Package Insert

Y36-002-588
Package Insert

DUPLEX®
DRUG DELIVERY SYSTEM

CefOTAXime for Injection USP
and Dextrose Injection

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

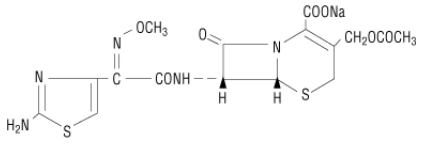
Rx only

DESCRIPTION

Cefotaxime for Injection USP and Dextrose Injection is a sterile, nonpyrogenic, single use, packaged combination of Cefotaxime Sodium and Dextrose Injection (diluent) in the DUPLEX sterile container. The DUPLEX Container is a flexible dual chamber container.

The drug chamber is filled with sterile Cefotaxime Sodium USP, 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-carboxylate 7^2 (Z)-(o-methyloxime), acetate (ester). The CAS Registry Number is 64485-93-4.

Cefotaxime Sodium has the following structural formula:

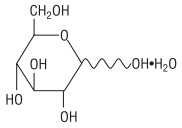


The empirical formula of Cefotaxime Sodium is $C_{16}H_{16}N_5NaO_7S_2$, representing a molecular weight of 477.45.

Cefotaxime Sodium contains approximately 50.5 mg (2.2 mEq) of sodium per gram of cefotaxime activity.

The diluent chamber contains Dextrose Injection. The concentration of Hydrous Dextrose in Water for Injection USP has been adjusted to render the reconstituted drug product iso-osmotic. Dextrose Injection is sterile, nonpyrogenic, and contains no bacteriostatic or antimicrobial agents.

Hydrous Dextrose USP has the following structural (molecular) formula:



The molecular weight of Hydrous Dextrose USP is 198.17.

Cefotaxime Sodium is supplied as a dry powder form equivalent to either 1 g or 2 g of cefotaxime.

Dextrose hydrous USP has been added to the diluent to adjust osmolality (approximately 1.95 g and 1.2 g to 1 g and 2 g dosages, respectively).

After removing the peelable foil strip, activating the seals, and thoroughly mixing, the reconstituted drug product is intended for single intravenous use. When reconstituted, the approximate osmolality for the reconstituted solution for Cefotaxime for Injection USP and Dextrose Injection is 290 mOsmol/kg.

The DUPLEX dual chamber container is made from a specially formulated material. The product (diluent and drug) contact layer is a mixture of thermoplastic rubber and a polypropylene ethylene copolymer that contains no plasticizers. The safety of the container system is supported by USP biological evaluation procedures.

CLINICAL PHARMACOLOGY
There was a dose-dependent increase in serum levels after the IV administration of 500 mg, 1 g, and 2 g of cefotaxime (38.9, 101.7, and 214.4 μg/mL respectively) without alteration in the elimination half-life. There is no evidence of accumulation following repetitive IV infusion of 1 g 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 ^{14}C-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. (See **DOSAGE AND ADMINISTRATION** section.)

Additionally, no disulfiram-like reactions were reported in a study conducted in 22 healthy volunteers administered cefotaxime and ethanol.

Microbiology
The bactericidal activity of cefotaxime sodium results from inhibition of cell wall synthesis. Cefotaxime sodium has *in vitro* activity against a wide range of gram-positive and gram-negative organisms. Cefotaxime sodium has a high degree of stability in the presence of ß-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria. Cefotaxime sodium has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobes, Gram-positive:
Enterococcus spp.
*Staphylococcus aureus**, including ß-lactamase-positive and negative strains
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes (Group A beta-hemolytic streptococci)
Streptococcus spp.

*Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to cefotaxime sodium.

Aerobes, Gram-negative:
Acinetobacter spp.
Citrobacter spp.
Enterobacter spp.
Escherichia coli
Haemophilus influenzae (including ampicillin-resistant strains)
Haemophilus parainfluenzae
Klebsiella spp. (including *Klebsiella pneumoniae*)
Morganella morganii
Neisseria meningitidis
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

NOTE: Many strains of the above organisms that are multiply resistant to other antibiotics, e.g. penicillins, cephalosporins, and aminoglycosides, are susceptible to cefotaxime sodium. Cefotaxime sodium is active against some strains of *Pseudomonas aeruginosa*.

