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Y36-002-707
Package Insert

DUPLEX®
DRUG DELIVERY SYSTEM

CefTRIaxONE for Injection and Dextrose Injection

Rx only

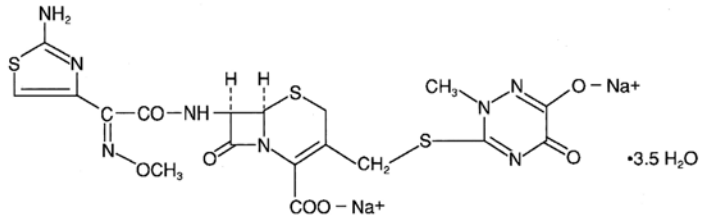
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ceftriaxone for Injection and Dextrose Injection and other antibacterial drugs, Ceftriaxone for Injection and Dextrose Injection should be used only to treat or prevent infections that are proven or strongly suspected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

DESCRIPTION

Ceftriaxone for Injection and Dextrose Injection is a sterile, nonpyrogenic, single use, packaged combination of Ceftriaxone 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 ceftriaxone sodium, a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous administration. Ceftriaxone sodium is (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-*as*-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7^2-(*Z*)-(*O*-methyloxime), disodium salt, sesquaterhydrate.

The chemical formula of ceftriaxone sodium is $C_{18}H_{16}N_8Na_2O_7S_3 \bullet 3.5H_2O$. It has a calculated molecular weight of 661.60 and the following structural formula:



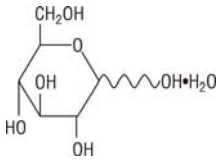
Ceftriaxone sodium is supplied as a dry powder form equivalent to either 1 g or 2 g of ceftriaxone. Ceftriaxone sodium is a white to yellowish-orange crystalline powder which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The pH of a 1% aqueous solution is approximately 6.7. The color of ceftriaxone sodium solutions ranges from light yellow to amber, depending on the length of storage and concentration.

Ceftriaxone sodium contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone 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 USP has been added to adjust osmolality (approximately 1.87 g and 1.11 g to 1 g and 2 g dosages, respectively). Dextrose Injection is sterile, nonpyrogenic, and contains no bacteriostatic or antimicrobial agents.

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

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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 for the reconstituted solution for Ceftriaxone for Injection and Dextrose Injection is 290 mOsmol/kg.

The DUPLEX Container is Latex-free, PVC-free, and DEHP-free.

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
Average plasma concentrations of ceftriaxone following a single 30-minute intravenous (IV) infusion of a 0.5, 1 or 2 g dose in healthy subjects are presented in Table 1.

TABLE 1. Ceftriaxone Plasma Concentrations After Single Dose Administration

Average Plasma Concentrations (mcg/mL)									
Dose/Route	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	16 hr	24 hr
0.5 gm IV*	82	59	48	37	29	23	15	10	5
1 gm IV*	151	111	88	67	53	43	28	18	9
2 gm IV*	257	192	154	117	89	74	46	31	15

*IV doses were infused at a constant rate over 30 minutes.

Multiple IV doses ranging from 0.5 to 2 g at 12- to 24-hour intervals resulted in 15% to 36% accumulation of ceftriaxone above single dose values.

Ceftriaxone concentrations in urine are high, as shown in Table 2.

TABLE 2. Urinary Concentrations of Ceftriaxone After Single Dose Administration

Average Urinary Concentrations (mcg/mL)						
Dose/Route	0-2 hr	2-4 hr	4-8 hr	8-12 hr	12-24 hr	24-48 hr
0.5 g IV	526	366	142	87	70	15
1 g IV	995	855	293	147	132	32
2 g IV	2692	1976	757	274	198	40

Thirty-three percent to 67% of a ceftriaxone dose was excreted in the urine as unchanged drug and the remainder was secreted in the bile and ultimately found in the feces as microbiologically inactive compounds. After a 1 g IV dose, average concentrations of ceftriaxone, determined from 1 to 3 hours after dosing, were 581 mcg/mL in the gallbladder bile, 788 mcg/mL in the common duct bile, 898 mcg/mL in the cystic duct bile, 78.2 mcg/g in the gallbladder wall and 62.1 mcg/mL in the concurrent plasma.

