

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-780

APPROVED DRAFT LABELING

Y36-002-435

Package Insert

DUPLEX™

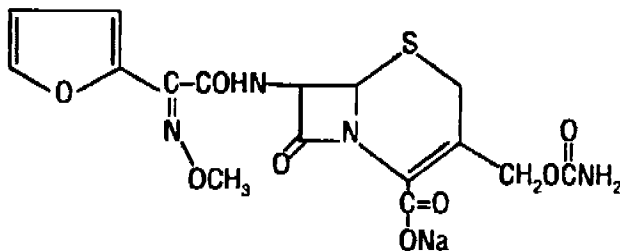
DRUG DELIVERY SYSTEM

Cefuroxime for Injection USP and Dextrose Injection USP

DESCRIPTION

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

The drug chamber is filled with sterile crystalline Cefuroxime for Injection USP, a semisynthetic, broad-spectrum, cephalosporin antibiotic for parenteral administration. It is the sodium salt of (6R,7R)-7-[2-(2-furyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7²-(Z)-(O-methyloxime), carbamate (ester).

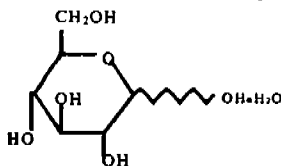


Cefuroxime Sodium USP has the following structural formula:

The empirical formula is $C_{16}H_{15}N_4NaO_8S$, representing a molecular weight of 446.4.

Cefuroxime contains approximately 54.2 mg (2.4 mEq) of sodium per gram of cefuroxime activity. The diluent chamber contains Dextrose Injection USP. The concentration of Hydrous Dextrose USP has been adjusted to render the reconstituted drug product iso-osmotic. Dextrose Injection USP 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

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 of the reconstituted solution for Cefuroxime for Injection USP and Dextrose Injection USP 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

Following IV doses of 750 mg and 1.5 g, serum concentrations were approximately 50 and 100 µg/mL, respectively, at 15 minutes. Therapeutic serum concentrations of approximately 2 µg/mL or more were maintained for 5.3 hours and 8 hours or more, respectively. There was no evidence of accumulation of cefuroxime in the serum following IV administration of 1.5 g doses every 8 hours to normal volunteers. The serum half-life after IV injection is approximately 80 minutes.

Approximately 89% of a dose of cefuroxime is excreted by the kidneys over an 8 hour period,

resulting in high urinary concentrations.

Intravenous doses of 750 mg and 1.5 g produced urinary levels averaging 1,150 and 2,500 µg/mL, respectively, during the first 8 hour period.

Cefuroxime is detectable in therapeutic concentrations in pleural fluid, joint fluid, bile, sputum, bone, cerebrospinal fluid (in patients with meningitis), and aqueous humor.

Cefuroxime is approximately 50% bound to serum protein.

Microbiology: Cefuroxime has *in vitro* activity against a wide range of gram-positive and gram-negative organisms, and it is highly stable in the presence of beta-lactamases of certain gram-negative bacteria. The bactericidal action of cefuroxime results from inhibition of cell-wall synthesis. Cefuroxime sodium has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic and facultative Gram-positive microorganisms

Staphylococcus aureus (including penicillinase-producing strains)

Streptococcus pneumoniae

Streptococcus pyogenes

Aerobic and facultative Gram-negative microorganisms

Enterobacter spp.

Escherichia coli

Haemophilus influenzae (including ampicillin-resistant strains)

Klebsiella spp.

Neisseria gonorrhoeae (including penicillinase-producing strains)

Neisseria meningitidis

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for cefuroxime sodium. However, the safety and effectiveness of cefuroxime sodium in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic and facultative Gram-positive microorganisms

Staphylococcus epidermidis

NOTE: Most strains of *Enterococcus* are resistant to cefuroxime sodium. Methicillin-resistant *Staphylococcus* and *Listeria monocytogenes* are resistant to cefuroxime sodium.

Aerobic and facultative Gram-negative microorganisms

Haemophilus parainfluenzae

Moraxella catarrhalis (including ampicillin- and cephalothin-resistant strains)

Proteus mirabilis

Providencia rettgeri

NOTE: Some strains of *Morganella morganii*, *Enterobacter cloacae*, and *Citrobacter* spp. have been shown by *in vitro* tests to be resistant to cefuroxime sodium and other cephalosporins. *Pseudomonas* and *Campylobacter* spp., *Acinetobacter calcoaceticus*, and most strains of *Serratia* spp. and *Proteus vulgaris* are resistant to most first- and second-generation cephalosporins (including cefuroxime sodium). For *Salmonella* spp. and *Shigella* spp., first- and second-generation cephalosporins (including cefuroxime sodium) may appear active *in vitro* but are not effective clinically and should NOT be reported as susceptible.