Anaerobes:
Bacteroides spp., including some strains of *Bacteroides fragilis*
Clostridium spp. (**Note:** Most strains of *Clostridium difficil*e are resistant.)
Fusobacterium spp. (including *Fusobacterium nucleatum*).
Peptococcus spp.
Peptostreptococcus spp.

Cefotaxime sodium also demonstrates *in vitro* activity against the following microorganisms **but the clinical significance is unknown**. Cefotaxime sodium exhibits *in vitro* minimal inhibitory concentrations (MIC's) of 8 μg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of cefotaxime sodium in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials:

Aerobes, Gram-negative:
Providencia spp.
Salmonella spp. (including *Salmonella typhi*)
Shigella spp.

Cefotaxime sodium is highly stable *in vitro* to four of the five major classes of ß-lactamases described by Richmond et al.[1], including type IIIa (TEM) which is produced by many gram-negative bacteria. The drug is also stable to *ß*-lactamase (penicillinase) produced by staphylococci. In addition, cefotaxime sodium shows high affinity for penicillin-binding proteins in the cell wall, including PBP: Ib and III.

Cefotaxime sodium and aminoglycosides have been shown to be synergistic *in vitro* against some strains of *Pseudomonas aeruginosa* but the clinical significance is unknown.

Susceptibility Tests
Dilution techniques:
Quantitative methods that are used to determine minimum inhibitory concentrations (MIC's) provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method[2] (broth or agar) or equivalent with cefotaxime sodium powder. The MIC values obtained should be interpreted according to the following criteria:

When testing organisms[a] other than *Haemophilus* spp. and *Streptococcus* spp.

MIC (µg/mL)	Interpretation
≤8	Susceptible (S)
16-32	Intermediate (I)
≥64	Resistant (R)

When testing *Haemophilus* spp.[b]

MIC (µg/mL)	Interpretation[c]
≤2	Susceptible (S)

When testing *Streptococcus*[d]

MIC (µg/mL)	Interpretation
≤0.5	Susceptible (S)
1	Intermediate (I)
≥2	Resistant (R)

a. Staphylococci exhibiting resistance to methicillin/oxacillin, should be reported as also resistant to cefotaxime despite apparent *in vitro* susceptibility.

b. Interpretive criteria is applicable only to tests performed by broth microdilution method using Haemophilus Test Media.[2]

c. The absence of resistant strains precludes defining any interpretations other than susceptible.

d. *Streptococcus pneumoniae* must be tested using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal and if the microorganism is not fully susceptible to alternative clinically feasible drugs the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable, other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedure.[3] Standard cefotaxime sodium powder should provide the following MIC values:

Microorganism	MIC (µg/mL)
Escherichia coli ATCC 25922	0.03-0.12
Staphylococcus aureus ATCC 29213	1-4
Pseudomonas aeruginosa ATCC 27853	8-12
Haemophilus influenzae[a] ATCC 49247	0.12-0.5
Streptococcus pneumoniae[b] ATCC 49619	0.03-0.12

a. Ranges applicable only to tests performed by broth microdilution method using Haemophilus Test Media.[2]

b. Ranges applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.[2]

Diffusion Techniques:
Quantitative methods that require measurements of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[4] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 μg cefotaxime sodium to test the susceptibility of microorganisms to cefotaxime sodium. Reports from the laboratory providing results of the standard single-disk susceptibility test using a 30 μg cefotaxime sodium disk should be interpreted according to the following criteria:

When testing organisms[a] other than *Haemophilus* spp. and *Streptococcus* spp.

Zone Diameter (mm)	Interpretation
≥23	Susceptible (S)
15-22	Intermediate (I)
≤14	Resistant (R)

When testing *Haemophilus* spp.[b]

Zone Diameter (mm)	Interpretation[c]
≥26	Susceptible (S)

When testing *Streptococcus* other than *Streptococcus pneumoniae*

Zone Diameter (mm)	Interpretation
≥28	Susceptible (S)
26-27	Intermediate (I)
≤25	Resistant (R)

a. Staphylococci exhibiting resistance to methicillin/oxacillin, should be reported as also resistant to cefotaxime despite apparent *in vitro* susceptibility.

