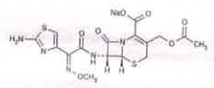
CEFOTAXIME

SITIXIME
1 g Powder for Injection
I.M/I.V.
Antibacterial

Formulation:
Each Vial contains:
Cefotaxime (as Sodium), USP 1g

Product Description
Cefotaxime nbsodium is a semisynthetic, broad spectrum cephalosporin antibiotic for parenteral administration. It is the sodium salt of 7-[2-(2-amino-4-thiazolyl) glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylate7[2] (Z)-(o-methyloxime), acetate (ester).



Solutions of Cefotaxime sodium range from very pale yellow to light amber depending on the concentration and the diluent used. The pH of the injectable solutions usually ranges from 5.0 to 7.5. The CAS Registry Number is 64485-93-4. It has the following structure:

$C_{16}H_{16}N_5NaO_7S_2$ 477.45

Pharmacodynamics / Pharmacokinetics

Pharmacodynamic properties
Pharmacotherapeutic group: cephalosporins and related substances.
Mechanism of action: Cefotaxime sodium is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Cefotaxime has activity in the presence of some beta-lactamases, both penicillinases and cephalosporinases, of Gram-negative and Gram-positive bacteria.
Mechanism of Resistance
Resistance to cefotaxime is primarily through hydrolysis by beta-lactamase, alteration of penicillin-binding proteins (PBPs), and decreased permeability.
Susceptibility to cefotaxime will vary geographically and may change over time; local susceptibility data should be consulted, if available. Cefotaxime has been shown to be active against most isolates of the following bacteria both *in vitro* and in clinical infections as described in the INDICATIONS section:

Gram-positive bacteria
Enterococcus spp.
Staphylococcus aureus (methicillin-susceptible isolates only) , *Staphylococcus epidermidis Streptococcus pneumonia, Streptococcus pyogenes* (Group A beta-hemolytic streptococci), *Streptococcus spp.* (Viridans group streptococci)

Gram-negative bacteria
Acinetobacter spp.
Citrobacter spp.
Enterobacter spp.
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella spp. (including Klebsiella pneumoniae)
Morganella morganii
Neisseria gonorrhoeae (including beta-lactamase-positive and negative strains)
Neisseria meningitidis
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens
Enterococcus species may be intrinsically resistant to cefotaxime.Most extended spectrum beta-lactamase (ESBL)-producing and carbapenemase-producing isolates are resistant to cefotaxime.

Anaerobic bacteria
Bacteroides spp., including some isolates of *Bacteroides fragilis. Clostridium* spp. (most isolates of *Clostridium difficile* are *resistant*) *Fusobacterium* spp. (including *Fusobacterium nucleatum*). *Peptococcus* spp. *Peptostreptococcus* spp.

Pharmacokinetic properties
Following IM administration of a single 500mg or 1g dose of Cefotaxime to normal volunteers, mean peak serum concentrations of 11.7 and 20.5 mcg/mL respectively were attained within 30 minutes and declined with an elimination half-life of approximately 1 hour. There was a dose-dependent increase in serum levels after the IV administration of 500mg, 1g, and 2g of Cefotaxime (38.9, 101.7, and 214.4 mcg/mL respectively) without alteration in the elimination half-life. There is no evidence of accumulation following repetitive IV infusion of 1g doses every 6 hours for 14 days as there are no alterations of serum or renal clearance. About 60% of the administered dose was recovered from urine during the first 6 hours following the start of the infusion.
Approximately 20-36% of an intravenously administered dose of 14C-cefotaxime is excreted by the kidney as unchanged cefotaxime and 15-25% as the desacetyl derivative, the major metabolite. The desacetyl metabolite has been shown to contribute to the bactericidal activity. Two other urinary metabolites (M_2 and M_3) account for about 20-25%. They lack bactericidal activity.
A single 50 mg/kg dose of Cefotaxime was administered as an intravenous infusion over a 10- to 15-minute period to 29 newborn infants grouped according to birth weight and age. The mean half-life of cefotaxime in infants with lower birth weights (≤1500 grams), regardless of age, was longer (4.6 hours) than the mean half-life (3.4 hours) in infants whose birth weight was greater than 1500 grams. Mean serum clearance was also smaller in the lower birth weight infants. Although the differences in mean half-life values are statistically significant for weight, they are not clinically important. Therefore, dosage should be based solely on age.