Over a 0.15 to 3 g dose range in healthy adult subjects, the values of elimination half-life ranged from 5.8 to 8.7 hours; apparent volume of distribution from 5.78 to 13.5 L; plasma clearance from

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0.58 to 1.45 L/hour; and renal clearance from 0.32 to 0.73 L/hour. Ceftriaxone is reversibly bound to human plasma proteins, and the binding decreased from a value of 95% bound at plasma concentrations of <25 mcg/mL to a value of 85% bound at 300 mcg/mL. Ceftriaxone crosses the blood placenta barrier.

The average values of maximum plasma concentration, elimination half-life, plasma clearance and volume of distribution after a 50 mg/kg IV dose and after a 75 mg/kg IV dose in pediatric patients suffering from bacterial meningitis are shown in Table 3. Ceftriaxone penetrated the inflamed meninges of infants and pediatric patients; CSF concentrations after a 50 mg/kg IV dose and after a 75 mg/kg IV dose are also shown in Table 3.

TABLE 3. Average Pharmacokinetic Parameters of Ceftriaxone in Pediatric Patients With Meningitis

	50 mg/kg IV	75 mg/kg IV
Maximum Plasma Concentrations (mcg/mL)	216	275
Elimination Half-life (hr)	4.6	4.3
Plasma Clearance (mL/hr/kg)	49	60
Volume of Distribution (mL/kg)	338	373
CSF Concentration – inflamed meninges (mcg/mL)	5.6	6.4
Range (mcg/mL)	1.3 – 18.5	1.3 – 44
Time after dose (hr)	3.7 (±1.6)	3.3 (±1.4)

Compared to that in healthy adult subjects, the pharmacokinetics of ceftriaxone were only minimally altered in elderly subjects and in patients with renal impairment or hepatic dysfunction (Table 4); therefore, dosage adjustments are not necessary for these patients with ceftriaxone dosages up to 2 g per day. Ceftriaxone was not removed to any significant extent from the plasma by hemodialysis. In 6 of 26 dialysis patients, the elimination rate of ceftriaxone was markedly reduced, suggesting that plasma concentrations of ceftriaxone should be monitored in these patients to determine if dosage adjustments are necessary.

TABLE 4. Average Pharmacokinetic Parameters of Ceftriaxone in Humans

Subject Group	Elimination Half-Life (hr)	Plasma Clearance (L/hr)	Volume of Distribution (L)
Healthy Subjects	5.8 – 8.7	0.58 – 1.45	5.8 – 13.5
Elderly Subjects (mean age, 70.5 yr)	8.9	0.83	10.7
Patients with Renal Impairment			
Hemodialysis Patients (0-5 mL/min)*	14.7	0.65	13.7
Severe (5-15 mL/min)	15.7	0.56	12.5
Moderate (16-30 mL/min)	11.4	0.72	11.8
Mild (31-60 mL/min)	12.4	0.70	13.3
Patients With Liver Disease	8.8	1.1	13.6

*Creatinine clearance.

Interaction with Calcium

Two *in vitro* studies, one using adult plasma and the other neonatal plasma from umbilical cord blood have been carried out to assess interaction of Ceftriaxone for Injection and Dextrose Injection and calcium. Ceftriaxone for Injection and Dextrose Injection concentrations up to 1 mM (in excess of concentrations achieved *in vivo* following administration of 2 grams Ceftriaxone for Injection and Dextrose Injection infused over 30 minutes) were used in combination with calcium concentrations up to 12 mM (48 mg/dL). Recovery of Ceftriaxone for Injection and Dextrose

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Injection from plasma was reduced with calcium concentrations of 6 mM (24 mg/dL) or higher in adult plasma or 4 mM (16 mg/dL) or higher in neonatal plasma. This may be reflective of ceftriaxone-calcium precipitation.

