

CEFOBID[®]

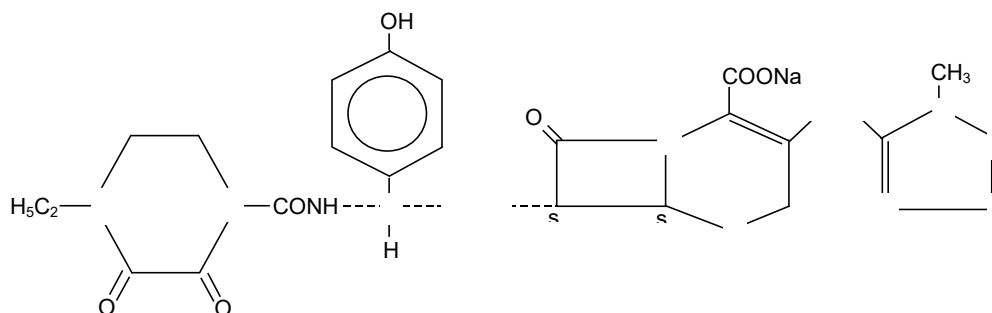
(sterile cefoperazone)

For Intravenous or Intramuscular Use

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CEFOBID and other antibacterial drugs, CEFOBID should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

CEFOBID[®] (sterile cefoperazone), formerly known as sterile cefoperazone sodium, contains cefoperazone as cefoperazone sodium. It is a semisynthetic, broad-spectrum cephalosporin antibacterial drug. Chemically, cefoperazone sodium is sodium (6*R*,7*R*)-7-[(*R*)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-(*p*-hydroxyphenyl)-acetamido-3-[[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. Its molecular formula is C₂₅H₂₆N₉NaO₈S₂ with a molecular weight of 667.65. The structural formula is given below:



CEFOBID (sterile cefoperazone) contains 34 mg sodium (1.5 mEq) per gram (g). CEFOBID is a white powder which is freely soluble in water. The pH of a 25% (w/v) freshly reconstituted solution varies between 4.5–6.5 and the solution ranges from colorless to straw yellow depending on the concentration.

CEFOBID (sterile cefoperazone) in crystalline form is supplied in vials containing 1 g or 2 g cefoperazone as cefoperazone sodium for intravenous or intramuscular administration.

CLINICAL PHARMACOLOGY

High serum and bile levels of CEFOBID are attained after a single dose of the drug. Table 1 demonstrates the serum concentrations of CEFOBID in normal volunteers following either a single 15-minute constant rate intravenous infusion of 1, 2, 3 or 4 g of the drug, or a single intramuscular injection of 1 or 2 g of the drug.

Table 1. Cefoperazone Serum Concentrations

Dose/Route	Mean Serum Concentrations (mcg/mL)						
	0*	0.5 hr	1 hr	2 hr	4 hr	8 hr	12 hr
1 g IV	153	114	73	38	16	4	0.5
2 g IV	252	153	114	70	32	8	2
3 g IV	340	210	142	89	41	9	2
4 g IV	506	325	251	161	71	19	6
1 g IM	32**	52	65	57	33	7	1
2 g IM	40**	69	93	97	58	14	4

* Hours post-administration, with 0 time being the end of the infusion.
** Values obtained 15 minutes post-injection.

The mean serum half-life of CEFOBID is approximately 2.0 hours, independent of the route of administration.

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

In vitro studies with human serum indicate that the degree of CEFOBID reversible protein binding varies with the serum concentration from 93% at 25 mcg/mL of CEFOBID to 90% at 250 mcg/mL and 82% at 500 mcg/mL.

CEFOBID achieves therapeutic concentrations in the following body tissues and fluids:

Table 2.

Tissue or Fluid	Dose	Concentration
Ascitic Fluid	2 g	64 mcg/mL
Cerebrospinal Fluid (in patients with inflamed meninges)	50 mg/kg	1.8 mcg/mL to 8.0 mcg/mL
Urine	2 g	3,286 mcg/mL
Sputum	3 g	6.0 mcg/mL
Endometrium	2 g	74 mcg/g
Myometrium	2 g	54 mcg/g
Palatine Tonsil	1 g	8 mcg/g
Sinus Mucous Membrane	1 g	8 mcg/g
Umbilical Cord Blood	1 g	25 mcg/mL
Amniotic Fluid	1 g	4.8 mcg/mL
Lung	1 g	28 mcg/g
Bone	2 g	40 mcg/g

CEFOBID is excreted mainly in the bile. Maximum bile concentrations are generally obtained between one and three hours following drug administration and exceed concurrent serum concentrations by up to 100 times. Reported biliary concentrations of CEFOBID range from 66 mcg/mL at 30 minutes to as high as 6000 mcg/mL at 3 hours after an intravenous bolus injection of 2 g.

Following a single intramuscular or intravenous dose, the urinary recovery of CEFOBID over a 12-hour period averages 20–30%. No significant quantity of metabolites has been found in the urine. Urinary concentrations greater than 2200 mcg/mL have been obtained following a 15-minute infusion of a 2 g dose. After an IM injection of 2 g, peak urine concentrations of almost 1000 mcg/mL have been obtained, and therapeutic levels are maintained for 12 hours.

Repeated administration of CEFOBID at 12-hour intervals does not result in accumulation of the drug in normal subjects. Peak serum concentrations, areas under the curve (AUC's), and serum half-lives in patients with severe renal insufficiency are not significantly different from those in normal volunteers. In patients with hepatic dysfunction, the serum half-life is prolonged and urinary excretion is increased. In patients with combined renal and hepatic insufficiencies, CEFOBID may accumulate in the serum.

CEFEBID has been used in pediatrics, but the safety and effectiveness in children have not been established. The half-life of CEFEBID in serum is 6–10 hours in low birth-weight neonates.

Microbiology

Mechanism of Action

Cefoperazone, a third-generation cephalosporin, interferes with cell wall synthesis by binding to the penicillin-binding proteins (PBPs), thus preventing cross-linking of nascent peptidoglycan.