Indications
Cefotaxime is indicated for the treatment of patients with serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below.
(1) **Lower respiratory tract infections,** including pneumonia, caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), *Streptococcus pyogenes** (Group A streptococci) and other streptococci (excluding enterococci, e.g., *Enterococcus faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli, Klebsiella* species, *Haemophilus influenzae* (including ampicillin resistant strains), *Haemophilus parainfluenzae, Proteus mirabilis, Serratia marcescens**, *Enterobacter* species, indole positive *Proteus and Pseudomonas* species (including *P. aeruginosa*).
(2) **Genitourinary infections.** Urinary tract infections caused by *Enterococcus species, Staphylococcus epidermidis, Staphylococcus aureus*, (penicillinase and non-penicillinase producing), *Citrobacter* species, *Enterobacter* species, *Escherichia coli, Klebsiella* species, *Proteus mirabilis, Proteus vulgaris**, *Providencia stuartii, Morganella morganii**, *Providencia rettgeri**, *Serratia marcescens* and *Pseudomonas species* (including *P. aeruginosa*). Also, uncomplicated gonorrhea (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including penicillinase producing strains.
(3) **Gynecologic infections,** including pelvic inflammatory disease, endometritis and pelvic cellulitis caused by *Staphylococcus epidermidis, Streptococcus* species, *Enterococcusspecies, Enterobacter* species*, *Klebsiella* species* , *Escherichia coli, Proteus mirabilis, Bacteroides* species (including *Bacteroides fragilis*)*, *Clostridium* species, and anaerobic cocci (including *Peptostreptococcus* species and *Peptococcus* species) and *Fusobacterium* species (including *F. nucleatum*)*.
Cefotaxime, like other cephalosporins, has no activity against *Chlamydia trachomatis*. Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and *C. trachomatis* is one of the suspected pathogens, appropriate anti- chlamydial coverage should be added.
(4) **Bacteremia/Septicemia** caused by *Escherichia coli, Klebsiella* species, and *Serratia marcescens, Staphylococcus aureus* and *Streptococcus* species (including *S. pneumonia*).
(5) **Skin and skin structure infections** caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Staphylococcus epidermidis, Streptococcus pyogenes* (Group A streptococci) and other streptococci, *Enterococcus* species, *Acinetobacter* species*, *Escherichia coli, Citrobacter* species (including *C. freundii**), *Enterobacter* species, *Klebsiella* species, *Proteus mirabilis, Proteus vulgaris**, *Morganella morganii, Providencia rettgeri**, *Pseudomonas* species, *Serratia marcescens, Bacteroides* species, and anaerobic cocci (including *Peptostreptococcus** species and *Peptococcus* species).
(6) **Intra-abdominal infections** including peritonitis caused by *Streptococcus* species*, *Escherichia coli, Klebsiella* species, *Bacteroides* species, and anaerobic cocci (including *Peptostreptococcus** species and *Peptococcus** species) *Proteus mirabilis**, and *Clostridium* species*.
(7) **Bone and/or joint infections** caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing strains), *Streptococcus* species (including *S. pyogenes**), *Pseudomonas* species (including *P. aeruginosa**), and *Proteus mirabilis**.
(8) **Central nervous system infections,** e.g., meningitis and ventriculitis, caused by *Neisseria meningitidis, Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae** and *Escherichia coli**.
(*) Efficacy for this organism, in this organ system, has been studied in fewer than 10 infections.
Although many strains of enterococci (e.g., *E. faecalis*) and Pseudomonas species are resistant to cefotaxime sodium *in vitro*, it has been used successfully in treating patients with infections caused by susceptible organisms.
Specimens for bacteriologic culture should be obtained prior to therapy in order to isolate and identify causative organisms and to determine their susceptibilities to cefotaxime. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, cefotaxime may be used concomitantly with an aminoglycoside. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition. Renal function should be carefully monitored, especially if higher dosages of the aminoglycosides are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. It is possible that nephrotoxicity may be potentiated if cefotaxime is used concomitantly with an aminoglycoside.

Prevention
The administration of Cefotaxime preoperatively reduces the incidence of certain infections in patients undergoing surgical procedures (e.g., abdominal or vaginal hysterectomy, gastrointestinal and genitourinary tract surgery) that may be classified as contaminated or potentially contaminated.
In patients undergoing cesarean section, intraoperative (after clamping the umbilical cord) and postoperative use of Cefotaxime may also reduce the incidence of certain postoperative infections.
Effective use for elective surgery depends on the time of administration. To achieve effective tissue levels, Cefotaxime should be given 1/2 or 1 1/2 hours before surgery.

Recommended Dose
ADULTS: Dosage and route of administration should be determined by susceptibility of the causative organisms, severity of the infection, and the condition of the patient (see table for dosage guideline).
Cefotaxime may be administered IM or IV after reconstitution. The maximum daily dosage should not exceed 12 grams.

