has been documented and may occur in patients with a history of penicillin allergy. If an allergic reaction to cefepime occurs, discontinue the drug and institute supportive treatment as appropriate.

In patients with impaired renal function, the dose of Cefepime-TF should be adjusted to compensate for the slower rate of renal elimination. Serious adverse events have been reported including the following: disturbance of consciousness including confusion, hallucinations, stupor. Most cases occurred in patients with renal impairment (especially elderly patients) who received doses of cefepime that exceeded recommendations. In the majority of cases, symptoms of neurotoxicity were reversible and resolved after discontinuation of cefepime and/or after hemodialysis.

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It is important to consider this pseudomembranous colitis in patients who present with diarrhea during the Cefepime-TF administration. While mild forms of colitis do not require the symptomatic therapy, the moderate or severe cases may require special treatment. Cefepime-TF should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

As with other antibiotics, prolonged use of Cefepime-TF may result in overgrowth of nonsusceptible organisms. Thus careful supervision is required during therapy.

Many cephalosporins 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. Positive direct Coombs' tests have been reported during treatment with Cefepime-TF that are caused by the drug administration.

The administration of cefepime may result in a false-positive reaction for glucose in the urine when using Benedict's reagent. It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

Arginine has been shown to alter glucose metabolism and elevate serum potassium transiently when administered at 33 times the amount provided by the maximum recommended human dose of Cefepime-TF. The effect of lower doses is not presently known.

Pediatric use

The safety profile of the drug product when used in children and adults remains unaltered.

Safety and effectiveness in pediatric patients below the age of 2 months have not been established. The drug product is recommended in children over 2 months of age.

Geriatric use

Of the more than 6400 adults treated with Cefepime-TF in clinical studies, 35% were 65 years or older while 16% were 75 years or older. When geriatric patients received the usual recommended adult dose, clinical efficacy and safety were comparable to clinical efficacy and safety in nongeriatric adult patients.

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.

Effects on ability to drive and use machines weren't studied.

Posology and method of administration

The dosage and route of administration should be determined according to the susceptibility of the causative organisms, the severity of the infection, and the condition and renal function of the patient. Guidelines for dosage of Cefepime-TF in patients with normal renal function (creatinine clearance of more than 60 ml/ min) are provided in the table below.

Site and typr of infection	Dose	Dosing frequency	Treatment duration
Moderate to severe pneumonia	1-2 g intravenously	Each 8-12 hours	10 days
Empiric therapy in febrile neutropenic patients	2 g intravenously	Each 8 hours	7 days *
Mild to moderate urinary tract infections (uncomplicated and complicated), including pyelonephritis	0.5-1 g intravenously or intramuscularly **	Each 12 hours	7-10 days
Severe urinary tract infections (uncomplicated and complicated), including pyelonephritis	2 g intravenously	Each 12 hours	10 days
Uncomplicated skin and soft tissue infections (moderate to severe)	2 g intravenously	Each 12 hours	10 days
Complicated intra-abdominal infections (in combination with metronidazole)	2 g intravenously	Each 8-12 hours	7-10 days
The maximum dose for pediatric patients aged 2 months up to 16 years should not exceed the recommended adult dose. The usual recommended dosage in pediatric patients up to 40 kg in weight for uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and soft tissue infections, and pneumonia is 50 mg per kg per dose, administered every 12 hours (50 mg per kg per dose, every 8 hours for febrile neutropenic patients), for durations as given above.			

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* or until resolution of neutropenia. In patients whose fever resolves but who remain neutropenic for more than 7 days, the need for continued antimicrobial therapy should be re-evaluated frequently. ** Intramuscular route of administration is indicated only for mild to moderate, uncomplicated or complicated urinary tract infections.

No dose adjustment is necessary for *patients with hepatic impairment*.

In *patients with renal impairment* (with creatinine clearance less than or equal to 60 ml/min) the dose of the drug product should be adjusted. The recommended initial dose of Cefepime-TF should be the same as in patients with normal renal function except in patients undergoing hemodialysis. The recommended maintenance schedule of Cefepime-TF in patients with renal impairment depends on the creatinine clearance.

Creatinine clearance (ml/min)	Recommended doses			
	>60 Normal recommended dosing schedule	500 mg every 12 hours	1 g every 12 hours	2 g each 12 hours
60-30	500 mg every 24 hours	1 g every 24 hours	2 g each 24 hours	2 g each 12 hours
29-11	500 mg every 24 hours	500 mg every 24 hours	1 g each 24 hours	2 g each 24 hours
≤ 10	250 mg every 24 hours	250 mg every 24 hours	500 each 24 hours	1 g each 24 hours
CAPD	500 mg every 48 hours	1 g every 48 hours	2 g each 48 hours	2 g each 48 hours
Hemodialysis *	1 g on the first day, then 500 mg given every 24 hours*			1 g every 24 hours

* On hemodialysis days, cefepime should be administered following hemodialysis. Whenever possible, cefepime should be administered at the same time each day.