Resistance

There are 3 principal mechanisms of resistance to cefoperazone: mutations in the target PBPs, which occur primarily in gram-positive bacteria; production of extended spectrum beta-lactamases or over-expression of chromosomally determined beta-lactamases in gram-negative bacteria; reduced uptake or active efflux in certain gram-negative bacteria.

Interactions with Other Antimicrobials

When tested *in vitro*, cefoperazone has demonstrated synergistic interactions with aminoglycosides against gram-negative bacilli. The clinical significance of these *in vitro* findings is unknown.

Antimicrobial Activity

Cefoperazone has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections (see INDICATIONS AND USAGE).

Aerobic bacteria:

Gram-positive bacteria

- *Staphylococcus aureus* (methicillin-susceptible isolates only)
- *Staphylococcus epidermidis* (methicillin-susceptible isolates only)
- *Streptococcus agalactiae* (Group B beta-hemolytic streptococci)
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes* (Group A beta-hemolytic streptococci)

Gram-negative bacteria

- *Citrobacter* species
- *Enterobacter* species
- *Escherichia coli*
- *Haemophilus influenzae*
- *Klebsiella* species
- *Morganella morganii*
- *Neisseria gonorrhoeae*
- *Proteus mirabilis*
- *Proteus vulgaris*
- *Providencia rettgeri*
- *Providencia stuartii*
- *Pseudomonas* species
- *Serratia marcescens*

Anaerobic bacteria:

- Gram-positive cocci (including *Peptococcus* and *Peptostreptococcus* spp.)
- *Clostridioides* species
- *Bacteroides* species

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for cefoperazone against isolates of similar genus or organism group. However, the efficacy of cefoperazone in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

Aerobic bacteria:**Gram-negative bacteria**

- *Bordetella pertussis*
- *Neisseria meningitidis*
- *Salmonella* spp.
- *Serratia liquefaciens*
- *Shigella* spp.
- *Yersinia enterocolytica*

Anaerobic bacteria:

- *Eubacterium* spp.
- *Fusobacterium* spp.

Susceptibility Test Methods

For specific information regarding susceptibility test interpretive criteria, and associated test methods and quality control standards recognized by FDA for this drug, please see <https://www.fda.gov/STIC>.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CEFOBID and other antibacterial drugs. CEFOBID should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CEFOBID 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** (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), *Clostridioides* 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*, *Clostridioides* spp.,* *Bacteroides* species (including *Bacteroides fragilis*), and anaerobic gram-positive cocci.

Cefobid® has no activity against *Chlamydia trachomatis*. Therefore, when Cefobid is used in the treatment of patients with pelvic inflammatory disease and *C. trachomatis* is one of the suspected 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.

* Efficacy against this organism in this organ system was studied in fewer than 10 infections.

Combination Therapy

Synergy between CEFOBID and aminoglycosides has been demonstrated with many gram-negative bacilli. However, such enhanced activity of these combinations is not predictable. If such therapy is considered, *in vitro* susceptibility tests should be performed to determine the activity of the drugs in combination, and renal function should be monitored carefully. (See PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections.)

CONTRAINDICATIONS

CEFOBID is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class or in patients who have demonstrated severe hypersensitivity to beta-lactams (see WARNINGS).

WARNINGS

Hypersensitivity Reactions

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING BETA-LACTAM ANTIBACTERIALS, INCLUDING CEFOPERAZONE. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. BEFORE THERAPY WITH CEFOBID IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, CARBAPENEMS OR OTHER DRUGS. IF AN ALLERGIC REACTION OCCURS, CEFOPERAZONE SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED.

Severe and occasionally fatal skin reactions such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and exfoliative dermatitis have been reported in patients on CEFOBID therapy. If a severe skin reaction occurs CEFOBID should be discontinued and appropriate therapy should be initiated (see ADVERSE REACTIONS).

***Clostridioides difficile*-Associated Diarrhea**

Clostridioides difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CEFOBID, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Hemorrhage

Serious hemorrhage cases, including fatalities, have been reported with cefoperazone. Monitor for signs of bleeding, thrombocytopenia, and coagulopathy. Discontinue CEFOBID if there is persistent bleeding and no alternative explanations are identified.

Encephalopathy

Encephalopathy (including decreased consciousness, delirium, seizures) has been reported with the use of CEFOBID. Most cases occurred in patients with renal impairment. The adverse reactions resolved after discontinuation of CEFOBID and/or hemodialysis/continuous veno-venous hemofiltration. If encephalopathy occurs, consider discontinuing CEFOBID and institute supportive measures.

PRECAUTIONS

General

Prescribing CEFOBID in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

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

CEFOBID is extensively excreted in bile. The serum half-life of CEFOBID 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 CEFOBID (see CLINICAL PHARMACOLOGY), patients with renal failure require no adjustment in dosage when usual doses are administered. When high doses of CEFOBID 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 CEFOBID 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, CEFOBID dosage should not exceed 1–2 g daily without close monitoring of serum concentrations.

As with other antibacterial drugs, vitamin K deficiency resulting in coagulopathy has occurred in patients treated with CEFOBID. The mechanism is 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). Hypoprothrombinemia with or without bleeding has been reported. Prothrombin time should be monitored in these patients, and patients receiving anticoagulant therapy, 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 CEFOBID administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOBID.

Prolonged use of CEFOBID 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.

CEFOBID should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Information for Patients

Patients should be counseled that antibacterial drugs including CEFOBID should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When CEFOBID is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treated by CEFOBID or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibacterial drugs which usually ends when the drug is discontinued. Sometimes after starting treatment with antibacterial drugs, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial drug. If this occurs, patients should contact their physician as soon as possible.

