Biocon

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Cefoperazone and Tazobactam for injection

CEGAVA™ TZ 562.5mg / 1.125g xÉaÉÉuÉÉ ÊO eÉQ 562.5 LqéeÉÏ / 1.125eÉÏ

COMPOSITION

CEGAVA™ TZ 562.5 mg

Each vial contains:

Cefoperazone Sodium IP
Eq. to Cefoperazone 500mg
Tazobactam Sodium
Eq. to Tazobactam 62.5mg

CEGAVA™ TZ 1.125 g

Each vial contains:

Cefoperazone Sodium IP
Eq. to Cefoperazone 1000mg
Tazobactam Sodium
Eq. to Tazobactam 125mg

PHARMACEUTICAL FORM

Powder for injection.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Cefoperazone, combinations
ATC code: J01DD62.

Mechanism of Action

Cefoperazone is bactericidal in action. The antibacterial activity of the drug results from inhibition of nucleopeptide synthesis in the bacterial cell wall.

Tazobactam has little, clinically relevant activity against bacteria due to its reduced affinity to penicillin binding proteins. It is a β-lactamase inhibitor of the Richmond-Sykes class III penicillinases and cephalosporinases. It does not induce chromosomally mediated β-lactamases.

Spectrum

Cefoperazone is a broad spectrum antibiotic. Cefoperazone is generally less active *in vitro* against susceptible staphylococci than a first generation cephalosporin but has expanded spectrum of activity against gram negative bacteria. Cefoperazone with tazobactam is a useful combination for the treatment of infection due to extended-spectrum beta-lactamase (ESBL) producing organisms.

The following bacteria are sensitive to cefoperazone and tazobactam combination:

Gram-positive Aerobic Bacteria
Streptococcus pyogenes (Group A beta-hemolytic streptococci)
Streptococcus agalactiae (Group B beta-hemolytic streptococci)
Streptococcus viridans, *Streptococcus pneumonia*, *Streptococcus faecium* and *Streptococcus durans,* and *Enterococcus faecalis.*

Gram-negative Aerobic Bacteria
Citrobacter species (*Citrobacter diversus, Citrobacter freundi)*
Enterobacter species *(Enterobacter aerogens, Enterobacter cloacae)*
Escherichia coli, Klebsiella species *(Klebsiella oxytoca, Klebsiella pneumonia)*

Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia, Salmonella, Shigella, Yersinia enterocolitica, Pseudomonas aeruginosa, and certain other *Pseudomonas* species, *Haemophilus influenzae* and *Haemophilus parainfluenzae, Neisseria gonorrhoeae* including penicillinase producing strains, *Neisseria meningitides, and Bordetella pertussis.*

Anaerobic Bacteria
Gram-negative bacilli (including *Bacteroides fragilis*, other *Bacteroides* species, and *Fusobacterium* species).

Gram-positive and gram-negative cocci (including *Peptococcus*, *Peptostreptococcus,* and *Veillonella* species).

Gram-positive bacilli (including *Clostridium* and *Eubacterium*).

Pharmacokinetic Properties

Absorption

Cefoperazone is given parenterally as the sodium salt. Cefoperazone and tazobactam is not appreciably absorbed from the gastrointestinal tract. On intramuscular administration of cefoperazone (1 or 2 g) peak plasma concentrations were attained ranging from 65 to 97 micrograms/mL after 1 to 2 hours, whereas after a dose of 2 g of tazobactam, peak plasma concentrations ranged from 30 to 40 micrograms/mL within 30 to 50 minutes. The pharmacokinetics of tazobactam is reported to be nonlinear and dose-dependent. The plasma half-life of cefoperazone is about 2 hours, and tazobactam is 1 hour, but may be prolonged in neonates, in patients with hepatic or biliary-tract disease, severe renal impairment and end stage renal disease, and in patients with both renal and hepatic impairment. Cefoperazone is 82% to 93% bound to plasma proteins, depending on the concentration and 20% in case of tazobactam.

Distribution

Cefoperazone and tazobactam are widely distributed in body tissues and fluids, although penetration into the cerebrospinal fluid (CSF) is generally poor. The CSF concentration of cefoperazone is generally higher in patients with inflammation to the meninges. It crosses the placenta, and low concentrations have been detected in breast milk.

Metabolism and Excretion

Cefoperazone is excreted mainly in the bile where it rapidly achieves high concentrations. Up to 20% of tazobactam is also found to be excreted through bile. About 60% to 80% of tazobactam is excreted unchanged in the urine by glomerular filtration and tubular secretion within 24 hours. Up to 30% of cefoperazone is excreted unchanged in the urine within 12 to 24 hours; this proportion may be increased in patients with hepatic or biliary disease. Cefoperazone A, a degradation product less active than cefoperazone, has been found *in vivo,* rarely. Plasma concentrations of tazobactam are enhanced by probenecid. Tazobactam can be removed by hemodialysis.