b. Interpretive criteria is applicable only to tests performed by disk diffusion method using Haemophilus Test Media.[4]

c. The absence of resistant strains precludes defining any interpretations other than susceptible.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefotaxime sodium.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30 μg cefotaxime sodium disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 25922	29-35
Staphylococcus aureus ATCC 25923	25-31
Pseudomonas aeruginosa ATCC 27853	18-22
Haemophilus influenzae[a] ATCC 49247	31-39

a. Ranges applicable only to tests performed by disk diffusion method using Haemophilus Test Media.[4]

Anaerobic Techniques:
For anaerobic bacteria, the susceptibility to cefotaxime sodium as MICs can be determined by standardized test methods.[5] The MIC values obtained should be interpreted according to the following criteria:

MIC (μg/mL)	Interpretation
≤16	Susceptible (S)
32	Intermediate (I)
≥64	Resistant (R)

Interpretation is identical to that stated above for results using dilution techniques.

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standardized cefotaxime sodium powder should provide the following MIC values:

Microorganism	MIC (µg/mL)
Bacteroides fragilis[a] ATCC 25285	8-32
Bacteroides thetaiotaomicron ATCC 29741	16-64
Eubacterium lantem ATCC 43055	64-256

a. Ranges applicable only to tests performed by agar dilution method.

INDICATIONS AND USAGE

Treatment

Cefotaxime for Injection USP and Dextrose Injection 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, 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*).

(3) **Gynecologic infections,** including pelvic inflammatory disease, endometritis and pelvic cellulitis caused by *Staphylococcus epidermidis, Streptococcus* species, *Enterococcus* species, *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. pneumoniae*).

(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*, cefotaxime 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. See **DOSAGE AND ADMINISTRATION** section.

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. See **DOSAGE AND ADMINISTRATION** section.

For patients undergoing gastrointestinal surgery, preoperative bowel preparation by mechanical cleansing as well as with a non-absorbable antibiotic (e.g., neomycin) is recommended.

If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapy may be instituted.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefotaxime for Injection USP and Dextrose Injection and other antibacterial drugs, Cefotaxime for Injection USP and Dextrose Injection should be used only to treat or prevent 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.

CONTRAINDICATIONS
Cefotaxime for Injection USP and Dextrose Injection is contraindicated in patients who have shown hypersensitivity to cefotaxime sodium or the cephalosporin group of antibiotics.

Solutions containing dextrose may be contraindicated in patients with hypersensitivity to corn products.

WARNINGS

BEFORE THERAPY WITH CEFOTAXIME FOR INJECTION USP AND DEXTROSE INJECTION 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 FOR INJECTION USP AND DEXTROSE INJECTION 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 **DOSAGE AND ADMINISTRATION** section.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Cefotaxime for Injection USP and Dextrose Injection, 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 for Injection USP and Dextrose Injection 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 for Injection USP and Dextrose Injection 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.

It is suggested that, based upon the data available from published studies 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[6] (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.

$$\text{Males:} \quad \frac{\text{Weight (kg) x (140 - age)}}{72 \text{ x serum creatinine}}$$

Females: 0.85 x 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.

As with other dextrose-containing solutions, Cefotaxime for Injection USP and Dextrose Injection should be prescribed with caution in patients with overt or known subclinical diabetes mellitus or carbohydrate intolerance for any reason.

If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

Use only if solution is clear and container and seals are intact.

Information for Patients

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, 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 antibiotic. If this occurs, patients should contact their physician as soon as possible.

Patients should be counseled that antibacterial drugs including Cefotaxime for Injection USP and Dextrose Injection should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Cefotaxime for Injection USP and Dextrose Injection 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 treatable by Cefotaxime for Injection USP and Dextrose Injection or other antibacterial drugs in the future.

Drug Interactions

Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Drug/Laboratory Test Interactions

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

Carcinogenesis, Mutagenesis

Lifetime studies in animals to evaluate carcinogenic potential have not been conducted. Cefotaxime was not mutagenic in the mouse micronucleus test or in the Ames' test. Cefotaxime did not impair fertility to rats when administered subcutaneously at doses up to 250 mg/kg/day (0.2 times the maximum recommended human dose based on mg/m^2) or in mice when administered intravenously at doses up to 2000 mg/kg/day (0.7 times the recommended human dose based on mg/m^2).

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.

Pediatric Use
See **PRECAUTIONS** above regarding perivascular extravasation.

Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX® Container is designed to deliver a 1 g or 2 g dose of cefotaxime. To prevent unintentional overdose, this product should not be used in pediatric patients who require less than the full adult dose of cefotaxime.