Drug/Laboratory Test Interactions

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. The maximum duration of CEFOBID animal toxicity studies is six months. In none of the *in vivo* or *in vitro* genetic toxicology studies did CEFOBID show any mutagenic potential at either the chromosomal or subchromosomal level. CEFOBID produced no impairment of fertility and had no effects on general reproductive performance or fetal development when administered

subcutaneously at daily doses up to 500 to 1000 mg/kg prior to and during mating, and to pregnant female rats during gestation. These doses are 10 to 20 times the estimated usual single clinical dose. CEFOBID had adverse effects on the testes of prepubertal rats at all doses tested. Subcutaneous administration of 1000 mg/kg per day (approximately 16 times the average adult human dose) resulted in reduced testicular weight, arrested spermatogenesis, reduced germinal cell population and vacuolation of Sertoli cell cytoplasm. The severity of lesions was dose dependent in the 100 to 1000 mg/kg per day range; the low dose caused a minor decrease in spermatocytes. This effect has not been observed in adult rats. Histologically the lesions were reversible at all but the highest dosage levels. However, these studies did not evaluate subsequent development of reproductive function in the rats. The relationship of these findings to humans is unknown.

Usage in Pregnancy

Reproduction studies have been performed in mice, rats, and monkeys at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to CEFOBID. Cefoperazone crosses the placental barrier. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Usage in Nursing Mothers

Only low concentrations of CEFOBID are excreted in human milk. Although CEFOBID passes poorly into breast milk of nursing mothers, caution should be exercised when CEFOBID is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established. For information concerning testicular changes in prepubertal rats (see **Carcinogenesis, Mutagenesis, Impairment of Fertility**).

Geriatric Use

Clinical studies of CEFOBID[®] (sterile cefoperazone sodium) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Clinical Trials Experience

In clinical studies the following adverse effects were observed and were considered to be related to CEFOBID therapy or of uncertain etiology:

Hypersensitivity: As with all cephalosporins, hypersensitivity manifested by skin reactions (1 patient in 45), drug fever (1 in 260), or a change in Coombs' test (1 in 60) has been reported.

These reactions are more likely to occur in patients with a history of allergies, particularly to penicillin.

Hematology: As with other beta-lactam antibacterial drugs, reversible neutropenia may occur with prolonged administration. Slight decreases in neutrophil count (1 patient in 50) have been reported. Decreased hemoglobins (1 in 20) or hematocrits (1 in 20) have been reported, which is consistent with published literature on other cephalosporins. Transient eosinophilia has occurred in 1 patient in 10.

Hepatic: Of 1285 patients treated with cefoperazone in clinical trials, one patient with a history of liver disease developed significantly elevated liver function enzymes during CEFOBID therapy. Clinical signs and symptoms of nonspecific hepatitis accompanied these increases. After CEFOBID therapy was discontinued, the patient's enzymes returned to pre-treatment levels and the symptomatology resolved. As with other antibacterial drugs that achieve high bile levels, mild transient elevations of liver function enzymes have been observed in 5–10% of the patients receiving CEFOBID therapy. The relevance of these findings, which were not accompanied by overt signs or symptoms of hepatic dysfunction, has not been established.

Gastrointestinal: Diarrhea or loose stools has been reported in 1 in 30 patients. Most of these experiences have been mild or moderate in severity and self-limiting in nature. In all cases, these symptoms responded to symptomatic therapy or ceased when cefoperazone therapy was stopped. Nausea and vomiting have been reported rarely.

Symptoms of pseudomembranous colitis can appear during or for several weeks subsequent to antibacterial therapy (see WARNINGS).

Renal Function Tests: Transient elevations of the BUN (1 in 16) and serum creatinine (1 in 48) have been noted.

Local Reactions: CEFOBID is well tolerated following intramuscular administration. Occasionally, transient pain (1 in 140) may follow administration by this route. When CEFOBID is administered by intravenous infusion some patients may develop phlebitis (1 in 120) at the infusion site.

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of CEFOBID. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Coagulopathy, thrombocytopenia, hypoprothrombinaemia (see PRECAUTIONS)

Immune System disorders: Anaphylactic reaction including shock and fatal cases (see WARNINGS), acute myocardial ischemia with or without myocardial infarction may occur as part of an allergic reaction.

Hepatobiliary Disorders: Jaundice, hepatic dysfunction

Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, pruritus

Vascular Disorders: Hemorrhage (see WARNINGS)

Nervous System Disorders: Encephalopathy (including decreased consciousness, delirium, seizures) (see WARNINGS)

DOSAGE AND ADMINISTRATION

The usual adult daily dose of CEFOBID (sterile cefoperazone) is 2 to 4 g 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 g divided into 2, 3 or 4 administrations ranging from 1.5 to 4 g per dose.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least 10 days.

If *C. trachomatis* is a suspected pathogen, appropriate anti-chlamydial coverage should be added, because cefoperazone has no activity against this organism.

Solutions of CEFOBID and aminoglycoside should not be directly mixed, since there is a physical incompatibility between them. If combination therapy with CEFOBID and an aminoglycoside is contemplated (see INDICATIONS AND USAGE) 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 CEFOBID be administered prior to the aminoglycoside. *In vitro* testing of the effectiveness of drug combination(s) is recommended.

RECONSTITUTION

The following solutions may be used for the initial reconstitution of CEFOBID (sterile cefoperazone).

Table 3. Solutions for Initial Reconstitution

5% Dextrose Injection (USP)	0.9% Sodium Chloride Injection (USP)
5% Dextrose and 0.9% Sodium Chloride Injection (USP)	Normosol® M and 5% Dextrose Injection
5% Dextrose and 0.2% Sodium Chloride Injection (USP)	Normosol® R
10% Dextrose Injection (USP)	Sterile Water for Injection*

Bacteriostatic Water for Injection [Benzyl Alcohol or Parabens] (USP)*†

* Not to be used as a vehicle for intravenous infusion.

† Preparations containing Benzyl Alcohol should not be used in neonates.

General Reconstitution Procedures

CEFOBID (sterile cefoperazone) for intravenous or intramuscular use may be initially reconstituted with any compatible solution mentioned above in Table 3. 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 CEFOBID in higher concentrations (above 333 mg cefoperazone/mL). The maximum solubility of CEFOBID (sterile cefoperazone) is approximately 475 mg cefoperazone/mL of compatible diluent.

