TITLE - CEFEPIME + TAZOBACTAM / AUGEOZ MEDICATION PATIENT INFORMATION IN ENGLISH

Source : Biocon

Cefepime & Tazobactam for Injection 1.125g

CELRIM TZ® सेलरिम टि ज़ेड

Composition:
Each Vial Contains:
Cefepime HCL I.P. (Sterile)
Eq. to Anhydrous Cefepime 1000 mg
(A Sterile mixture of cefepime HCL and Arginine)
Tazobactam Sodium I.P. (Sterile)
Eq. to Tazobactam 125 mg

Pharmaceutical form: Powder for reconstitution (IV/IM use only).

ATC Code: H02AB07

DESCRIPTION
CELRIM TZ® (Cefepime and tazobactam for injection) is an injectable antibacterial combination product consisting of the Cefepime hydrochloride and the β-lactamase inhibitor tazobactam sodium for intramuscular or intravenous administration.

CEFEPIME (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-methylpyrrolidinium chloride, 72-(Z)-(O-methyloxime), monohydrochloride, monohydrate. Tazobactam sodium, a derivative of the penicillin nucleus, is a penicillanic acid sulfone. Its chemical name is sodium (2S, 3S,5R)-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide. The chemical formula is $C_{19}H_{17}N_9NaO_5S$ and the molecular weight is 322.3.

Tazobactam, a triazolylmethyl penicillanic acid sulphone, is a potent inhibitor of many b- lactamases, in particular the plasmid mediated enzymes which commonly cause resistance to penicillins and cephalosporins including third-generation cephalosporins.

Although tazobactam has minimal antibacterial activity when used alone, the combined use of cefepime with tazobactam results in a synergistic effect that expands the spectrum of activity of cefepime against many strains of beta-lactamase producing bacteria.

ANTI-MICROBIAL SPECTRUM:
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 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).

Zwitterions of cefepime enhances its movement across the cell membrane resulting in high concentration in the periplasmic space and relatively net resistance to drug hydrolysis and cefepime exhibits only modest inactivation.

Emergence of drug resistance to cefepime was considered as less of problem till recently. Extended spectrum beta- lactamases (ESBL) are capable of hydrolyzing penicillin, broad and extended spectrum cephalosporins. ESBL can be found in a variety of Enterobacteriaceae species Klebsiella pneumoniae, *K. oxytoca* and Escherichia coli. Other organisms to harbor ESBL are Enterobacter spp, Salmonella spp, Morganella morganii, Proteus mirabilis, Serratia marcescens and P. aeruginosa. Cefepime is active against most ESBL producing organisms however susceptibility appears to decrease with increasing inoculum *in-vitro* susceptibility tests and *in-vivo* experimental models. Use of cefepime alone has been associated with selection of ESBL producing organisms and outbreaks of infection.

Tazobactam generally acts as an irreversible inhibitor and inactivates both plasmid and chromosomally mediated beta-lactamases. The combination of cefepime with tazobactam is a useful combination for the treatment of infections due to ESBL producing organisms. Tazobactam augments and protects cefepime.

Pharmacokinetics:
Cefepime exhibits linear dose dependant pharmacokinetics over the dosage range 250 mg to 2 g and there is no evidence of drug accumulation following multiple doses in healthy adults with normal renal function.

Cefepime is almost completely absorbed following IM administration. The single 500 mg, 1 g or 2 g IM doses of cefepime attains peak plasma concentrations of 13.9, 29.6 or 57.5 mcg/ml respectively. Plasma concentration is attained within 1.4-1.6 hrs. After 8 hours the average plasma concentration averaged 1.9, 4.5 or 8.7 mcg/ml respectively.

Following IV infusion over 30 min of a single 500 mg, 1g or 2g dose of cefepime peak plasma concentrations of the drug averaged 31.6-39.1, 65.9-81.7 or 126-139.9 mcg/ml respectively, plasma concentrations 8 hours after the dose averaged 1.4, 2.4 and 3.9 mcg/ml respectively.