Preclinical Safety Data

Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

CLINICAL PARTICULARS

Therapeutic Indications

Cefoperazone and tazobactam injection is indicated for the treatment of gynecological infections, urinary tract infections, and post-operative infections.

Combination Therapy:

Because of the broad spectrum of activity of cefoperazone and tazobactam, most infections can be treated adequately with this antibiotic combination alone. However, cefoperazone and tazobactam may also be used concomitantly with other antibiotics, if indicated. If an aminoglycoside is used, renal function should be monitored during the course of therapy.

Posology and Method of Administration

Cefoperazone and tazobactam are preferably administered by IV infusion but may also be given by deep IM injection. An IV infusion should be given slowly over 15 to 30 minutes.
The usual adult dosage of cefoperazone and tazobactam is 2 to 4 g daily given in equally divided doses every 12 hours (in terms of cefoperazone).

Directions for Use

- CEGAVA™ TZ 1.125 g
  Dissolve the contents with 10 mL of sterile Water for Injections IP for IV use and 3.8 mL of sterile Water for Injections IP for IM use.
- CEGAVA™ TZ 562.5 mg
  Dissolve the contents with 5 mL of Sterile Water for Injection IP for IV use and 1.9 mL of Sterile Water for Injections IP for I.M. use.
- For IV use if further dilution is required, it can be diluted with Sterile Water for Injections IP.

The solution should be allowed to stand a while, following reconstitution to allow any foaming to dissipate and permit visual inspection for complete dissolution. Vigorous and prolonged agitation may be necessary to dissolve cefoperazone.

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Contraindications
Cefoperazone and tazobactam are contraindicated in patients with a known allergy to penicillins, tazobactam, cefoperazone, or any of the cephalosporins.

Use of cephalosporin should be avoided in patients who have had an immediate type I (anaphylactic) reaction to penicillins. If a hypersensitivity reaction occurs during cefoperazone and tazobactam therapy, the drug should be discontinued and the patient treated with appropriate therapy, eg, epinephrine, corticosteroids, and maintenance of an adequate airway and oxygen as indicated.

Special Warnings and Precautions for Use
Warnings
Careful inquiry should be made to determine whether the patient has had previous immediate hypersensitivity reaction to cefoperazone, cephalosporins, penicillins, or other drugs before therapy with cefoperazone and tazobactam is instituted.
Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Precautions
Pediatric safety and efficacy of cefoperazone and tazobactam in children, younger than 12 years of age have not been established.

Drug Interactions
A reaction characterized by flushing, sweating, headache, and tachycardia has been reported when alcohol was ingested during and as late as the fifth day after cefoperazone administration. A similar reaction has been reported with certain other cephalosporins and patients should be cautioned concerning ingestion of alcoholic beverages in conjunction with administration of cefoperazone and tazobactam. For patients requiring artificial feeding orally or parenterally, solutions containing ethanol should be avoided.

Pregnancy and Lactation
Pregnancy
There are no adequate and controlled studies using cefoperazone and tazobactam in pregnant women and the drug should be used during pregnancy only when clearly indicated.

Lactation
Cefoperazone and tazobactam is distributed into milk, the drug should be used with caution in nursing women.

Effects on Ability to Drive and Use Machines
No special requirements.

Undesirable Effects
The following undesirable effects have been observed:
Local precautions: Phlebitis, pain and inflammation at the site of injection.

Systemic side effects: Hypersensitivity reactions including skin rash, fever, eosinophilia, urticaria, pruritus.

Hematologic effects: Slight decrease in hemoglobin, reversible neutropenia, hypoprothrombinemia with or without bleeding and vitamin-K deficiency.

Gastrointestinal effects: Dyspepsia, nausea, vomiting.

Hepatic effects: Mild transient elevation of serum aspartate amino transaminase (AST), alanine amino transaminase (ALT), and alkaline phosphatase.

Renal effects: Transient elevation of blood urea nitrogen (BUN) and serum creatinine.

Overdose
Limited information is available on the acute toxicity of cefoperazone sodium and tazobactam in humans. Overdosage of the drug would be expected to produce manifestations that are principally extensions of adverse reactions reported with the drug.

The fact that high CSF concentrations of beta-lactam antibiotics may cause neurological effects, including seizures, should be considered. Because cefoperazone and tazobactam can be both removed from circulation by hemodialysis, this procedure may enhance the elimination of the drug from the body, if overdosage occurs in patients with impaired renal function.

PHARMACEUTICAL PARTICULARS

Incompatibilities
None reported.

Shelf Life
24 months.

Storage and Precautions
- Store in a cool, dry and dark place.
- Keep out of reach of children.

Special Precautions for Disposal and Other Handling
No special requirements.

Nature and Contents of Container
CEGAVA™ TZ 1.125 g
20 mL moulded glass clear vial with 10 mL Water for Injections.

CEGAVA™ TZ 562.5 mg
10 mL moulded glass clear vial with 5mL Water for Injections.

MANUFACTURED BY
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