GUIDELINES FOR DOSAGE OF Cefotaxime

Type of Infection	Daily Dose (grams)	Frequency and Route
Gonococcal urethritis/cervicitis in males and females	0.5	0.5 gram IM (single dose)
Rectal gonorrhea in females	0.5	0.5 gram IM (single dose)
Rectal gonorrhea in males	1	1 gram IM (single dose)
Uncomplicated infections	2	1 gram every 12 hours IM or IV
Moderate to severe infections	3-6	1-2 grams every 8 hours IM or IV
Infections commonly needing antibiotics in higher dosage (e.g., septicemia)	6-8	2 grams every 6-8 hours IV
Life-threatening infections	up to 12	2 grams every 4 hours IV

If *C. trachomatis* is a suspected pathogen, appropriate anti-chlamydial coverage should be added, because cefotaxime sodium has no activity against this organism.
To prevent postoperative infection in contaminated or potentially contaminated surgery, the recommended dose is a single 1 gram IM or IV administered 30 to 90 minutes prior to start of surgery.

Cesarean Section Patients
The first dose of 1 gram is administered intravenously as soon as the umbilical cord is clamped. The second and third doses should be given as 1 gram intravenously or intramuscularly at 6 and 12 hours after the first dose.

Neonates, Infants, and Children
The following dosage schedule is recommended:
Neonates (birth to 1 month):

0-1 week of age 50 mg/kg per dose every 12 hours IV
1-4 weeks of age 50 mg/kg per dose every 8 hours IV

It is not necessary to differentiate between premature and normal-gestational age infants. Infants and Children (1 month to 12 years):
For body weights less than 50 kg, the recommended daily dose is 50 to 180 mg/kg IM or IV body weight divided into four to six equal doses. The higher dosages should be used for more severe or serious infections, including meningitis. For body weights 50 kg or more, the usual adult dosage should be used; the maximum daily dosage should not exceed 12 grams.

Geriatric Use

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See **PRECAUTIONS,General and PRECAUTIONS,Geriatric Use.**)

Impaired Renal Function (see PRECAUTIONS, General)

NOTE: As with antibiotic therapy in general, administration of Cefotaxime should be continued for a minimum of 48 to 72 hours after the patient defervesces or after evidence of bacterial eradication has been obtained; a minimum of 10 days of treatment is recommended for infections caused by Group A beta-hemolytic streptococci in order to guard against the risk of rheumatic fever or glomerulonephritis; frequent bacteriologic and clinical appraisal is necessary during therapy of chronic urinary tract infection and may be required for several months after therapy has been completed; persistent infections may require treatment of several weeks and doses smaller than those indicated above should not be used.

Mode of Administration

Cefotaxime may be administered IM or IV after reconstitution.

Contraindication

Cefotaxime is contraindicated in patients who have shown hypersensitivity to cefotaxime sodium, or the cephalosporin group of antibiotics.

Warnings and Precautions

WARNINGS:

Before therapy with Cefotaxime is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to Cefotaxime Sodium, Cephalosporins, penicillins, or other drugs. This product should be given with caution to patients with type I hypersensitivity reactions to penicillin. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to Cefotaxime occurs, discontinue treatment with the drug. Serious hypersensitivity reactions may require epinephrine and other emergency measures.

During post-marketing surveillance, a potentially life-threatening arrhythmia was reported in each of six patients who received a rapid (less than 60 seconds) bolus injection of cefotaxime through a central venous catheter. Therefore, cefotaxime should only be administered as instructed in the RECOMMENDED DOSE section.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Cefotaxime, 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 antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic 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 antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS General

Prescribing Cefotaxime in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. Cefotaxime should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Because high and prolonged serum antibiotic concentrations can occur from usual doses in patients with transient or persistent reduction of urinary output because of renal insufficiency, the total daily dosage should be reduced when Cefotaxime is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organism.

Although there is no clinical evidence supporting the necessity of changing the dosage of cefotaxime sodium in patients with even profound renal dysfunction, it is suggested that, until further data are obtained, the dose of cefotaxime sodium be halved in patients with estimated

creatinine clearances of less than 20 mL/min/1.73 m^2 .

When only serum creatinine is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Weight (kg) x (140 - age)

Males: 72 × serum creatinine

Females: 0.85 × above value

As with other antibiotics, prolonged use of Cefotaxime may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

As with other beta-lactam antibiotics, granulocytopenia and, more rarely, agranulocytosis may develop during treatment with Cefotaxime, particularly if given over long periods. For courses of treatment lasting longer than 10 days, blood counts should therefore be monitored. Cefotaxime, like other parenteral anti-infective drugs, may be locally irritating to tissues. In most cases, perivascular extravasation of Cefotaxime responds to changing of the infusion site. In rare instances, extensive perivascular extravasation of Cefotaxime may result in tissue damage and require surgical treatment. To minimize the potential for tissue inflammation, infusion sites should be monitored regularly and changed when appropriate.