Geriatric Use
Of the 1409 subjects in clinical studies of cefotaxime, 632 (45%) were 65 and over, while 258 (18%) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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***).

ADVERSE REACTIONS
Cefotaxime is generally well tolerated. The most common adverse reactions have been local reactions following 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.

Hypersensitivity (2.4%)—Rash, pruritus, fever, eosinophilia and less frequently urticaria and anaphylaxis.

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:

Cardiovascular System—Potentially life-threatening arrhythmias following rapid (less than 60 seconds) bolus administration via central venous catheter have been observed.

Hematologic System—Neutropenia, transient leukopenia, eosinophilia, thrombocytopenia and agranulocytosis have been reported. Some individuals have developed positive direct Coombs Tests during treatment with cefotaxime and other cephalosporin antibiotics. Rare cases of hemolytic anemia have been reported.

Genitourinary System—Moniliasis, vaginitis.

Central Nervous System—Headache, encephalopathy.

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.

Cutaneous—As with other cephalosporins, isolated cases of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported.

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. See **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**. If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE
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. Patients who receive an acute overdosage should be carefully observed and given supportive treatment.

DOSAGE AND ADMINISTRATION
This product is intended for intravenous administration only.
Adults
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***).

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 for Injection USP and Dextrose Injection is intended for IV administration after reconstitution. The maximum daily dosage should not exceed 12 grams.

GUIDELINES FOR DOSAGE OF CEFOTAXIME FOR INJECTION USP
AND DEXTROSE INJECTION

Type of Infection	Daily Dose (grams)	Frequency
Uncomplicated infections	2	1 gram every 12 hours
Moderate to severe infections	3-6	1-2 grams every 8 hours
Infections commonly needing antibiotics in higher dosage (e.g., septicemia)	6-8	2 grams every 6-8 hours
Life-threatening infections	up to 12	2 grams every 4 hours

To prevent postoperative infection in contaminated or potentially contaminated surgery, the recommended dose is a single 1 gram 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 at 6 and 12 hours after the first dose.

Pediatric Patients
For body weights less than 50 kg, the recommended daily dose is 50 to 180 mg/kg 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.

Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX® Container is designed to deliver 1 g or 2 g dose of cefotaxime. To prevent unintentional overdose, this product should not be used in pediatric patients who require less than the full adult dose of cefotaxime.

Impaired Renal Function—see **PRECAUTIONS** section.
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.

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

DUPLEX® Drug Delivery System Directions for Use
Removal from Multi-Pack Tray

- Tear tape strips from one or both sides of the tray. Remove top tray.

- To avoid inadvertent activation, DUPLEX Container should remain in the folded position until activation is intended.

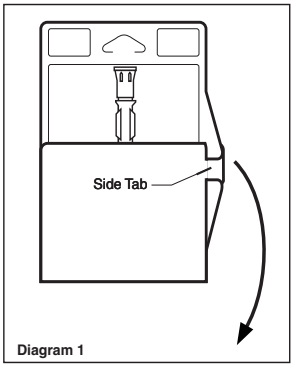


Diagram 1

Patient Labeling and Drug Powder/Diluent Inspection

- Apply patient-specific label on foil side of container. USE CARE to avoid activation. Do not cover any portion of foil strip with patient label.

- Unlatch side tab and unfold Duplex Container. (See Diagram 1.)

- Visually inspect diluent chamber for particulate matter.
- Use only if container and seals are intact.
- To inspect the drug powder for foreign matter or discoloration, peel foil strip from drug chamber. (See Diagram 2.)
- Protect from light after removal of foil strip.

Note: If foil strip is removed, product must be used within 30 days, but not beyond the labeled expiration date.

- The product should be re-folded and the side tab latched until ready to activate.

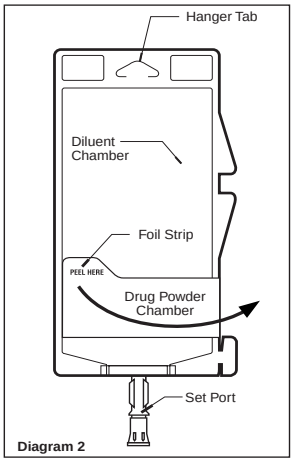


Diagram 2

Reconstitution (Activation)

- Do not use directly after storage by refrigeration, allow the product to equilibrate to room temperature before patient use.
- Unfold the DUPLEX Container and point the set port in a downward direction. Starting at the hanger tab end, fold the DUPLEX Container just below the diluent meniscus trapping all air above the fold. To activate, squeeze the folded diluent chamber until the seal between the diluent and powder opens, releasing diluent into the drug powder chamber. (See Diagram 3.)
- Agitate the liquid-powder mixture until the drug powder is completely dissolved.

