Package leaflet: Information for the user

CEFOZONE® (sterile cefoperazone, IP)
Formerly known as sterile cefoperazone sodium, IP

CEFOZONE® (cefoperazone), formerly known as cefoperazone sodium, is a sterile, semisynthetic, broad-spectrum, parenteral cephalosporin antibiotic for intravenous or intramuscular administration. It is the sodium salt of 7-[(R)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-(p -hydroxyphenyl)acetamido-3-[[(1-methyl- H -tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2. 0]oct-2-ene-2-carboxylate.

CEFOZONE is indicated for the treatment of the following infections when caused by susceptible organisms: Respiratory Tract Infections caused by S. pneumoniae, H. influenzae, S. aureus (penicillinase and non-penicillinase producing strains), S. pyogenesEfficacy of this organism in this organ system was studied in fewer than 10 infections. (Group A beta-hemolytic streptococci), P. aeruginosa, Klebsiella pneumoniae, E. coli, Proteus mirabilis, and Enterobacter species.

Peritonitis and Other Intra-abdominal Infections caused by E. coli, P. aeruginosa and anaerobic gram-negative bacilli (including Bacteroides fragilis).Bacterial Septicemia caused by S. pneumoniae, S. agalactiae, S. aureus, Pseudomonas aeruginosa, E. coli, Klebsiella spp., Klebsiella pneumoniae, Proteus species (indole-positive and indole-negative), Clostridium spp. and anaerobic gram-positive cocci.

Infections of the Skin and Skin Structures caused by S. aureus (penicillinase and non-penicillinase producing strains), S. pyogenes, and P. aeruginosa.
Pelvic Inflammatory Disease, Endometritis, and Other Infections of the Female Genital Tract caused by N. gonorrhoeae, S. epidermidis, S. agalactiae, E. coli, Clostridium spp., Bacteroides species (including Bacteroides fragilis), and anaerobic gram-positive cocci.

CEFOZONE, like other cephalosporins, has no activity against Chlamydia trachomatis. Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and C. trachomatis is one of the sIPected pathogens, appropriate anti-chlamydial coverage should be added.
Urinary Tract Infections caused by Escherichia coli and Pseudomonas aeruginosa. Enterococcal Infections: Although cefoperazone has been shown to be clinically effective in the treatment of infections caused by enterococci in cases of peritonitis and other intra-abdominal infections, infections of the skin and skin structures, pelvic inflammatory disease, endometritis and other infections of the female genital tract, and urinary tract infections, the majority of clinical isolates of enterococci tested are not susceptible to cefoperazone but fall just at or in the intermediate zone of susceptibility, and are moderately resistant to cefoperazone. However, in vitro susceptibility testing may not correlate directly with in vivo results. Despite this, cefoperazone therapy has resulted in clinical cures of enterococcal infections, chiefly in polymicrobial infections. Cefoperazone should be used in enterococcal infections with care and at doses that achieve satisfactory serum levels of cefoperazone.

Susceptibility Testing

Before instituting treatment with CEFOZONE, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Treatment may be started before results of susceptibility testing are available.

INDICATIONS AND USAGE

CEFOZONE is indicated for the treatment of the following infections when caused by susceptible organisms:

Respiratory Tract Infections caused by S. pneumoniae, H. influenzae, S. aureus (penicillinase and non-penicillinase producing strains), S. pyogenes [Efficacy of this organism in this organ system was studied in fewer than 10 infections.] (Group A beta-hemolytic streptococci), P. aeruginosa, Klebsiella pneumoniae, E. coli, Proteus mirabilis, and Enterobacter species.

Peritonitis and Other Intra-abdominal Infections caused by E. coli, P. aeruginosa and anaerobic gram-negative bacilli (including Bacteroides fragilis).

Bacterial Septicemia caused by S. pneumoniae, S. agalactiae, S. aureus, Pseudomonas aeruginosa, E. coli, Klebsiella spp., Klebsiella pneumoniae, Proteus species (indole-positive and indole-negative), Clostridium spp. and anaerobic gram-positive cocci.