Microbiology
The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria.

In an *in vitro* study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone.

Ceftriaxone has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections described in the **INDICATIONS AND USAGE** section.

Aerobic gram-negative microorganisms
Acinetobacter calcoaceticus
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae (including ampicillin-resistant and beta-lactamase producing strains)
Haemophilus parainfluenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis (including beta-lactamase producing strains)
Morganella morganii
Neisseria gonorrhoeae (including penicillinase- and nonpenicillinase-producing strains)
Neisseria meningitidis
Proteus mirabilis
Proteus vulgaris
Serratia marcescens

Ceftriaxone is also active against many strains of Pseudomonas aeruginosa.

NOTE: Many strains of the above organisms that are multiply resistant to other antibiotics, *e.g.*, penicillins, cephalosporins, and aminoglycosides, are susceptible to ceftriaxone.

Aerobic gram-positive microorganisms
Staphylococcus aureus (including penicillinase-producing strains)
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans group streptococci

NOTE: Methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone. Most strains of Group D streptococci and enterococci*, e.g.*, *Enterococcus (Streptococcus) faecalis*, are resistant.

Anaerobic microorganisms
Bacteroides fragilis
Clostridium species
Peptostreptococcus species

NOTE: Most strains of *Clostridium difficile* are resistant.

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The following *in vitro* data are available, **but their clinical significance is unknown**. Ceftriaxone exhibits *in vitro* minimal inhibitory concentrations (MICs) of ≤8 mcg/mL or less against most strains of the following microorganisms, however, the safety and effectiveness of ceftriaxone in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-negative microorganisms
Citrobacter diversus
Citrobacter freundii
Providencia species (including *Providencia rettgeri*)
Salmonella species (including *Salmonella typhi*)
Shigella species

Aerobic gram-positive microorganisms
Streptococcus agalactiae

Anaerobic microorganisms
Prevotella (Bacteroides) bivius
Porphyromonas (Bacteroides) melaninogenicus

Susceptibility Tests
Dilution Techniques
Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure.[1] Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ceftriaxone powder. The MIC values should be interpreted according to the following criteria[2] for aerobic organisms other than *Haemophilus* spp, *Neisseria gonorrhoeae*, and *Streptococcus* spp, including *Streptococcus pneumoniae*:

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

The following interpretive criteria[2] should be used when testing *Haemophilus* species using Haemophilus Test Media (HTM).

MIC (mcg/mL)	Interpretation
≤2	(S) Susceptible

The absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

The following interpretive criteria[2] should be used when testing *Neisseria gonorrhoeae* when using GC agar base and 1% defined growth supplement.

MIC (mcg/mL)	Interpretation
≤0.25	(S) Susceptible

The absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

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The following interpretive criteria[2] should be used when testing *Streptococcus* spp including *Streptococcus pneumoniae* using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.

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

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 results 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 the 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 laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standardized ceftriaxone powder should provide the following MIC values[2]:

Microorganism	ATCC®#	MIC (mcg/mL)
Escherichia coli	25922	0.03 – 0.12
Staphylococcus aureus	29213	1 – 8*
Pseudomonas aeruginosa	27853	8 – 32
Haemophilus influenzae	49247	0.06 – 0.25
Neisseria gonorrhoeae	49226	0.004 – 0.015
Streptococcus pneumoniae	49619	0.03 – 0.12

* A bimodal distribution of MICs results at the extremes of the acceptable range should be suspect and control validity should be verified with data from other control strains.

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] requires the use of standardized inoculum concentrations. This procedure uses paper discs impregnated with 30 mcg of ceftriaxone to test the susceptibility of microorganisms to ceftriaxone.

Reports from the laboratory providing results of the standard single-disc susceptibility test with a 30 mcg ceftriaxone disc should be interpreted according to the following criteria for aerobic organisms other than *Haemophilus* spp, *Neisseria gonorrhoeae*, and *Streptococcus* spp:

Zone Diameter (mm)	Interpretation
≥21	(S) Susceptible
14 – 20	(I) Intermediate
≤13	(R) Resistant

The following interpretive criteria[3] should be used when testing *Haemophilus* species when using Haemophilus Test Media (HTM).