Susceptibility Testing Methods:

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method^{1,2} (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefuroxime powder. The MIC values should be interpreted according to the following criteria:

For testing Enterobacteriaceae and *Staphylococcus* spp.

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

For testing *Haemophilus* spp.^a

MIC (µg/mL)	Interpretation
≤4	Susceptible (S)
8	Intermediate (I)
≥16	Resistant (R)

For testing *Neisseria gonorrhoeae*^b

MIC (µg/mL)	Interpretation
≤1	Susceptible (S)
2	Intermediate (I)
≥4	Resistant (R)

For testing *Streptococcus pneumoniae*^c

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

Alternatively, isolates of *Streptococcus pneumoniae* could be tested against a 1-µg oxacillin disk. Isolates with oxacillin zone sizes of ≥ 20 mm are susceptible to penicillin and can be considered susceptible to cefuroxime sodium.

For testing *Streptococcus* spp. other than *S. pneumoniae*

Isolates of *Streptococcus* spp. other than *S. pneumoniae* that are susceptible to penicillin (MIC ≤ 0.12 µg/mL) can be considered susceptible to cefuroxime sodium and need not be tested against cefuroxime sodium.

^aThese interpretive standards are applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using *Haemophilus* Test Medium (HTM)².

^bThese interpretive standards are applicable to agar dilution tests with GC agar base and 1% defined growth supplement².

^cThese interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood².

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, which 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 quality control microorganisms to control the technical aspects of the test procedures. Standard cefuroxime sodium powder should provide the following MIC values:

Microorganism	MIC Range (µg/mL)
<i>E. coli</i> ATCC 25922	2-8
<i>H. influenzae</i> ^d ATCC 49766	0.25-1
<i>S. aureus</i> ATCC 29213	0.5-2
<i>N. gonorrhoeae</i> ^e ATCC 49226	0.25-1
<i>S. pneumoniae</i> ^f ATCC 49619	0.25-1

^dThis quality control range is applicable to only *H. influenzae* ATCC 49766 tested by a microdilution procedure using HTM².

^eThis quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an agar dilution procedure using GC agar base with 1% defined growth supplement².

^fThis quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood².

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure^{3,4} requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30- μ g cefuroxime to test the susceptibility of microorganisms to cefuroxime sodium. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30- μ g cefuroxime disk should be interpreted according to the following criteria:

For testing Enterobacteriaceae and *Staphylococcus* spp.

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible (S)
15-17	Intermediate (I)
≤ 14	Resistant (R)

For testing *Haemophilus* spp.^g

Zone Diameter (mm)	Interpretation
≥ 20	Susceptible (S)
17-19	Intermediate (I)
≤ 16	Resistant (R)

For testing *Neisseria gonorrhoeae*^h

Zone Diameter (mm)	Interpretation
≥ 31	Susceptible (S)
26-30	Intermediate (I)
≤ 25	Resistant (R)

For testing *Streptococcus pneumoniae*ⁱ

Isolates of *Streptococcus pneumoniae* with oxacillin zone sizes of > 20 mm are susceptible to penicillin and can be considered susceptible to cefuroxime sodium.

For testing β -hemolytic streptococci onlyⁱ

A β -hemolytic streptococcal isolate that is susceptible to a 10-unit penicillin disk (zone diameter ≥ 28 mm) can be considered susceptible to cefuroxime sodium and need not be tested against cefuroxime sodium.

NOTE: Penicillin disk diffusion test is not reliable with viridans streptococci.

^gThese zone diameter standards are applicable only to tests with *Haemophilus* spp. using HTM⁴.

^hThese interpretive standards are applicable to disk diffusion tests with GC agar base and 1% defined growth supplement incubated in 5% CO₂⁴.

ⁱThis zone diameter standard only applies to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO₂⁴.

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 cefuroxime 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- μ g cefuroxime disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter Range (mm)
<i>E. coli</i> ATCC 25922	20-26
<i>H. influenzae</i> ^j ATCC 49766	28-36
<i>N. gonorrhoeae</i> ^k ATCC 49226	33-41
<i>S. aureus</i> ATCC 25923	27-35

^jThis quality control limit applies to tests conducted with *Haemophilus influenzae* ATCC 49766 using HTM⁴.