Following parenteral administration cefepime is widely distributed into tissues and fluids, including blister fluid bronchial mucosa, sputum, bile, peritoneal fluid, appendix, and gallbladder. Cefepime is distributed into CSF following parenteral administration. It is also excreted in human milk.
Cefepime is approximately 20% bound to serum proteins. Plasma half life of cefepime average 2-2.3 hours. Cefepime is partially metabolized *in vivo* to N-methyl pyrrilldine (NMP). The drug is eliminated principally unchanged in urine by glomerular filtration, 80-82% of a single dose cefepime is excreted unchanged in urine.

Cefepime is removed by haemodialysis and peritoneal dialysis. Tazobactam 0.5 g when infused over 30 min as a single dose, the peak serum level averages 27.1 mcg/ml, the half-life is 0.67 hour and its renal clearance is 268 ml per min.

Tazobactam is metabolised to a single metabolite which has been found to be micro-biologically inactive. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the administered dose appearing as unchanged drug and the remainder as the single metabolite.

INDICATIONS:
Cefepime and tazobactam is used parenterally for the treatment of moderate to severe infections caused by or suspected of being caused by susceptible beta-lactamases producing bacteria when cefepime alone would be ineffective.
Cefepime and tazobactam combination is used for following indications:

- For the treatment of uncomplicated and complicated urinary tract infections
- Uncomplicated skin and skin structure infections and
- Complicated intra-abdominal infections.

CONTRAINDICATIONS:
Cefepime and tazobactam combination is contraindicated in patients who are hypersensitive to the drugs or other cephalosporins and should be used with caution in patients with a history of hypersensitivity to penicillins. Use of cephalosporins should be avoided in patients who have had an immediate type (anaphylactic) hypersensitivity reaction to penicillins. If a hypersensitivity reaction occurs during cefepime and tazobactam therapy, the drug should be discontinued and the patient treated with appropriate therapy e.g. epinephrine, corticosteroids and maintenance of an adequate airway and oxygen as indicated.

WARNINGS:
Before therapy with cefepime and tazobactam for infection is instituted, careful inquiry should be made to determine whether the patient has had previous immediate hypersensitivity reaction to cefepime, cephalosporins, penicillins or other drugs.

PRECAUTIONS:
Precaution has to be taken in patients with renal and/or hepatic insufficiency. Dose adjustment is required in patients with renal failure with creatinine clearance <60 ml/min.

Pregnancy:
There are no adequate or controlled studies using cefepime and tazobactam in pregnant women or during labour and delivery and the drug should be used during pregnancy only when clearly indicated.

Lactation:
Cefepime is excreted in human breast milk in very low concentration following parenteral administration and the drug should be used with caution in nursing mothers.
Labour and Delivery:
Cefepime has not been studied for use during labour and delivery. Treatment should only be given if clearly indicated.

Rx

Cefepime & Tazobactam for Injection 1.125g

Biocon

CELRIM TZ® सेलरिम टि ज़ेड

DRUG INTERACTIONS:
Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with **CELRIM TZ®** 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.

ADVERSE EFFECTS:
Adverse effects with cefepime and tazobactam are similar to those reported with cefepime alone and generally are transient and mild to moderate in severity.
Adverse events reported with cefepime are:
Incidence equal to or greater than 1%: Local reactions (3.0%), including phlebitis (1.3%), pain and/or inflammation (0.6%); rash (1.1 %) Incidence less than 1 % but greater than 0.1 %: Colitis (including pseudomembranous colitis), diarrhea, fever, headache, nausea, oral moniliasis, pruritus, urticaria, vaginitis, vomiting.

At the higher dose of 2 g q8h, the incidence of probably-related adverse events was higher. They consisted of rash (4%), diarrhea (3%), nausea (2%), vomiting (1%), pruritus (1%), fever (1%), and headache (1%).

The following adverse laboratory changes, irrespective of relationship to therapy with cefepime, were reported Incidence equal to or greater than 1%: Positive Coombs' test (without hemolysis) (16.2%); decreased phosphorus (2.8%); increased ALT/SGPT (2.8%), AST/SGOT (2.4%), eosinophils (1.7%); abnormal PTT (1.6%), PT (1.4%).
Incidence less than 1 % but greater than 0.1 %: Increased alkaline phosphatase, BUN, calcium, creatinine, phosphorus, potassium, total bilirubin; decreased calcium, hematocrit, neutrophils, platelets, WBC.