Preparation for Intravenous Use

General: CEFOBID (sterile cefoperazone) concentrations between 2 mg/mL and 50 mg/mL are recommended for intravenous administration.

Preparation of Vials: Vials of CEFOBID (sterile cefoperazone) may be initially reconstituted with a minimum of 2.8 mL per g of cefoperazone of any compatible reconstituting solution appropriate for intravenous administration listed above in Table 3. For ease of reconstitution the use of 5 mL of compatible solution per g of CEFOBID is recommended. The entire quantity of the resulting solution should then be withdrawn for further dilution and administration using any of the following vehicles for intravenous infusion:

Table 4. Vehicles for Intravenous Infusion

5% Dextrose Injection (USP)	Lactated Ringer's Injection (USP)
5% Dextrose and Lactated Ringer's Injection	0.9% Sodium Chloride Injection (USP)
5% Dextrose and 0.9% Sodium Chloride Injection (USP)	Normosol [®] M and 5% Dextrose Injection
5% Dextrose and 0.2% Sodium Chloride Injection (USP)	Normosol [®] R
10% Dextrose Injection (USP)	

The resulting intravenous solution should be administered in one of the following manners:

Intermittent Infusion: Solutions of CEFOBID should be administered over a 15–30 minute time period.

Continuous Infusion: CEFOBID can be used for continuous infusion after dilution to a final concentration of between 2 and 25 mg cefoperazone per mL.

Preparation for Intramuscular Injection

Any suitable solution listed above may be used to prepare CEFOBID (sterile cefoperazone) for intramuscular injection. When concentrations of 250 mg/mL or more are to be administered, a lidocaine solution should be used. These solutions should be prepared using a combination of Sterile Water for Injection and 2% Lidocaine Hydrochloride Injection (USP) that approximates a 0.5% Lidocaine Hydrochloride Solution. A two-step dilution process as follows is

recommended: First, add the required amount of Sterile Water for Injection and agitate until CEFOBID powder is completely dissolved. Second, add the required amount of 2% lidocaine and mix.

	Final Cefoperazone Concentration	Step 1 Volume of Sterile Water	Step 2 Volume of 2% Lidocaine	Withdrawable Volume*†
1 g vial	333 mg/mL	2.0 mL	0.6 mL	3 mL
	250 mg/mL	2.8 mL	1.0 mL	4 mL
2 g vial	333 mg/mL	3.8 mL	1.2 mL	6 mL
	250 mg/mL	5.4 mL	1.8 mL	8 mL

When a diluent other than Lidocaine HCl Injection (USP) is used reconstitute as follows:

	Cefoperazone Concentration	Volume of Diluent to be Added	Withdrawable Volume*
1 g vial	333 mg/mL	2.6 mL	3 mL
	250 mg/mL	3.8 mL	4 mL
2 g vial	333 mg/mL	5.0 mL	6 mL
	250 mg/mL	7.2 mL	8 mL

* There is sufficient excess present to allow for withdrawal of the stated volume.

† Final lidocaine concentration will approximate that obtained if a 0.5% Lidocaine Hydrochloride Solution is used as diluent.

STORAGE AND STABILITY

CEFOBID (sterile cefoperazone) 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 CEFOBID provide stable solutions under the following conditions for the indicated time periods. (After the indicated time periods, unused portions of solutions should be discarded.)

Room Temperature (15°–25°C/59°–77°F)

24 Hours	Approximate Concentrations
Bacteriostatic Water for Injection [Benzyl Alcohol or Parabens] (USP).....	300 mg/mL
5% Dextrose Injection (USP).....	2 mg to 50 mg/mL
5% Dextrose and Lactated Ringer’s Injection.....	2 mg to 50 mg/mL
5% Dextrose and 0.9% Sodium Chloride Injection (USP).....	2 mg to 50 mg/mL
5% Dextrose and 0.2% Sodium Chloride Injection (USP).....	2 mg to 50 mg/mL
10% Dextrose Injection (USP).....	2 mg to 50 mg/mL
Lactated Ringer’s Injection (USP).....	2 mg/mL
0.5% Lidocaine Hydrochloride Injection (USP).....	300 mg/mL
0.9% Sodium Chloride Injection (USP).....	2 mg to 300 mg/mL
Normosol® M and 5% Dextrose Injection.....	2 mg to 50 mg/mL
Normosol® R.....	2 mg to 50 mg/mL
Sterile Water for Injection.....	300 mg/mL

Reconstituted CEFOBID solutions may be stored in glass or plastic syringes, or in glass or flexible plastic parenteral solution containers.

Refrigerator Temperature (2°–8°C/36°–46°F)

5 Days	Approximate Concentrations
Bacteriostatic Water for Injection [Benzyl Alcohol or Parabens] (USP).....	300 mg/mL
5% Dextrose Injection (USP).....	2 mg to 50 mg/mL
5% Dextrose and 0.9% Sodium Chloride Injection (USP).....	2 mg to 50 mg/mL
5% Dextrose and 0.2% Sodium Chloride Injection (USP).....	2 mg to 50 mg/mL
Lactated Ringer’s Injection (USP).....	2 mg/mL
0.5% Lidocaine Hydrochloride Injection (USP).....	300 mg/mL
0.9% Sodium Chloride Injection (USP).....	2 mg to 300 mg/mL
Normosol® M and 5% Dextrose Injection.....	2 mg to 50 mg/mL
Normosol® R.....	2 mg to 50 mg/mL
Sterile Water for Injection.....	300 mg/mL

Reconstituted CEFOBID solutions may be stored in glass or plastic syringes, or in glass or flexible plastic parenteral solution containers.

Freezer Temperature (–20° to –10°C/–4° to 14°F)

	Approximate Concentrations
3 Weeks	
5% Dextrose Injection (USP).....	50 mg/mL
5% Dextrose and 0.9% Sodium Chloride Injection (USP).....	2 mg/mL
5% Dextrose and 0.2% Sodium Chloride Injection (USP).....	2 mg/mL
5 Weeks	
0.9% Sodium Chloride Injection (USP).....	300 mg/mL
Sterile Water for Injection.....	300 mg/mL
Reconstituted CEFOBID 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

CEFOBID® (sterile cefoperazone) is available in vials containing cefoperazone sodium equivalent to 1 g cefoperazone × 10 (NDC 0049-1201-83) and 2 g cefoperazone × 10 (NDC 0049-1202-83) for intramuscular and intravenous administration.