In patients undergoing *hemodialysis*, 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. Cefepime-TF should be re-administered in the initial dose following the completion of hemodialysis. 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, 1 g or 2 g (depending on the severity of the infection) at a dosage interval of every 48 hours.

Changes in the dosing regimen proportional to those in adults (see the table above) are recommended for *pediatric patients with impaired renal function*.

The usual duration of therapy is 7-10 days; however, more severe infections may require longer treatment.

Instructions for preparation and administration of the solution

Cefepime-TF is administered intramuscularly or by intravenous drop infusion.

Preparation of solution for intravenous administration. Constitute Cefepime-TF with 0.9 % sodium chloride solution, 0.9 % sodium chloride solution with 5 % glucose solution, 5 % or 10 % glucose injection, M/6 sodium lactate injection, Lactated Ringers and 5 % glucose injection. The resulting solution should be administered over a period of approximately 30 minutes.

Preparation of solution for intramuscular administration. Constitute Cefepime-TF with the appropriate amounts of the following diluents: 0.9 % sodium chloride solution, sterile water for injection with parabens or benzyl alcohol, 5 % dextrose solution.

The amounts of the solvent required to prepare the solutions are given in the reconstitution table below:

Route of administration	Cefepime content per vial	Volume of solvent to be added, ml	Volume of the resulting solution, ml	Cefepime concentration, mg/ml
Intravenous administration	500 mg	5.0	5.7	90
	1 g	10.0	11.4	90
Intramuscular administration	500 mg	1.5	2.2	230
	1 g	3.0	4.4	230

Undesirable effects

Gastrointestinal disorders: diarrhea, nausea, vomiting, colitis (including pseudomembranous colitis); rare – abdominal pain, constipation, very rare – mouth sores.

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Allergic reactions: rash, pruritus, urticarial fever, fever, Stevens-Johnson syndrome; rare – anaphylactic reactions, eosinophilia, erythema multiforme, toxic epidermal necrolysis.

Nervous system disorders: headache, encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, status epilepticus without convulsions. Although in most cases these undesirable effects were observed in patients with renal impairment who received doses of cefepime that exceeded the recommended one, in some cases, neurotoxicity was observed in patients receiving a dose corresponding to the renal impairment severity. If the cefepime-associated neurotoxicity occurs, it is recommended to consider the treatment discontinuation or to make the appropriate dose adjustments in patients with renal impairment.

Dermatological reactions: skin redness. Most common reaction in children – rash.

Blood and the lymphatic system disorders: aplastic anemia, hemolytic anemia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, hypotension, vasodilatation, bleedings, pancytopenia.

Local reactions: intravenous administration may cause phlebitis, rarely – inflammation; intramuscular administration may cause inflammation or pain at the injection site.

Reproductive system and urinary disorders: vaginitis, impaired renal function, toxic nephropathy.

Investigations: decreased hematocrit, decreased serum phosphorus and calcium, altered prothrombin time and prothrombin index, elevated serum urea nitrogen, hypercreatinemia, hyperkalemia, hyperbilirubinemia, hyperphosphatemia, elevated serum calcium, elevated liver transaminases, elevated serum alkaline phosphatase, positive Coombs' test.

Other: impaired hepatic function, including cholestasis.

Overdose

Symptoms: Symptoms of major overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, status epilepticus without convulsions, and neuromuscular excitability.

Treatment: In case of an overdose, the treatment should be discontinued and the patient should be given supportive treatment. In cases of significant excess of recommended doses, especially in patients with impaired renal function, hemodialysis is recommended.

Interaction with other medicinal products and other forms of interaction

Cefepime-TF was found to increase the ototoxicity and nephrotoxicity of aminoglycosides, furosemide, and other loop diuretics. Solutions of cefepime, like solutions of most beta-lactam antibiotics, should not be added to solutions of ampicillin in concentration over 40 mg/ml, metronidazole, vancomycin, gentamicin, tobramycin, netilmicin sulfate, or aminophylline due to the possible interaction. However, if concurrent therapy with cefepime is indicated, each of these antibiotics can be administered separately to the same patient.

Storage conditions and shelf-life

Store in a dry and dark place at the temperature not above 25°C.

Keep out of reach of the children.

2 years. Do not use beyond the labeled expiration date.

Prescription status

Prescription only medicine.

Presentation

500 mg or 1 g in a 10 ml vial.

5 vials in a pack or 36 vials in a box (for inpatient facilities).

Manufacturing company

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