Postmarketing Experience:
In addition to the events reported above with cefepime, the following adverse experiences have been reported during worldwide postmarketing experience.

As with some other drugs in this class, encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures have been reported. Although most cases occurred in patients with renal impairment who received doses of cefepime that exceeded recommended dosage schedules, some cases of encephalopathy occurred in patients receiving a dosage adjustment for their renal function.

As with other cephalosporins, anaphylaxis including anaphylactic shock, transient leukopenia, neutropenia, agranulocytosis, and thrombocytopenia have been reported..

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.

DOSAGE: Cefepime and tazobactam combination preferably is administered by IV Infusion but also can be given by deep IM injection when indicated. Cefepime with tazobactam should be administered intravenously over 30 minutes. The recommended adult and paediatric dosage of cefepime and tazobactam are outlined in the following table:

Site and type of infection in adults	Dose	Frequency	Duration (Days)
Mild to moderate uncomplicated or complicated urinary tract infections	0.5-1g IV/IM	12 h	7-10
Severe uncomplicated or complicated urinary tract infections	2g IV	12h	10
Moderate to severe skin and skin structure infection	2g IV	12h	10
Intra-abdominal infections	2g IV	12h	7-10

Maximum adult dose of cefepime should not exceed 6 gm a day

The recommended maintenance doses of cefepime in patients with renal insufficiency (creatinine clearance <60 ml/min) are presented in the following Table

Creatinine clearance (ml/min)	Recommended maintenance schedule			
30-60	500mg q24h	1g q24h	2g q24h	2g q12h
11-29	500mg q24h	500mg q24h	1g q24h	2g q24h
<11	250mg q24h	250mg q24h	500mg q24h	1g q24h

Impaired Hepatic Function:
No adjustment is necessary for patients with impaired hepatic function.

Pediatric patients (2 months to 12 years):
The usual recommended dose for pediatrics patients is 40 to 50 mg/kg dose administered 8 to 12 hours depending on the severity of infection.

The maximum dose for pediatrics patients should not exceed recommended adult dose.
Reconstitution and administration:
IV Infusion: The contents of vials should be reconstituted with 10 ml of sterile water for injection IP provided. The appropriate dose of the drug should then be added to a compatible IV solution. The resultant solutions are stable for 24 hours when stored at temperature of 20-25°C. Intermittent IV infusion is given over approximately 30 minutes.

IM injection: Injection of cefepime and tazobactam is prepared by adding 2.4 ml sterile water for injection IP. The solution is stable for one hour when stored at room temperature of 20-25°C.

Compatibility and stability:
Intravenous: cefepime is compatible at concentrations between 1 and 40 mg/ml with the following IV infusion fluids: 0.9% sodium chloride injection, 5% and 10% dextrose injection. 5% dextrose and 0.9% sodium chloride injection and 5% dextrose injection. These solutions maybe stored up to 24 hours at temperature 20 to 25° C or 7 days in a refrigerator 2 to 8°C.

Solutions of **CELRIM TZ®** like those of most beta-lactam antibiotics, should not be added to solutions of ampicillin at a concentration greater than 40 mg/ml, and should not be added to metronidazole, vancomycin, gentamicin, tobramycin, netilmicin sulfate or aminophylline because of potential interaction. However, if concurrent therapy with **CELRIM TZ®** is indicated each of these antibiotics can be administered separately. **CELRIM TZ®** should not be used with other drugs in a syringe and/or infusion bottle since compatibility has not been established. **CELRIM TZ®** should not be added to blood or blood products and/or albumin hydrolysates.

Shelf Life: Please refer to carton / label.

Storage: Store at a temperature not exceeding 30°C.
Protect from light.
Keep out of reach of children.

Presentation:
CELRIM TZ® is available as vials of 1.125 g.

BF/LL/38887/01

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

® - Registered trademark

Leaflet revised September 2019

To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free No.: **1800 102 9465** or e mail us at **drugsafety@biocon.com**