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Zone Diameter (mm)	Interpretation
≥26	(S) Susceptible

The absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

The following interpretive criteria[3] should be used when testing *Neisseria gonorrhoeae* when using GC agar base and 1% defined growth supplement.

Zone Diameter (mm)	Interpretation
≥35	(S) Susceptible

The absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

The following interpretive criteria[3] should be used when testing *Streptococcus* spp other than *Streptococcus pneumoniae* when using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

Zone Diameter (mm)	Interpretation
≥27	(S) Susceptible
25 – 26	(I) Intermediate
≤24	(R) Resistant

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

Disc diffusion interpretive criteria for ceftriaxone discs against *Streptococcus pneumoniae* are not available, however, isolates of pneumococci with oxacillin zone diameters of >20 mm are susceptible (MIC ≤0.06 mcg/mL) to penicillin and can be considered susceptible to ceftriaxone. *Streptococcus pneumoniae* isolates should not be reported as penicillin (ceftriaxone) resistant or intermediate based solely on an oxacillin zone diameter of ≤19 mm. The ceftriaxone MIC should be determined for those isolates with oxacillin zone diameters ≤19 mm.

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 mcg ceftriaxone disc should provide the following zone diameters in these laboratory test quality control strains[3]:

Microorganism	ATCC®#	Zone Diameter Ranges (mm)
Escherichia coli	25922	29 – 35
Staphylococcus aureus	25923	22 – 28
Pseudomonas aeruginosa	27853	17 – 23
Haemophilus influenzae	49247	31 – 39
Neisseria gonorrhoeae	49226	39 – 51
Streptococcus pneumoniae	49619	30 – 35

Anaerobic Techniques
For anaerobic bacteria, the susceptibility to ceftriaxone as MICs can be determined by standardized test methods[4]. The MIC values obtained should be interpreted according to the following criteria:

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

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standardized ceftriaxone powder should provide the following MIC values for the indicated standardized anaerobic dilution[4] testing method:

Method	Microorganism	ATCC®#	MIC (mcg/mL)
Agar	*Bacteroides fragilis*	25285	32 – 128
	Bacteroides thetaiotaomicron	29741	64 – 256
Broth	*Bacteroides thetaiotaomicron*	29741	32 – 128

INDICATIONS AND USAGE
Before instituting treatment with Ceftriaxone for Injection and Dextrose Injection, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ceftriaxone for Injection and Dextrose Injection and other antibacterial drugs, Ceftriaxone for Injection 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.

Ceftriaxone for Injection and Dextrose Injection is indicated for the treatment of the following infections when caused by susceptible organisms:

LOWER RESPIRATORY TRACT INFECTIONS caused by *Streptococcus pneumoniae*, *Staphylococcus aureus, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Escherichia coli, Enterobacter aerogenes, Proteus mirabilis* or *Serratia marcescens*.

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes,* Viridans group streptococci*, Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Morganella morganii*, Pseudomonas aeruginosa, Serratia marcescens, Acinetobacter calcoaceticus, Bacteroides fragilis** or *Peptostreptococcus* species.

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *Escherichia coli, Proteus mirabilis, Proteus vulgaris, Morganella morganii* or *Klebsiella pneumoniae*.

PELVIC INFLAMMATORY DISEASE caused by *Neisseria gonorrhoeae*. Ceftriaxone sodium, like other cephalosporins, has no activity against *Chlamydia trachomatis*. Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and *Chlamydia trachomatis* is one of the suspected pathogens, appropriate antichlamydial coverage should be added.

BACTERIAL SEPTICEMIA caused by *Staphylococcus aureus*, *Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae* or *Klebsiella pneumoniae*.