OTHER SIZE PACKAGES AVAILABLE

CEFOBID® (sterile cefoperazone) is available in 10 g (NDC 0049-1219-28) Pharmacy Bulk Package for intravenous administration.

Rx only

This product’s labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.



Distributed by
Roerig
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New York, NY 10001

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CEFOBID[®]

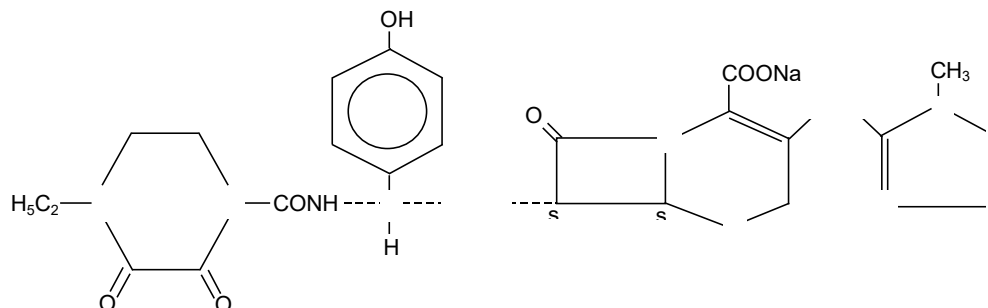
(sterile cefoperazone, USP)

PHARMACY BULK PACKAGE
NOT FOR DIRECT INFUSION

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CEFEBID and other antibacterial drugs, CEFEBID should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

CEFOBID[®] (cefoperazone), formerly known as cefoperazone sodium, is a sterile, semisynthetic, broad-spectrum, parenteral cephalosporin antibacterial drug 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-(1-methyl-*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. Its chemical formula is C₂₅H₂₆N₉NaO₈S₂ with a molecular weight of 667.65. The structural formula is given below:



CEFOBID contains 34 mg sodium (1.5 mEq) per gram (g). CEFEBID is a white powder which is freely soluble in water. The pH of a 25% (w/v) freshly reconstituted solution varies between 4.5–6.5 and the solution ranges from colorless to straw yellow depending on the concentration.

CEFOBID in crystalline form is supplied in vials equivalent to 1 g or 2 g of cefoperazone.

A pharmacy bulk package is a container of a sterile preparation for parenteral use that contains many single doses.

This Pharmacy Bulk Package is for use in a pharmacy admixture service; it provides many single doses of cefoperazone for addition to suitable parenteral fluids in the preparation of admixtures for intravenous infusion. (See DOSAGE AND ADMINISTRATION, and DIRECTIONS FOR PROPER USE OF PHARMACY BULK PACKAGE.)

CLINICAL PHARMACOLOGY

High serum and bile levels of CEFOBID are attained after a single dose of the drug. Table 1 demonstrates the serum concentrations of CEFOBID in normal volunteers following either a single 15-minute constant rate intravenous infusion of 1, 2, 3 or 4 g of the drug, or a single intramuscular injection of 1 or 2 g of the drug.

Table 1. Cefoperazone Serum Concentrations

Dose/Route	Mean Serum Concentrations (mcg/mL)						
	0*	0.5 hr	1 hr	2 hr	4 hr	8 hr	12 hr
1 g IV	153	114	73	38	16	4	0.5
2 g IV	252	153	114	70	32	8	2
3 g IV	340	210	142	89	41	9	2
4 g IV	506	325	251	161	71	19	6
1 g IM	32**	52	65	57	33	7	1
2 g IM	40**	69	93	97	58	14	4

* Hours post-administration, with 0 time being the end of the infusion.

** Values obtained 15 minutes post-injection.

The mean serum half-life of CEFOBID is approximately 2.0 hours, independent of the route of administration.

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

In vitro studies with human serum indicate that the degree of CEFOBID reversible protein binding varies with the serum concentration from 93% at 25 mcg/mL of CEFOBID to 90% at 250 mcg/mL and 82% at 500 mcg/mL.

CEFOBID achieves therapeutic concentrations in the following body tissues and fluids:

Table 2.

Tissue or Fluid	Dose	Concentration
Ascitic Fluid	2 g	64 mcg/mL
Cerebrospinal Fluid (in patients with inflamed meninges)	50 mg/kg	1.8 mcg/mL to 8.0 mcg/mL
Urine	2 g	3,286 mcg/mL
Sputum	3 g	6.0 mcg/mL
Endometrium	2 g	74 mcg/g
Myometrium	2 g	54 mcg/g
Palatine Tonsil	1 g	8 mcg/g
Sinus Mucous Membrane	1 g	8 mcg/g
Umbilical Cord Blood	1 g	25 mcg/mL
Amniotic Fluid	1 g	4.8 mcg/mL
Lung	1 g	28 mcg/g
Bone	2 g	40 mcg/g

CEFOBID is excreted mainly in the bile. Maximum bile concentrations are generally obtained between one and three hours following drug administration and exceed concurrent serum concentrations by up to 100 times. Reported biliary concentrations of CEFOBID range from 66 mcg/mL at 30 minutes to as high as 6000 mcg/mL at 3 hours after an intravenous bolus injection of 2 g.

Following a single intramuscular or intravenous dose, the urinary recovery of CEFOBID over a 12-hour period averages 20–30%. No significant quantity of metabolites has been found in the urine. Urinary concentrations greater than 2200 mcg/mL have been obtained following a 15-minute infusion of a 2 g dose. After an IM injection of 2 g, peak urine concentrations of almost 1000 mcg/mL have been obtained, and therapeutic levels are maintained for 12 hours.