^kThis quality control range is only applicable to tests performed by disk diffusion using GC agar base and 1% defined growth supplement⁴.

INDICATIONS AND USAGE

Cefuroxime for Injection USP and Dextrose Injection USP is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the

following diseases:

1. **Lower Respiratory Tract Infections**, including pneumonia, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* spp., *Staphylococcus aureus* (including penicillinase-producing strains), *Streptococcus pyogenes*, and *Escherichia coli*.
2. **Urinary Tract Infections** caused by *Escherichia coli* and *Klebsiella* spp.
3. **Skin and Skin-Structure Infections** caused by *Staphylococcus aureus* (including penicillinase-producing strains), *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella* spp., and *Enterobacter* spp.
4. **Septicemia** caused by *Staphylococcus aureus* (including penicillinase-producing strains), *Streptococcus pneumoniae*, *Escherichia coli*, *Haemophilus influenzae* (including ampicillin-resistant strains), and *Klebsiella* spp.
5. **Meningitis** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including ampicillin-resistant strains), *Neisseria meningitidis*, and *Staphylococcus aureus* (including penicillinase-producing strains).
6. **Gonorrhea**: Uncomplicated and disseminated gonococcal infections due to *Neisseria gonorrhoeae* (including penicillinase-producing strains) in both males and females.
7. **Bone and Joint Infections** caused by *Staphylococcus aureus* (including penicillinase-producing strains).

Clinical microbiological studies in skin and skin-structure infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. Cefuroxime has been used successfully in these mixed infections in which several organisms have been isolated. Appropriate cultures and susceptibility studies should be performed to determine the susceptibility of the causative organisms to cefuroxime.

Therapy may be started while awaiting the results of these studies; 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, cefuroxime may be used concomitantly with an aminoglycoside (see **PRECAUTIONS**). The recommended doses of both antibiotics may be given depending on the severity of the infection and the patient's condition.

Prevention: The preoperative prophylactic administration of Cefuroxime for Injection USP and Dextrose Injection USP may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (e.g., vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. Cefuroxime for Injection USP and Dextrose Injection USP should usually be given one-half to 1 hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance.

The perioperative use of Cefuroxime for Injection USP and Dextrose Injection USP has also been effective during open heart surgery for surgical patients in whom infections at the operative site would present a serious risk. For these patients it is recommended that cefuroxime therapy be continued for at least 48 hours after the surgical procedure ends. If an infection is present, specimens for culture should be obtained for the identification of the causative organism, and appropriate antimicrobial therapy should be instituted.

CONTRAINDICATIONS

Cefuroxime for Injection USP and Dextrose Injection USP is contraindicated in patients with known allergy to the cephalosporin group of antibiotics. Solutions containing dextrose may be contraindicated in patients with hypersensitivity to corn products.

WARNINGS

BEFORE THERAPY WITH CEFUROXIME FOR INJECTION USP AND DEXTROSE INJECTION USP IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN

ALLERGIC REACTION TO CEFUROXIME OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefuroxime, and may range from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

General

Although Cefuroxime for Injection USP and Dextrose Injection USP rarely produce alterations in kidney function, evaluation of renal status during therapy is recommended, especially in seriously ill patients receiving the maximum doses. Cephalosporins should be given with caution to patients receiving concurrent treatment with potent diuretics as these regimens are suspected of adversely affecting renal function.

The total daily dose of cefuroxime should be reduced in patients with transient or persistent renal insufficiency (see **DOSAGE AND ADMINISTRATION**), because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.

As with other antibiotics, prolonged use of cefuroxime may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

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

As with other therapeutic regimens used in the treatment of meningitis, mild-to-moderate hearing loss has been reported in a few pediatric patients treated with cefuroxime sodium. Persistence of positive CSF (cerebrospinal fluid) cultures at 18 to 36 hours has also been noted with cefuroxime sodium injection, as well as with other antibiotic therapies; however, the clinical relevance of this is unknown.

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

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

Drug/Drug Interactions: The concomitant oral administration of probenecid with cefuroxime slows tubular secretion, decreases renal clearance by approximately 40%, increases the peak serum level by approximately 30%, and increases the serum half-life by approximately 30%.

Drug/Laboratory Test Interactions: 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., Tes-Tape®). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving cefuroxime.

Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Although lifetime studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic activity was found for cefuroxime in the mouse lymphoma assay and a battery of bacterial mutation tests. Positive results were obtained in an *in vitro* chromosome aberration assay, however, negative results were found in an *in vivo* micronucleus test at

doses up to 10 g/kg. Reproduction studies in mice at doses up to 3200 mg/kg per day (3.1 times the recommended maximum human dose based on mg/m²) have revealed no impairment of fertility.

Pregnancy - Teratogenic Effects - Pregnancy Category B.

Reproduction studies have been performed in mice at doses up to 6400 mg/kg per day (6.3 times the recommended maximum human dose based on mg/m²), and in rabbits at doses up to 400 mg/kg per day (2.1 times the recommended maximum human dose based on mg/m²) have revealed no evidence of harm to the fetus due to cefuroxime. 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.

Nursing Mothers

Since cefuroxime is excreted in human milk, caution should be exercised when cefuroxime is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below 3 months of age have not been established. Accumulation of other members of the cephalosporin class in newborn infants (with resulting prolongation of drug half-life) has been reported.

Cefuroxime for Injection USP and Dextrose Injection USP in the DUPLEX™ Container is designed to deliver a 750 mg or 1.5 g dose of cefuroxime. To prevent unintentional overdose, this product should not be used in pediatric patients who require less than the full adult dose of cefuroxime.

ADVERSE REACTIONS

Cefuroxime is generally well tolerated. The most common adverse effects have been local reactions following IV administration. Other adverse reactions have been encountered only rarely.

Local Reactions: Thrombophlebitis has occurred with IV administration in 1 in 60 patients.

Gastrointestinal: Gastrointestinal symptoms occurred in 1 in 150 patients and included diarrhea (1 in 220 patients) and nausea (1 in 440 patients). Onset of pseudomembranous colitis symptoms may occur during or after treatment (see WARNINGS).

Hypersensitivity Reactions: Hypersensitivity reactions have been reported in fewer than 1% of the patients treated with cefuroxime and include rash (1 in 125). Pruritus, urticaria, and positive Coombs' test each occurred in fewer than 1 in 250 patients, and, as with other cephalosporins, rare cases of anaphylaxis, drug fever, erythema multiforme, interstitial nephritis, toxic epidermal necrolysis, and Stevens-Johnson syndrome have occurred.

Blood: A decrease in hemoglobin and hematocrit has been observed in 1 in 10 patients and transient eosinophilia in 1 in 14 patients. Less common reactions seen were transient neutropenia (fewer than 1 in 100 patients) and leukopenia (1 in 750 patients). A similar pattern and incidence were seen with other cephalosporins used in controlled studies. As with other cephalosporins, there have been rare reports of thrombocytopenia.

Hepatic: Transient rise in AST (SGOT) and ALT (SGPT) (1 in 25 patients), alkaline phosphatase (1 in 50 patients), LDH (1 in 75 patients), and bilirubin (1 in 500 patients) levels has been noted. One case of ischemic hepatitis secondary to toxic epidermal necrolysis has been reported in a cirrhotic patient receiving cefuroxime and gentamicin.

Kidney: Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine clearance have been observed, but their relationship to cefuroxime is unknown.

Postmarketing Experience with Cefuroxime: In addition to the adverse events reported during clinical trials, the following events have been observed during clinical practice in patients treated with cefuroxime and were reported spontaneously. Data are generally insufficient to allow an estimate of incidence or to establish causation.

Neurologic: Seizure and encephalopathy.

Non-site specific: Angioedema.

Cephalosporin-class Adverse Reactions: In addition to the adverse reactions listed above that have been observed in patients treated with cefuroxime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Vomiting, abdominal pain, colitis, vaginitis including vaginal

candidiasis, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, and hemorrhage.

Encephalopathy and seizures have been reported in renally impaired patients treated with unadjusted dosing regimens of cefuroxime. Several cephalosporins, including cefuroxime, have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see DOSAGE AND ADMINISTRATION). If seizures associated with drug therapy should occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Altered Laboratory Tests: Prolonged prothrombin time, pancytopenia, agranulocytosis.

OVERDOSAGE

Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. Serum levels of cefuroxime can be reduced by hemodialysis and peritoneal dialysis.

DOSAGE AND ADMINISTRATION

This product is intended for intravenous administration only.