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BONE AND JOINT INFECTIONS caused by *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae* or *Enterobacter species.*

INTRA-ABDOMINAL INFECTIONS caused by *Escherichia coli, Klebsiella pneumoniae, Bacteroides fragilis, Clostridium* species (NOTE: most strains of *Clostridium difficile* are resistant) or *Peptostreptococcus* species.

MENINGITIS caused by *Haemophilus influenzae, Neisseria meningitidis* or *Streptococcus pneumoniae*. Ceftriaxone sodium has also been used successfully in a limited number of cases of meningitis and shunt infection caused by *Staphylococcus epidermidis** and *Escherichia coli*.*

* Efficacy for this organism in this organ system was studied in fewer than ten infections.

SURGICAL PROPHYLAXIS: The preoperative administration of a single 1 g dose of Ceftriaxone for Injection and Dextrose Injection may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (*e.g.*, vaginal or abdominal hysterectomy or cholecystectomy for chronic calculous cholecystitis in high-risk patients, such as those over 70 years of age, with acute cholecystitis not requiring therapeutic antimicrobials, obstructive jaundice or common duct bile stones) and in surgical patients for whom infection at the operative site would present serious risk (*e.g.*, during coronary artery bypass surgery). Although ceftriaxone sodium has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery.

When administered prior to surgical procedures for which it is indicated, a single 1 g dose of Ceftriaxone for Injection and Dextrose Injection provides protection from most infections due to susceptible organisms throughout the course of the procedure.

CONTRAINDICATIONS
Ceftriaxone for Injection and Dextrose Injection is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

Neonates (≤28 days)
Hyperbilirubinemic neonates, especially prematures, should not be treated with Ceftriaxone for Injection and Dextrose Injection. *In vitro* studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.

Ceftriaxone for Injection and Dextrose Injection is contraindicated in neonates if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium (see CLINICAL PHARMACOLOGY, WARNINGS and DOSAGE AND ADMINISTRATION).

A small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving Ceftriaxone for Injection and Dextrose Injection and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both Ceftriaxone for Injection and Dextrose Injection and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom Ceftriaxone for Injection and Dextrose Injection and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.

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

WARNINGS
Hypersensitivity

BEFORE THERAPY WITH CEFTRIAXONE FOR INJECTION AND DEXTROSE INJECTION 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. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Interaction with Calcium-Containing Products

Precipitation of ceftriaxone-calcium can occur when Ceftriaxone for Injection and Dextrose Injection is mixed with calcium-containing solutions in the same IV administration line. Ceftriaxone for Injection and Dextrose Injection must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, Ceftriaxone for Injection and Dextrose Injection and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. *In vitro* studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

Clostridium difficile

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

Hemolytic Anemia

An immune mediated hemolytic anemia has been observed in patients receiving cephalosporin class antibacterials including Ceftriaxone for Injection and Dextrose Injection. Severe cases of hemolytic anemia, including fatalities, have been reported during treatment in both adults and children. If a patient develops anemia while on Ceftriaxone for Injection and Dextrose Injection,

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the diagnosis of a cephalosporin associated anemia should be considered and Ceftriaxone for Injection and Dextrose Injection stopped until the etiology is determined.

PRECAUTIONS

General

Prescribing Ceftriaxone for Injection 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.

Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of ceftriaxone sodium is similar to that of other cephalosporins.

Ceftriaxone is excreted via both biliary and renal excretion (see **CLINICAL PHARMACOLOGY**). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Ceftriaxone for Injection and Dextrose Injection are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, Ceftriaxone for Injection and Dextrose Injection dosage should not exceed 2 g daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients treated with ceftriaxone sodium. Patients with impaired vitamin K synthesis or low vitamin K stores (*e.g.*, chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Ceftriaxone for Injection and Dextrose Injection treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolonged use of Ceftriaxone for Injection and Dextrose Injection may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Ceftriaxone for Injection and Dextrose Injection should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

There have been reports of sonographic abnormalities in the gallbladder of patients treated with ceftriaxone sodium; some of these patients also had symptoms of gallbladder disease. These abnormalities appear on sonography as an echo without acoustical shadowing suggesting sludge or as an echo with acoustical shadowing which may be misinterpreted as gallstones. The chemical nature of the sonographically detected material has been determined to be predominantly a ceftriaxone-calcium salt. **The condition appears to be transient and reversible upon discontinuation of ceftriaxone sodium and institution of conservative management.** Therefore, Ceftriaxone for Injection and Dextrose Injection should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above.