Note: Following reconstitution (<u>activation</u>), product must be used within 12 hours if stored at room temperature or within 5 days if stored under refrigeration.

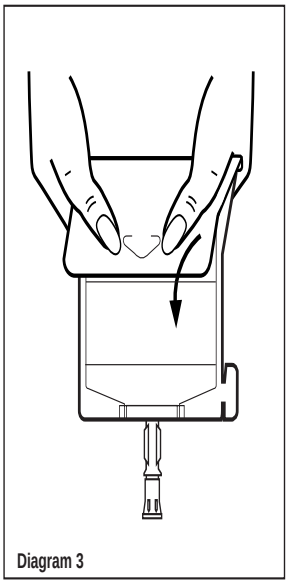


Diagram 3

Administration

- Visually inspect the reconstituted solution for particulate matter.
- Point the set port in a downwards direction. Starting at the hanger tab end, fold the DUPLEX® Container just below the solution meniscus trapping all air above the fold. Squeeze the folded DUPLEX Container until the seal between reconstituted drug solution and set port opens, releasing liquid to set port.
  (See Diagram 4.)
- Prior to attaching the IV set, check for minute leaks by squeezing container firmly. If leaks are found, discard container and solution as sterility may be impaired.
- Using aseptic technique, remove the set port cover from the set port and attach sterile administration set.
- Refer to Directions for Use accompanying the administration set.

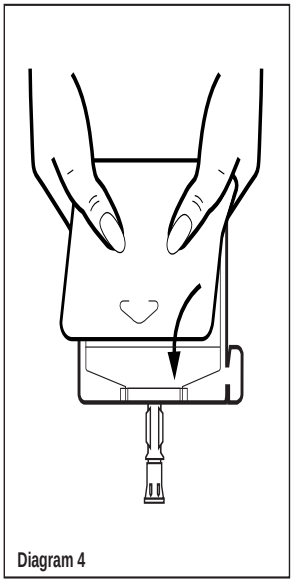


Diagram 4

Precautions

- As with other cephalosporins, reconstituted Cefotaxime for Injection USP and Dextrose Injection tends to darken depending on storage conditions, within the stated recommendations. However, product potency is not adversely affected.
- Use only if prepared solution is clear and free from particulate matter.

- Do not use in series connection.
- Do not introduce additives into the DUPLEX Container.
- Do not freeze.

HOW SUPPLIED

Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX Drug Delivery System is a flexible dual chamber container supplied in two concentrations. After reconstitution, the concentrations are equivalent to 1 g and 2 g cefotaxime. The diluent chamber contains approximately 50 mL of Dextrose Injection. Dextrose Injection has been adjusted to 3.9% and 2.4% for the 1 g and 2 g doses, respectively, such that the reconstituted solution is iso-osmotic.

Cefotaxime for Injection USP and Dextrose Injection is supplied sterile and nonpyrogenic in the DUPLEX Drug Delivery System Containers packaged 12 units per tray, 2 trays per case.

NDC	Cat. No.	Dose	Volume
Cefotaxime for Injection USP and Dextrose Injection			
0264-3133-11	3133-11	1 g	50 mL
Cefotaxime for Injection USP and Dextrose Injection			
0264-3135-11	3135-11	2 g	50 mL

Store the unactivated unit at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F).

REFERENCES

1) Richmond, M. H. and Sykes R. B.: The ß-Lactamases of Gram-Negative Bacteria and their Possible Physiological Role, Advances in Microbial Physiology 9:31-88, 1973.
2) National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.
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4) National Committee for Clinical Laboratory Standards. Performance Standard for Antimicrobial Disk Susceptibility Tests - Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.
5) National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria - Third Edition. Approved Standard NCCLS Document M11-A3, NCCLS, Villanova, PA, December, 1993.
6) Cockcroft, D.W. and Gault, M.H.: Prediction of Creatinine Clearance from Serum Creatinine, Nephron 16:31-41, 1976.

Made in USA

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