

CEFOBID[®]

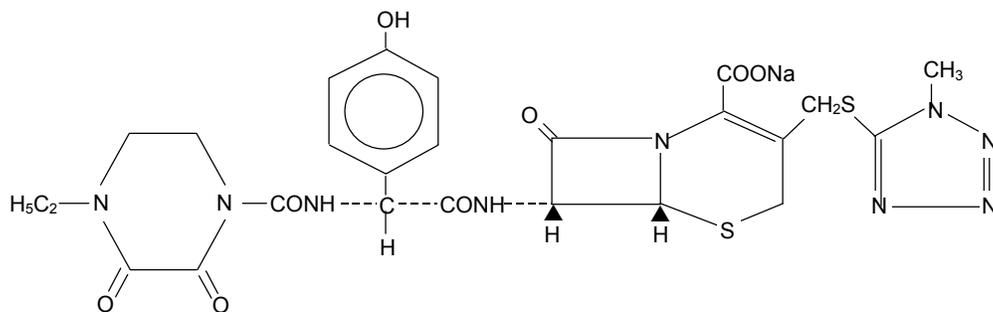
(sterile cefoperazone)

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 $C_{25}H_{26}N_9NaO_8S_2$ 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. 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 grams of the drug, or a single intramuscular injection of 1 or 2 grams 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 grams 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:

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 grams.

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. Cefoperazone is stable to penicillinases and has a high degree of stability to many beta-lactamases produced by gram-negative bacteria.

Mechanisms of 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.

Cefoperazone has been shown to be active against the following microorganisms, both *in vitro* and in clinical infections [see *INDICATIONS AND USAGE*].

Gram-positive aerobic 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 aerobic 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 gram-positive bacteria:

- Gram-positive cocci (including *Peptococcus* and *Peptostreptococcus* spp.)
- *Clostridium* species (with the exception of *C. difficile*)

Anaerobic gram-negative bacteria:

- *Bacteroides* species

The following *in vitro* data are available, but their clinical significance is unknown. In addition, at least 90% of organisms in the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the cefoperazone susceptible breakpoint of 8 mcg/mL. However, the safety and efficacy of cefoperazone in treating clinical infections due to these bacteria have not been established in adequate well-controlled clinical trials.

Gram-negative aerobic bacteria:

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

Gram-positive anaerobic bacteria

- *Eubacterium* spp.

Gram-negative anaerobic bacteria

- *Fusobacterium* spp.

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug for treatment.

Dilution Techniques

Quantitative methods are used to determine minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method.^{1,2,3} The MIC values should be interpreted according to the criteria provided in Table 2.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.^{3,4} This procedure uses paper disks impregnated with 75 mcg cefoperazone to test the susceptibility of bacteria to cefoperazone. The disk diffusion interpretive criteria are provided in Table 2.

Table 2. Susceptibility Test Criteria for Cefoperazone

Pathogen	Susceptibility Interpretative Criteria					
	Minimal Inhibitory Concentrations (MIC in mcg/mL)					
	S		R			
<i>Enterobacteriaceae</i>	≤8		≥16			
Other non- <i>Enterobacteriaceae</i> ^a	≤8		≥16			
Anaerobic bacteria ^b	≤8		≥16			

Susceptibility interpretive criteria are based on a dose of 3 g every 6 hours or 4 g every 8 hours in patients with normal renal function.

Methicillin-susceptible *Staphylococcus* spp., as determined by susceptibility to oxacillin can be considered susceptible to cefoperazone.

^a These include nonfastidious glucose-nonfermenting gram-negative bacilli with the exception of: *Pseudomonas aeruginosa*, *Acinetobacter* species, *Burkholderia* species and *Stenotrophomonas maltophilia*.

^b MICs for anaerobic bacteria are determined using agar dilution methodology.

A report of *Susceptible* (S) indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration at the site of infection. A report of *Resistance* (R) indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the site of infection; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.^{1,2,3,4} Standardized cefoperazone powder should provide the following range of MIC values noted in Table 3. For the diffusion technique using the 75 mcg cefoperazone disk, the criteria in Table 3 should be achieved.

Table 3. Acceptable Quality Control Ranges for Cefoperazone

	Minimum Inhibitory Ranges (MIC in mcg/mL)	Disk Diffusion Ranges (Zone Diameters in mm)
<i>Bacteroides fragilis</i> ATCC 25285	32 – 128 ^a	--
<i>Bacteroides thetaiotaomicron</i> ATCC 29741	32 – 128 ^a	--
<i>Eubacterium lentum</i> ATCC 43055	32 – 128 ^a	--
<i>Escherichia coli</i> ATCC 25922	0.12 – 0.5	28 - 34
<i>Pseudomonas aeruginosa</i> ATCC 27853	2 - 8	23 - 29
<i>Staphylococcus aureus</i> ATCC 29213	1 - 4	--
<i>Staphylococcus aureus</i> ATCC 25923	--	24 - 33
Quality Control Ranges for Oxacillin vs. <i>S. aureus</i>		
<i>Staphylococcus aureus</i> ATCC 29213	0.12 – 0.5	--

ATCC® = American Type Culture Collection.

^a MICs for anaerobic bacteria are determined using agar dilution methodology.

Susceptibility of staphylococci to cefotaxime may be deduced from testing only penicillin and either ceftaxime or oxacillin.

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), *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.

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

CEFEBID is contraindicated in patients with known allergy to the cephalosporin-class of antibacterial drugs.

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 CEFEBID IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, CARBAPENEMS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO BETA-LACTAM ALLERGIC PATIENTS. 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 CEFEBID therapy. If a severe skin reaction occurs CEFEBID should be discontinued and appropriate therapy should be initiated [see ADVERSE REACTIONS].

***Clostridium difficile*-Associated Diarrhea**

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CEFEBID, 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.

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 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 CEFEBID animal toxicity studies is six months. In none of the *in vivo* or *in vitro* genetic toxicology studies did CEFEBID show any mutagenic potential at either the chromosomal or subchromosomal level. CEFEBID 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

Pregnancy Category B: 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. 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)

Hepatobiliary Disorders: Jaundice, hepatic dysfunction

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

Vascular Disorders: Hemorrhage (See WARNINGS)

DOSAGE AND ADMINISTRATION

The usual adult daily dose of CEFOBID (sterile cefoperazone) 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 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) 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 4. 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 4. 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 gram of cefoperazone of any compatible reconstituting solution appropriate for intravenous administration listed above in Table 4. For ease of reconstitution the use of 5 mL of compatible solution per gram 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 5. 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)	
3 Weeks	Approximate Concentrations
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.

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

REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard—Tenth Edition*. CLSI document M07-A10. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
2. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard—Eighth Edition*. CLSI document M11-A8. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
3. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing: Twenty-Fifth Informational Supplement*. CLSI document M 100-S25. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

4. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard - Twelfth Edition*. CLSI document M02-A12. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

Rx only

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.



Distributed by

Roerig

Division of Pfizer Inc, NY, NY 10017

LAB-0033-8.1
Revised
September 2017