Cases of pancreatitis, possibly secondary to biliary obstruction, have been reported rarely in patients treated with ceftriaxone sodium. Most patients presented with risk factors for biliary stasis and biliary sludge (preceding major therapy, severe illness, total parenteral nutrition). A cofactor role of ceftriaxone-related biliary precipitation cannot be ruled out.

The elimination of ceftriaxone is not altered by probenecid.

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As with other cephalosporins, anaphylactic shock cannot be ruled out even if a thorough patient history is taken.

As with other dextrose-containing solutions, Ceftriaxone for Injection 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
Patients should be counseled that antibacterial drugs including Ceftriaxone for Injection and Dextrose Injection should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When Ceftriaxone for Injection 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 Ceftriaxone for Injection and Dextrose Injection or other antibacterial drugs in the future.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was 6 months.

Mutagenesis: Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.

Impairment of Fertility: Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 g/day.

Pregnancy: *Teratogenic* Effects:
Pregnancy Category B. Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately 3 times the human dose.

There are, however, no adequate and 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: In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including

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postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

Nursing Mothers
Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Ceftriaxone for Injection and Dextrose Injection is administered to a nursing woman.

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

Safety and effectiveness of Ceftriaxone for Injection and Dextrose Injection in neonates, infants and pediatric patients have been established for the dosages described in the **DOSAGE AND ADMINISTRATION** section. *In vitro* studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone for Injection and Dextrose Injection should not be administered to hyperbilirubinemic neonates, especially prematures (see **CONTRAINDICATIONS**).

Geriatric Use
Of the total number of subjects in clinical studies of ceftriaxone sodium, 32% were 60 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.

The pharmacokinetics of ceftriaxone were only minimally altered in geriatric patients compared to healthy adult subjects and dosage adjustments are not necessary for geriatric patients with ceftriaxone dosages up to 2 grams per day (see **CLINICAL PHARMACOLOGY**).

No dosage adjustment is necessary for patients with impairment of renal or hepatic function; however, blood levels should be monitored in patients with severe renal impairment (*e.g.*, dialysis patients) and in patients with both renal and hepatic dysfunctions.

ADVERSE REACTIONS
Ceftriaxone sodium is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to ceftriaxone sodium therapy or of uncertain etiology, were observed:

LOCAL REACTIONS—pain, induration and tenderness was 1% overall. Phlebitis was reported in <1% after IV administration.

HYPERSENSITIVITY—rash (1.7%). Less frequently reported (<1%) were pruritus, fever or chills.

HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (<1%) were anemia, hemolytic anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.

GASTROINTESTINAL—diarrhea (2.7%). Less frequently reported (<1%) were nausea or vomiting, and dysgeusia. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment (see **WARNINGS**).

HEPATIC—elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (<1%) were elevations of alkaline phosphatase and bilirubin.

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RENAL—elevations of the BUN (1.2%). Less frequently reported (<1%) were elevations of creatinine and the presence of casts in the urine.

CENTRAL NERVOUS SYSTEM—headache or dizziness were reported occasionally (<1%).

GENITOURINARY—moniliasis or vaginitis were reported occasionally (<1%).

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (<1%).

Other rarely observed adverse reactions (<0.1%) include abdominal pain, agranulocytosis, allergic pneumonitis, anaphylaxis, basophilia, biliary lithiasis, bronchospasm, colitis, dyspepsia, epistaxis, flatulence, gallbladder sludge, glycosuria, hematuria, jaundice, leukocytosis, lymphocytosis, monocytosis, nephrolithiasis, palpitations, a decrease in the prothrombin time, renal precipitations, seizures, and serum sickness.