Interactions with Other Medicaments

Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics. Probenecid interferes with the renal tubular transfer of cefotaxime, decreasing the total clearance of cefotaxime by approximately 50% and increasing the plasma concentrations of cefotaxime. Administration of cefotaxime in excess of 6 grams/day should be avoided in patients receiving probenecid.

Drug/Laboratory Interactions

Cephalosporins, including cefotaxime sodium, are known to occasionally induce a positive direct Coombs' test.

A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with CLINITEST® tablets), but not with enzyme-based tests for glycosuria (e.g., CLINISTIX® or TesTape®). There are no reports in published literature that link elevations of plasma glucose levels to the use of cefotaxime.

Pregnancy and Lactation

Pregnancy: Teratogenic Effects: Pregnancy Category B:

Reproduction studies have been performed in pregnant mice given Cefotaxime intravenously at doses up to 1200 mg/kg/day (0.4 times the recommended human dose based on mg/m)^2 or in pregnant rats when administered intravenously at doses up to 1200 mg/kg/day (0.8 times the recommended human dose based on mg/m)^2. No evidence of embryotoxicity or teratogenicity was seen in these studies. There are no well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

Use of the drug in women of child-bearing potential requires that the anticipated benefit be weighed against the possible risks.

In perinatal and postnatal studies with rats, the pups in the group given 1200 mg/kg/day of Cefotaxime were significantly lighter in weight at birth and remained smaller than pups in the control group during the 21 days of nursing.

Nursing Mothers

Cefotaxime is excreted in human milk in low concentrations. Caution should be exercised when Cefotaxime is administered to a nursing woman.

Adverse Effects

Cefotaxime is generally well tolerated. The most common adverse reactions have been local reactions following IM or IV injection. Other adverse reactions have been encountered infrequently.

The most frequent adverse reactions (greater than 1%) are:

Local (4.3%)—Injection site inflammation with IV administration. Pain, induration, and tenderness after IM injection. Hypersensitivity (2.4%) — Rash, pruritus, fever, eosinophilia. Gastrointestinal (1.4%) — Colitis, diarrhea, nausea, and vomiting.

Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Less frequent adverse reactions (less than 1%) are:

Hematologic System - Neutropenia, transient leukopenia, have been reported. Some individuals have developed positive direct Coombs Tests during treatment with Cefotaxime and other cephalosporin antibiotics.

Genitourinary System — Moniliasis, vaginitis. Central Nervous System — Headache.

Liver — Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase levels have been reported.

Kidney — As with some other cephalosporins, interstitial nephritis and transient elevations of BUN and creatinine have been occasionally observed with Cefotaxime.

Cephalosporin Class Labeling

In addition to the adverse reactions listed above which have been observed in patients treated with cefotaxime sodium, the following adverse reactions and altered laboratory tests have been reported for cephalosporin class antibiotics: allergic reactions, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage, and false-positive test for urinary glucose. Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Reporting of Suspected Adverse Drug Reaction:

To allow continued monitoring of benefit/risk balance of the medicinal product, reporting of adverse reaction is necessary. Healthcare professionals are encouraged to report any suspected adverse reaction directly to the importer/distributor and/or report to FDA: www.fda.gov.ph.

Patients are advised to seek immediate medical attention at the first sign/s of adverse reactions.

Overdose and Treatment

The acute toxicity of Cefotaxime was evaluated in neonatal and adult mice and rats. Significant mortality was seen at parenteral doses in excess of 6000 mg/kg/day in all groups. Common toxic signs in animals that died were a decrease in spontaneous activity, tonic and clonic convulsions, dyspnea, hypothermia, and cyanosis.

Cefotaxime sodium overdosage has occurred in patients. Most cases have shown no overt toxicity. The most frequent reactions were elevations of BUN and creatinine. There is a risk of reversible encephalopathy in cases of administration of high doses of beta-lactam antibiotics including cefotaxime. No specific antidote exists. Patients who receive an acute overdosage should be carefully observed and given supportive treatment.

Storage Condition

Store at temperatures not exceeding 30°C. Protect from elevated temperatures and excessive light.

Packaging Available

10mL-Capacity USP Type I Clear and Colorless Glass Vial with Butyl Rubber Stopper and Aluminum Seal with Blue-colored Plastic Flip-Off Cap (Box of 1's)

FDA Registration Number: DR-XY47815
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