Repeated administration of CEFOBID at 12-hour intervals does not result in accumulation of the drug in normal subjects. Peak serum concentrations, areas under the curve (AUC's), and serum half-lives in patients with severe renal insufficiency are not significantly different from those in normal volunteers. In patients with hepatic dysfunction, the serum half-life is prolonged and urinary excretion is increased. In patients with combined renal and hepatic insufficiencies, CEFOBID may accumulate in the serum.

CEFOBID has been used in pediatrics, but the safety and effectiveness in children have not been established. The half-life of CEFOBID in serum is 6–10 hours in low birth-weight neonates.

Microbiology

Mechanism of Action

Cefoperazone, a third-generation cephalosporin, interferes with cell wall synthesis by binding to the penicillin-binding proteins (PBPs), thus preventing cross-linking of nascent peptidoglycan.

Resistance

There are 3 principal mechanisms of resistance to cefoperazone: mutations in the target PBPs, which occur primarily in gram-positive bacteria; production of extended spectrum beta-lactamases or over-expression of chromosomally determined beta-lactamases in gram-negative bacteria; reduced uptake or active efflux in certain gram-negative bacteria.

Interactions with Other Antimicrobials

When tested *in vitro*, cefoperazone has demonstrated synergistic interactions with aminoglycosides against gram-negative bacilli. The clinical significance of these *in vitro* findings is unknown.

Antimicrobial Activity

Cefoperazone has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections (see INDICATIONS AND USAGE).

Aerobic bacteria:**Gram-positive bacteria**

- *Staphylococcus aureus* (methicillin-susceptible isolates only)
- *Staphylococcus epidermidis* (methicillin-susceptible isolates only)
- *Streptococcus agalactiae* (Group B beta-hemolytic streptococci)
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes* (Group A beta-hemolytic streptococci)

Gram-negative bacteria

- *Citrobacter* species
- *Enterobacter* species
- *Escherichia coli*
- *Haemophilus influenzae*
- *Klebsiella* species
- *Morganella morganii*
- *Neisseria gonorrhoeae*
- *Proteus mirabilis*
- *Proteus vulgaris*
- *Providencia rettgeri*
- *Providencia stuartii*
- *Pseudomonas* species
- *Serratia marcescens*

Anaerobic bacteria:

- Gram-positive cocci (including *Peptococcus* and *Peptostreptococcus* spp.)
- *Clostridioides* species
- *Bacteroides* species

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for cefoperazone against isolates of similar genus or organism group. However, the efficacy of cefoperazone in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

Aerobic bacteria:**Gram-negative bacteria**

- *Bordetella pertussis*
- *Neisseria meningitidis*
- *Salmonella* spp.
- *Serratia liquefaciens*
- *Shigella* spp.
- *Yersinia enterocolytica*

Anaerobic bacteria:

- *Eubacterium* spp.
- *Fusobacterium* spp.

Susceptibility Test Methods

For specific information regarding susceptibility test interpretive criteria, and associated test methods and quality control standards recognized by FDA for this drug, please see <https://www.fda.gov/STIC>.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CEFOBID and other antibacterial drugs. CEFOBID should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CEFOBID 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** (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), *Clostridioides* 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*, *Clostridioides* spp.,* *Bacteroides* species (including *Bacteroides fragilis*), and anaerobic gram-positive cocci.

Cefobid® has no activity against *Chlamydia trachomatis*. Therefore, when Cefobid is used in the treatment of patients with pelvic inflammatory disease and *C. trachomatis* is one of the suspected 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.

* Efficacy against this organism in this organ system was studied in fewer than 10 infections.

Combination Therapy

Synergy between CEFOBID and aminoglycosides has been demonstrated with many gram-negative bacilli. However, such enhanced activity of these combinations is not predictable. If such therapy is considered, *in vitro* susceptibility tests should be performed to determine the activity of the drugs in combination, and renal function should be monitored carefully. (See PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections.)

CONTRAINDICATIONS

CEFOBID is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class or in patients who have demonstrated severe hypersensitivity to beta-lactams (see WARNINGS).

WARNINGS

Hypersensitivity Reactions

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING BETA-LACTAM ANTIBACTERIALS, INCLUDING CEFOPERAZONE. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. BEFORE THERAPY WITH CEFOBID IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, CARBAPENEMS OR OTHER DRUGS. IF AN ALLERGIC REACTION OCCURS, CEFOPERAZONE SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED.

Severe and occasionally fatal skin reactions such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and exfoliative dermatitis have been reported in patients on CEFOBID therapy. If a severe skin reaction occurs CEFOBID should be discontinued and appropriate therapy should be initiated (see ADVERSE REACTIONS).

***Clostridioides difficile*-Associated Diarrhea**

Clostridioides difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CEFOBID, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Hemorrhage

Serious hemorrhage cases, including fatalities, have been reported with cefoperazone. Monitor for signs of bleeding, thrombocytopenia, and coagulopathy. Discontinue CEFOBID if there is persistent bleeding and no alternative explanations are identified.

Encephalopathy

Encephalopathy (including decreased consciousness, delirium, seizures) has been reported with the use of CEFOBID. Most cases occurred in patients with renal impairment. The adverse reactions resolved after discontinuation of CEFOBID and/or hemodialysis/continuous veno-venous hemofiltration. If encephalopathy occurs, consider discontinuing CEFOBID and institute supportive measures.

PRECAUTIONS

General

Prescribing CEFOBID in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

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

CEFOBID is extensively excreted in bile. The serum half-life of CEFOBID 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 CEFOBID (see CLINICAL PHARMACOLOGY), patients with renal failure require no adjustment in dosage when usual doses are administered. When high doses of CEFOBID 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 CEFOBID 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, CEFOBID dosage should not exceed 1–2 g daily without close monitoring of serum concentrations.

As with other antibacterial drugs, vitamin K deficiency resulting in coagulopathy has occurred in patients treated with CEFOBID. The mechanism is 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). Hypoprothrombinemia with or without bleeding has been reported. Prothrombin time should be monitored in these patients, and patients receiving anticoagulant therapy, 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 CEFOBID administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOBID.

Prolonged use of CEFOBID 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.