Cases of fatal reactions with ceftriaxone-calcium precipitates in lung and kidneys in neonates have been described. In some cases the infusion lines and times of administration of ceftriaxone and calcium-containing solutions differed (see **CONTRAINDICATIONS**).

Postmarketing Experience
In addition to the adverse reactions reported during clinical trials, the following adverse experiences have been reported during clinical practice in patients treated with Ceftriaxone for Injection and Dextrose Injection. Data are generally insufficient to allow an estimate of incidence or to establish causation.

A small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving Ceftriaxone for Injection and Dextrose Injection and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both Ceftriaxone for Injection and Dextrose Injection and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom Ceftriaxone for Injection and Dextrose Injection and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.

GASTROINTESTINAL—stomatitis and glossitis.

GENITOURINARY—oliguria.

DERMATOLOGIC—exanthema, allergic dermatitis, urticaria, edema. As with many medications, isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens-Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis) have been reported.

Cephalosporin Class Adverse Reactions
In addition to the adverse reactions listed above which have been observed in patients treated with ceftriaxone, the following adverse reactions and altered laboratory test results have been reported for cephalosporin class antibiotics:

Adverse Reactions: Allergic reactions, drug fever, serum sickness-like reaction, renal dysfunction, toxic nephropathy, reversible hyperactivity, hypertonia, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage, and superinfection.

Altered Laboratory Tests: Positive direct Coombs' test, false-positive test for urinary glucose, and elevated LDH.

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Several cephalosporins 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 occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE
In the case of overdosage, drug concentration would not be reduced by hemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdosage should be symptomatic.

DOSAGE AND ADMINISTRATION
Ceftriaxone for Injection and Dextrose Injection is intended for intravenous administration only.

Ceftriaxone for Injection and Dextrose Injection and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age, even via different infusion lines at different sites (see CONTRAINDICATIONS and WARNINGS).

NEONATES: Hyperbilirubinemic neonates, especially prematures, should not be treated with Ceftriaxone for Injection and Dextrose Injection (see **CONTRAINDICATIONS**).

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

For the treatment of skin and skin structure infections, the recommended total daily dose is 50 to 75 mg/kg given once a day (or in equally divided doses twice a day). The total daily dose should not exceed 2 grams.

For the treatment of serious miscellaneous infections other than meningitis, the recommended total daily dose is 50 to 75 mg/kg, given in divided doses every 12 hours. The total daily dose should not exceed 2 grams.

In the treatment of meningitis, it is recommended that the initial therapeutic dose be 100 mg/kg (not to exceed 4 grams). Thereafter, a total daily dose of 100 mg/kg/day (not to exceed 4 grams daily) is recommended. The daily dose may be administered once a day (or in equally divided doses every 12 hours). The usual duration of therapy is 7 to 14 days.

ADULTS: The usual adult daily dose is 1 to 2 grams given once a day (or in equally divided doses twice a day) depending on the type and severity of infection. The total daily dose should not exceed 4 grams.

If *Chlamydia trachomatis* is a suspected pathogen, appropriate antichlamydial coverage should be added, because ceftriaxone sodium has no activity against this organism.

For preoperative use (surgical prophylaxis), a single dose of 1 gram administered intravenously 1/2 to 2 hours before surgery is recommended.

Generally, Ceftriaxone for Injection and Dextrose Injection therapy should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration of therapy is 4 to 14 days; in complicated infections, longer therapy may be required.

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

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No dosage adjustment is necessary for patients with impairment of renal or hepatic function; however, blood levels should be monitored in patients with severe renal impairment (*e.g.*, dialysis patients) and in patients with both renal and hepatic dysfunctions.

DIRECTIONS FOR USE: Ceftriaxone for Injection and Dextrose Injection should be administered intravenously by infusion over a period of 30 minutes.