Dosage: Adults: The usual adult dosage range for cefuroxime is 750 mg to 1.5 grams every 8 hours, usually for 5 to 10 days. In uncomplicated urinary tract infections, skin and skin-structure infections, disseminated gonococcal infections, and uncomplicated pneumonia, a 750 mg dose every 8 hours is recommended. In severe or complicated infections, a 1.5 gram dose every 8 hours is recommended.

In bone and joint infections, a 1.5 gram dose every 8 hours is recommended. In clinical trials, surgical intervention was performed when indicated as an adjunct to cefuroxime therapy. A course of oral antibiotics was administered when appropriate following the completion of parenteral administration of cefuroxime.

In life-threatening infections or infections due to less susceptible organisms, 1.5 grams every 6 hours may be required. In bacterial meningitis, the dosage should not exceed 3 grams every 8 hours. For preventive use for clean-contaminated or potentially contaminated surgical procedures, a 1.5 gram dose administered intravenously just before surgery (approximately one-half to 1 hour before the initial incision) is recommended. Thereafter, give 750 mg intravenously every 8 hours when the procedure is prolonged.

For preventive use during open heart surgery, a 1.5 gram dose administered intravenously at the induction of anesthesia and every 12 hours thereafter for a total of 6 grams is recommended.

Impaired Renal Function: A reduced dosage must be employed when renal function is impaired. Dosage should be determined by the degree of renal impairment and the susceptibility of the causative organism (see Table 1).

Table 1: Dosage of Cefuroxime in Adults with Reduced Renal Function

Creatinine Clearance (mL/min)	Dose	Frequency
>20	750 mg-1.5 grams	q8h
10-20	750 mg	q12h
<10	750 mg	q24h*

*Since cefuroxime is dialyzable, patients on hemodialysis should be given a further dose at the end of the dialysis.

When only serum creatinine is available, the following formula⁵ (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.

Males: Creatinine clearance (mL/min) = $\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$

Females: 0.85 x male value

Note: As with antibiotic therapy in general, administration of Cefuroxime for Injection USP and Dextrose Injection USP should be continued for a minimum of 48 to 72 hours after the patient becomes asymptomatic or after evidence of bacterial eradication has been obtained; a minimum of 10 days of treatment is recommended in infections caused by *Streptococcus pyogenes* 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 for several weeks; and doses smaller than those indicated above should not be used. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated.

Pediatric Patients Above 3 Months of Age: Administration of 50 to 100 mg/kg per day in equally divided doses every 6 to 8 hours has been successful for most infections susceptible to cefuroxime. The higher dosage of 100 mg/kg per day (not to exceed the maximum adult dosage) should be used for the more severe or serious infections.

In bone and joint infections, 150 mg/kg per day (not to exceed the maximum adult dosage) is recommended in equally divided doses every 8 hours. In clinical trials, a course of oral antibiotics was administered to pediatric patients following the completion of parenteral administration of cefuroxime.

In cases of bacterial meningitis, a larger dosage of cefuroxime is recommended, 200 to 240 mg/kg per day intravenously in divided doses every 6 to 8 hours.

In pediatric patients with renal insufficiency, the frequency of dosing should be modified consistent with the recommendations for adults.

Cefuroxime for Injection USP and Dextrose for Injection USP in the DUPLEX™ Container is designed to deliver a 750 mg or 1.5 g dose of cefuroxime. To prevent unintentional overdose, this product should not be used in pediatric patients who require less than the full adult dose.

For intermittent IV infusion with a Y-type administration set, dosing can be accomplished through the tubing system by which the patient may be receiving other IV solutions. However, during infusion of the solution containing Cefuroxime, it is advisable to temporarily discontinue administration of any other solutions at the same site.

Solutions of cefuroxime, like those of most beta-lactam antibiotics, should not be added to solutions of aminoglycoside antibiotics because of potential interaction.

However, if concurrent therapy with cefuroxime and an aminoglycoside is indicated, each of these antibiotics can be administered separately to the same patient.

Use sterile equipment.

Caution: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

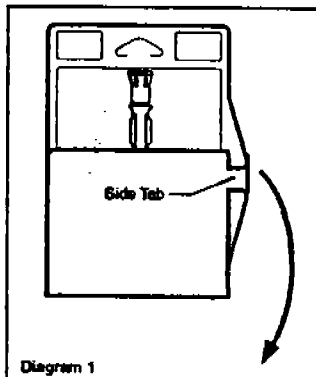
DUPLEX™ Drug Delivery System Directions for Use

Removal from Multi-Pack Tray

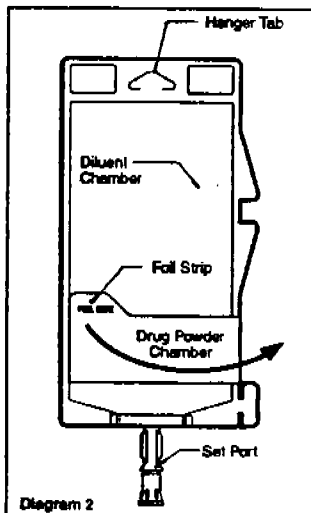
- Tear tape strips from one or both sides of the tray. Remove top tray.
- To avoid inadvertent activation, Duplex Container should remain in the folded position until activation is intended.