CEFEBID should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Information for Patients

Patients should be counseled that antibacterial drugs including CEFEBID should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When CEFEBID is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treated by CEFEBID or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibacterial drugs which usually ends when the drug is discontinued. Sometimes after starting treatment with antibacterial drugs, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial drug. If this occurs, patients should contact their physician as soon as possible.

Drug/Laboratory Test Interactions

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. The maximum duration of CEFOBID animal toxicity studies is six months. In none of the *in vivo* or *in vitro* genetic toxicology studies did CEFOBID show any mutagenic potential at either the chromosomal or subchromosomal level. CEFOBID produced no impairment of fertility and had no effects on general reproductive performance or fetal development when administered subcutaneously at daily doses up to 500 to 1000 mg/kg prior to and during mating, and to pregnant female rats during gestation. These doses are 10 to 20 times the estimated usual single clinical dose. CEFOBID had adverse effects on the testes of prepubertal rats at all doses tested. Subcutaneous administration of 1000 mg/kg per day (approximately 16 times the average adult human dose) resulted in reduced testicular weight, arrested spermatogenesis, reduced germinal cell population and vacuolation of Sertoli cell cytoplasm. The severity of lesions was dose dependent in the 100 to 1000 mg/kg per day range; the low dose caused a minor decrease in spermatocytes. This effect has not been observed in adult rats. Histologically the lesions were reversible at all but the highest dosage levels. However, these studies did not evaluate subsequent development of reproductive function in the rats. The relationship of these findings to humans is unknown.

Usage in Pregnancy

Reproduction studies have been performed in mice, rats and monkeys at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to CEFOBID. Cefoperazone crosses the placental barrier. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Usage in Nursing Mothers

Only low concentrations of CEFOBID are excreted in human milk. Although CEFOBID passes poorly into breast milk of nursing mothers, caution should be exercised when CEFOBID is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established. For information concerning testicular changes in prepubertal rats (see **Carcinogenesis, Mutagenesis, Impairment of Fertility**).

Geriatric Use

Clinical studies of CEFOBID[®] (sterile cefoperazone sodium) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be

cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Clinical Trials Experience

In clinical studies the following adverse effects were observed and were considered to be related to CEFOBID therapy or of uncertain etiology:

Hypersensitivity: As with all cephalosporins, hypersensitivity manifested by skin reactions (1 patient in 45), drug fever (1 in 260), or a change in Coombs' test (1 in 60) has been reported. These reactions are more likely to occur in patients with a history of allergies, particularly to penicillin.

Hematology: As with other beta-lactam antibacterial drugs, reversible neutropenia may occur with prolonged administration. Slight decreases in neutrophil count (1 patient in 50) have been reported. Decreased hemoglobins (1 in 20) or hematocrits (1 in 20) have been reported, which is consistent with published literature on other cephalosporins. Transient eosinophilia has occurred in 1 patient in 10.

Hepatic: Of 1285 patients treated with cefoperazone in clinical trials, one patient with a history of liver disease developed significantly elevated liver function enzymes during CEFOBID therapy. Clinical signs and symptoms of nonspecific hepatitis accompanied these increases. After CEFOBID therapy was discontinued, the patient's enzymes returned to pre-treatment levels and the symptomatology resolved. As with other antibacterial drugs that achieve high bile levels, mild transient elevations of liver function enzymes have been observed in 5–10% of the patients receiving CEFOBID therapy. The relevance of these findings, which were not accompanied by overt signs or symptoms of hepatic dysfunction, has not been established.

Gastrointestinal: Diarrhea or loose stools has been reported in 1 in 30 patients. Most of these experiences have been mild or moderate in severity and self-limiting in nature. In all cases, these symptoms responded to symptomatic therapy or ceased when cefoperazone therapy was stopped. Nausea and vomiting have been reported rarely.

Symptoms of pseudomembranous colitis can appear during or for several weeks subsequent to antibacterial therapy (see WARNINGS).

Renal Function Tests: Transient elevations of the BUN (1 in 16) and serum creatinine (1 in 48) have been noted.

Local Reactions: CEFOBID is well tolerated following intramuscular administration. Occasionally, transient pain (1 in 140) may follow administration by this route. When CEFOBID is administered by intravenous infusion some patients may develop phlebitis (1 in 120) at the infusion site.

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of CEFOBID. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Coagulopathy, thrombocytopenia, hypoprothrombinaemia (see PRECAUTIONS)

Immune System Disorders: Anaphylactic reaction including shock and fatal cases (see WARNINGS), acute myocardial ischemia with or without myocardial infarction may occur as part of an allergic reaction

Hepatobiliary Disorders: Jaundice, hepatic dysfunction

Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, pruritus

Vascular Disorders: Hemorrhage (see WARNINGS)

Nervous System Disorders: Encephalopathy (including decreased consciousness, delirium, seizures) (see WARNINGS)

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 CEFOBID is 2 to 4 g 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 g divided into 2, 3, or 4 administrations ranging from 1.5 to 4 g per dose.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least 10 days.

If *C. trachomatis* is a suspected pathogen, appropriate anti-chlamydial coverage should be added, because cefoperazone has no activity against this organism.

Solutions of CEFOBID and aminoglycoside should not be directly mixed, since there is a physical incompatibility between them. If combination therapy with CEFOBID and an aminoglycoside is contemplated (see INDICATIONS AND USAGE) 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 CEFOBID be administered prior to the aminoglycoside. *In vitro* testing of the effectiveness of drug combination(s) is recommended.

RECONSTITUTION

The following solutions may be used for the initial reconstitution of CEFOBID sterile powder:

Table 3. Solutions for Initial Reconstitution

5% Dextrose Injection (USP)	0.9% Sodium Chloride Injection (USP)
5% Dextrose and 0.9% Sodium Chloride Injection (USP)	Normosol [®] M and 5% Dextrose
5% Dextrose and 0.2% Sodium Chloride Injection (USP)	Injection
10% Dextrose Injection (USP)	Normosol [®] R
Bacteriostatic Water for Injection [Benzyl Alcohol or Parabens] (USP)*†	Sterile Water for Injection*

* Not to be used as a vehicle for intravenous infusion.