Infections of the Skin and Skin Structures caused by S. aureus (penicillinase and non-penicillinase producing strains), S. pyogenes, and P. aeruginosa.

Pelvic Inflammatory Disease, Endometritis, and Other Infections of the Female Genital Tract caused by N. gonorrhoeae, S. epidermidis, S. agalactiae, E. coli, Clostridium spp., Bacteroides species (including Bacteroides fragilis), and anaerobic gram-positive cocci. CEFOZONE, like other cephalosporins, has no activity against Chlamydia trachomatis. Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and C. trachomatis is one of the sIPected pathogens, appropriate anti-chlamydial coverage should be added.

Urinary Tract Infections caused by Escherichia coli and Pseudomonas aeruginosa.
Enterococcal Infections: Although cefoperazone has been shown to be clinically effective in the treatment of infections caused by enterococci in cases of peritonitis and other intra-abdominal infections, infections of the skin and skin structures, pelvic inflammatory disease, endometritis and other infections of the female genital tract, and urinary tract infections, the majority of clinical isolates of enterococci tested are not susceptible to cefoperazone but fall just at or in the intermediate zone of susceptibility, and are moderately resistant to cefoperazone. However, in vitro susceptibility testing may not correlate directly with in vivo results. Despite this, cefoperazone therapy has resulted in clinical cures of enterococcal infections, chiefly in polymicrobial infections. Cefoperazone should be used in enterococcal infections with care and at doses that achieve satisfactory serum levels of cefoperazone.

Susceptibility Testing
Before instituting treatment with CEFOZONE, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Treatment may be started before results of susceptibility testing are available.
DOSAGE AND ADMINISTRATION
Sterile cefoperazone sodium can be administered by IM or IV injection (following dilution). However, the intent of this pharmacy bulk package is for the preparation of solutions for IV infusion only.
The usual adult daily dose of CEFOZONE is 2 to 4 grams per day administered in equally divided doses every 12 hours.
In severe infections or infections caused by less sensitive organisms, the total daily dose and/or frequency may be increased. Patients have been successfully treated with a total daily dosage of 6–12 grams divided into 2, 3, or 4 administrations ranging from 1.5 to 4 grams per dose.
When treating infections caused by Streptococcus pyogenes, therapy should be continued for at least 10 days.
If C. trachomatis is a sIPected pathogen, appropriate anti-chlamydial coverage should be added, because cefoperazone has no activity against this organism.

Solutions of CEFOZONE and aminoglycoside should not be directly mixed, since there is a physical incompatibility between them. If combination therapy with CEFOZONE and an aminoglycoside is contemplated (see INDICATIONS) this can be accomplished by sequential intermittent intravenous infusion provided that separate secondary intravenous tubing is used, and that the primary intravenous tubing is adequately irrigated with an approved diluent between doses. It is also suggested that CEFOZONE be administered prior to the aminoglycoside. In vitro testing of the effectiveness of drug combination(s) is recommended.

In a pharmacokinetic study, a total daily dose of 16 grams was administered to severely immunocompromised patients by constant infusion without complications. Steady-state serum concentrations were approximately 150 mcg/mL in these patients.

RECONSTITUTION
The following solutions may be used for the initial reconstitution of CEFOZONE sterile powder: General Reconstitution Procedures

CEFOZONE sterile powder for intravenous or intramuscular use may be initially reconstituted with any compatible solution mentioned above in Table 1. Solutions should be allowed to stand after reconstitution to allow any foaming to dissipate to permit visual inspection for complete solubilization. Vigorous and prolonged agitation may be necessary to solubilize CEFOZONE in higher concentrations (above 333 mg cefoperazone/mL). The maximum solubility of CEFOZONE sterile powder is approximately 475 mg cefoperazone/mL of compatible diluent.