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.)



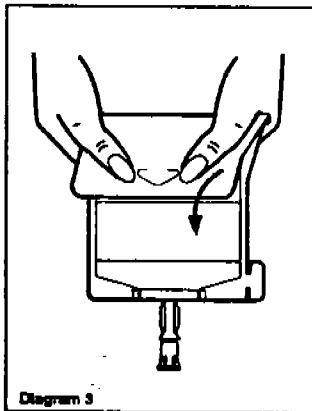
- Protect from light after removal of foil strip.

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.

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 (activation), product must be used within 24 hours if stored at room temperature or within 7 days if stored under refrigeration.

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.)

NDA 50-780: Cefuroxime and Dextrose for Injection in the DUPLEX™ Container

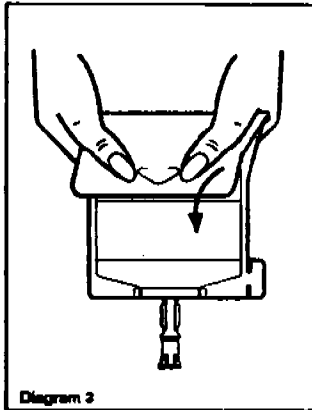


Diagram 3

- Agitate the liquid-powder mixture until the drug powder is completely dissolved.

Note: Following reconstitution (activation), product must be used within 24 hours if stored at room temperature or within 7 days if stored under refrigeration (5°C).

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.)

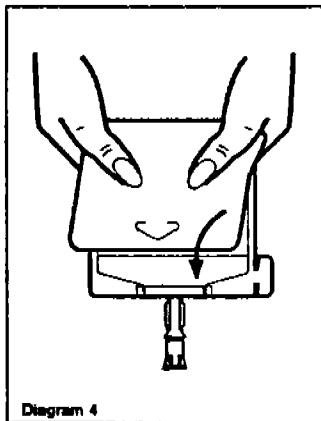


Diagram 4

- 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.

Precautions

- As with other cephalosporins, reconstituted Cefuroxime for Injection USP and Dextrose Injection USP 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.

NDA 50-780: Cefuroxime and Dextrose for Injection in the DUPLEX™ Container

- Do not freeze.

HOW SUPPLIED

Cefuroxime for Injection USP and Dextrose Injection USP in the DUPLEX Drug Delivery System is a flexible dual chamber container supplied in two concentrations. After reconstitution, the concentrations are equivalent to 750 mg and 1.5 g cefuroxime. The diluent chamber contains approximately 50 mL of Dextrose Injection USP. Dextrose Injection USP has been adjusted to 4.1% and 2.9% for the 750 mg and 1.5 g doses, respectively, such that the reconstituted solution is iso-osmotic.

Cefuroxime for Injection USP and Dextrose Injection USP 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
	Cefuroxime for Injection USP and Dextrose Injection USP		
0264-3112-11	3112-11	750 mg	50 mL
	Cefuroxime for Injection USP and Dextrose Injection USP		
0264-3114-11	3114-11	1.5 g	50 mL

Store the unactivated unit at room temperature.

Rx only

Issued: March 2000

- 1 National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing. Third Informational Supplement. NCCLS Document M100-S3, Vol. 11, No. 17. Villanova, Pa: NCCLS; 1991.
- 2 Cockcroft, DW., and Gault MH.: Prediction of creatinine clearance from serum creatinine. Nephron. 16:31-41, 1976.

DUPLEX™ is a trademark of B. Braun Medical Inc.

Clinitest® is a registered trademark of Ames Division, Miles Laboratories, Inc.

Tes-Tape® is a registered trademark of Eli Lilly and Company.

U.S. Patent Nos. D388,168, D397,789, D407,816 and D402,366; other patents pending.

B|BRAUN

B. Braun Medical Inc.

Irvine CA USA 92614-5895