† Preparations containing Benzyl Alcohol should not be used in neonates.

General Reconstitution Procedures

CEFOBID sterile powder for intravenous or intramuscular use may be initially reconstituted with any compatible solution mentioned above in Table 3. 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 CEFOBID in higher concentrations (above 333 mg cefoperazone/mL). The maximum solubility of CEFOBID sterile powder is approximately 475 mg cefoperazone/mL of compatible diluent.

Preparation for Intravenous Use

General: CEFOBID concentrations between 2 mg/mL and 50 mg/mL are recommended for intravenous administration.

Table 4. Vehicles for Intravenous Infusion

5% Dextrose Injection (USP)	Lactated Ringer's Injection (USP)
5% Dextrose and Lactated Ringer's Injection	0.9% Sodium Chloride Injection (USP)
5% Dextrose and 0.9% Sodium Chloride Injection (USP)	Normosol [®] M and 5% Dextrose
5% Dextrose and 0.2% Sodium Chloride Injection (USP)	Injection
10% Dextrose Injection (USP)	Normosol [®] R

DIRECTIONS FOR PROPER USE OF PHARMACY BULK PACKAGE

The 10 g vial should be reconstituted with 95 mL of sterile water for injection in two separate aliquots in a suitable work area such as a laminar flow hood. Add 45 mL of solution, shake to dissolve and add 50 mL, shake for final solution. The resulting solution will contain 100 mg/mL of cefoperazone. This closure may be penetrated only one time after reconstitution, if needed, using a suitable sterile transfer device or dispensing set which allows measured dispensing of the contents.

Discard unused solution within 24 hours of initial entry.

Reconstituted Bulk Solutions Should Not Be Used For Direct Infusion.

Although after reconstitution of the Pharmacy Bulk Package, no significant loss of potency occurs for 24 hours at room temperature and for 5 days if refrigerated, transfer individual dose to appropriate intravenous infusion solutions as soon as possible following reconstitution of the bulk package. Discard unused portions of solution held longer than these recommended periods at room temperature or under refrigeration. The stability of the solution which has been transferred into a container varies according to diluent and concentration. (See STORAGE AND STABILITY.)

The 10 g vials may be further diluted with the parenteral diluents listed under **Table 4. Vehicles for Intravenous Infusion**. The parenteral diluents and approximate concentrations of CEFOBID that provide stable solutions are presented under STORAGE AND STABILITY.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

STORAGE AND STABILITY

CEFOBID 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 CEFOBID provide stable solutions under the following conditions for the indicated time periods. (After the indicated time periods, unused portions of solutions should be discarded.)

Controlled Room Temperature (15°–25°C/59°–77°F)	Approximate Concentrations
24 Hours	
Bacteriostatic Water for Injection [Benzyl Alcohol or Parabens] (USP)	300 mg/mL
5% Dextrose Injection (USP)	2 mg to 50 mg/mL
5% Dextrose and Lactated Ringer’s Injection	2 mg to 50 mg/mL
5% Dextrose and 0.9% Sodium Chloride Injection (USP)	2 mg to 50 mg/mL
5% Dextrose and 0.2% Sodium Chloride Injection (USP)	2 mg to 50 mg/mL
10% Dextrose Injection (USP)	2 mg to 50 mg/mL
Lactated Ringer’s Injection (USP)	2 mg/mL
0.5% Lidocaine Hydrochloride Injection (USP)	300 mg/mL
0.9% Sodium Chloride Injection (USP)	2 mg to 300 mg/mL
Normosol® M and 5% Dextrose Injection	2 mg to 50 mg/mL
Normosol® R	2 mg to 50 mg/mL
Sterile Water for Injection	100 mg to 300 mg/mL

Reconstituted CEFOBID solutions may be stored in glass or plastic syringes, or in glass or flexible plastic parenteral solution containers.

Refrigerator Temperature (2°–8°C/36°–46°F)	Approximate Concentrations
5 Days	
Bacteriostatic Water for Injection [Benzyl Alcohol or Parabens] (USP)	300 mg/mL
5% Dextrose Injection (USP)	2 mg to 50 mg/mL
5% Dextrose and 0.9% Sodium Chloride Injection (USP)	2 mg to 50 mg/mL
5% Dextrose and 0.2% Sodium Chloride Injection (USP)	2 mg to 50 mg/mL
Lactated Ringer’s Injection (USP)	2 mg/mL
0.5% Lidocaine Hydrochloride Injection (USP)	300 mg/mL
0.9% Sodium Chloride Injection (USP)	2 mg to 300 mg/mL
Normosol® M and 5% Dextrose Injection	2 mg to 50 mg/mL
Normosol® R	2 mg to 50 mg/mL
Sterile Water for Injection	100 mg to 300 mg/mL

Reconstituted CEFOBID solutions may be stored in glass or plastic syringes, or in glass or flexible plastic parenteral solution containers.

Freezer Temperature (–20° to –10°C/–4° to 14°F)	Approximate Concentrations
3 Weeks	
5% Dextrose Injection (USP)	50 mg/mL
5% Dextrose and 0.9% Sodium Chloride Injection (USP)	2 mg/mL
5% Dextrose and 0.2% Sodium Chloride Injection (USP)	2 mg/mL
5 Weeks	
0.9% Sodium Chloride Injection (USP)	300 mg/mL
Sterile Water for Injection.	300 mg/mL

Reconstituted CEFOBID 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

CEFOBID® sterile powder is available in Pharmacy Bulk Package containing cefoperazone sodium equivalent to 10 g cefoperazone × 1 (NDC 0049-1219-28).

OTHER SIZE PACKAGES AVAILABLE

CEFOBID® sterile powder is available in vials containing cefoperazone sodium equivalent to 1 g cefoperazone × 10 (NDC 0049-1201-83) and 2 g cefoperazone × 10 (NDC 0049-1202-83) for intramuscular and intravenous administration.

This product’s labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

Rx only



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