Preparation for Intravenous Use
General : CEFOZONE concentrations between 2 mg/mL and 50 mg/mL are recommended for intravenous administration.

STORAGE AND STABILITY
CEFOZONE sterile powder is to be stored at or below 25°C (77°F) and protected from light prior to reconstitution. After reconstitution, protection from light is not necessary.
The following parenteral diluents and approximate concentrations of CEFOZONE provide stable solutions under the following conditions for the indicated time periods. (After the indicated time periods, unused portions of solutions should be discarded.)
Reconstituted CEFOZONE solutions may be stored in plastic syringes, or in flexible plastic parenteral solution containers.

Frozen samples should be thawed at room temperature before use. After thawing, unused portions should be discarded.
Do not refreeze.

HOW SUPPLIED
CEFOZONE sterile powder is available in Pharmacy Bulk Package containing cefoperazone sodium equivalent to 10 g cefoperazone × 10 mL.

OTHER SIZE PACKAGES AVAILABLE
CEFOZONE sterile powder is available in vials containing cefoperazone sodium equivalent to 1 g cefoperazone × 10 and 2 g cefoperazone × 10 for intramuscular and intravenous administration.

Rx only
WARNINGS
BEFORE THERAPY WITH CEFOZONE IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.
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.

Treatment with broad-spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by Clostridium difficile is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by C. difficile. Other causes of colitis should also be considered.

PRECAUTIONS

Although transient elevations of the BUN and serum creatinine have been observed, CEFOZONE alone does not appear to cause significant nephrotoxicity. However, concomitant administration of aminoglycosides and other cephalosporins has caused nephrotoxicity.

CEFOZONE is extensively excreted in bile. The serum half-life of CEFOZONE is increased 2–4 fold in patients with hepatic disease and/or biliary obstruction. In general, total daily dosage above 4 g should not be necessary in such patients. If higher dosages are used, serum concentrations should be monitored.

Because renal excretion is not the main route of elimination of CEFOZONE (see CLINICAL PHARMACOLOGY), patients with renal failure require no adjustment in dosage when usual doses are administered. When high doses of CEFOZONE are used, concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

The half-life of CEFOZONE is reduced slightly during hemodialysis. Thus, dosing should be scheduled to follow a dialysis period. In patients with both hepatic dysfunction and significant renal disease, CEFOZONE dosage should not exceed 1–2 g daily without close monitoring of serum concentrations.
As with other antibiotics, vitamin K deficiency has occurred rarely in patients treated with CEFOZONE. The mechanism is most probably related to the suppression of gut flora which normally synthesize this vitamin. Those at risk include patients with a poor nutritional status, malabsorption states (e.g., cystic fibrosis), alcoholism, and patients on prolonged hyper-alimentation regimens (administered either intravenously or via a naso-gastric tube).

Prothrombin time should be monitored in these patients and exogenous vitamin K administered as indicated.
A disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia has been reported when alcohol (beer, wine) was ingested within 72 hours after CEFOZONE administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOZONE. A similar reaction has been reported with other cephalosporins.
Prolonged use of CEFOZONE may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Not all pack sizes may be marketed.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

SCHEDULE 'H1' DRUG - Warning :
It is dangerous to take this preparation except in accordance with the medical advice.- Not to be sold by retail without the prescription of a Registered Medical Practitioner".

Mfg. Lic.No.: G/28A/5871-A
Manufactured in India By:
TAJ PHARMACEUTICALS LTD.
at : 615, GIDC, Kerala, Bavla, Dist.Ahmedabad - 438225.
Gujarat, INDIA
WHO-cGMP & ISO 9001:2015 Certified Company

Marketed by: TAJ PHARMA INDIA LTD.
15-6-108 Afzal Gunj,Hyderabad TS 500 012, India.

INDIA : Combi Pack Vial +Water for Injection PER PACK.
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CEFOZONE
Sterile cefoperazone sodium
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