Vancomycin, amsacrine, aminoglycosides, and fluconazole are physically incompatible with ceftriaxone in admixtures. When any of these drugs are to be administered concomitantly with ceftriaxone by intermittent intravenous infusion, it is recommended that they be given sequentially, with thorough flushing of the intravenous lines (with one of the compatible fluids) between the administrations.

Ceftriaxone for Injection and Dextrose Injection should *not* be physically mixed with or piggybacked into solutions containing other antimicrobial drugs due to possible incompatibility (see **WARNINGS**).

After the indicated stability time periods, unused portions of solutions should be discarded.

CAUTION: Do not use plastic containers in series connections. Such use would 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.

NOTE: Parenteral drug products should be inspected visually for particulate matter before administration.

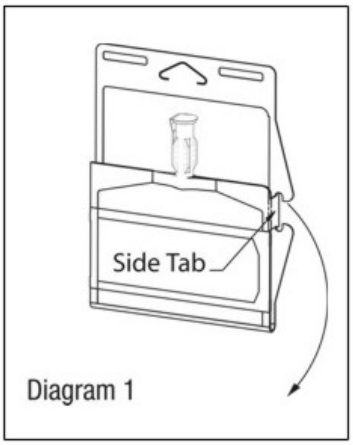
Directions for Use of DUPLEX Drug Delivery System

- 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.

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- To inspect the drug powder for foreign matter or discoloration, peel foil strip from drug chamber. (See Diagram 2.)

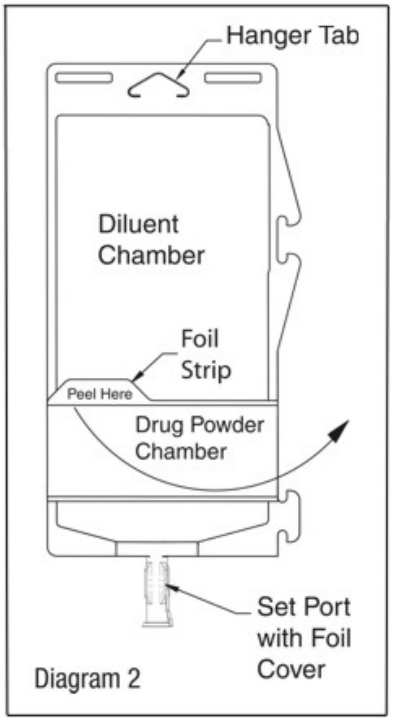


Diagram 2

- Protect from light after removal of foil strip.

  NOTE: If foil strip is removed, product must be used within 7 days, but not beyond the labeled expiration date.

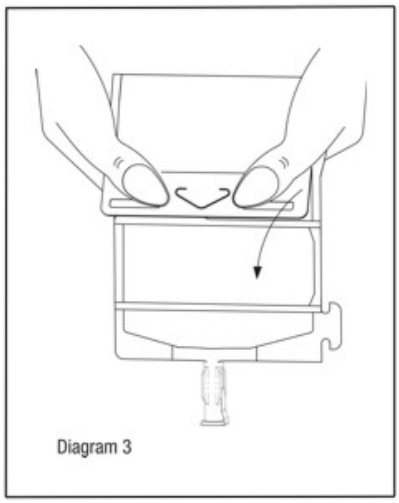
- The product should be re-folded and the side tab latched until ready to activate.

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.)

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Diagram 3

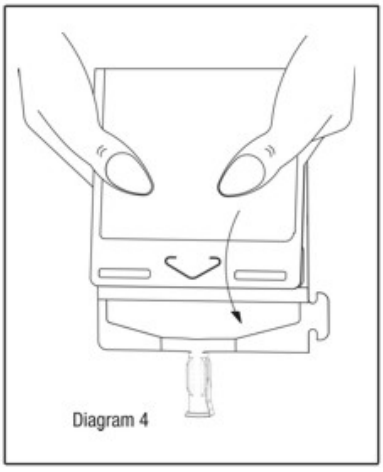
- Agitate the liquid-powder mixture until the drug powder is completely dissolved.

  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.)


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, peel foil cover from the set port and attach sterile administration set. (See Diagram 5.)

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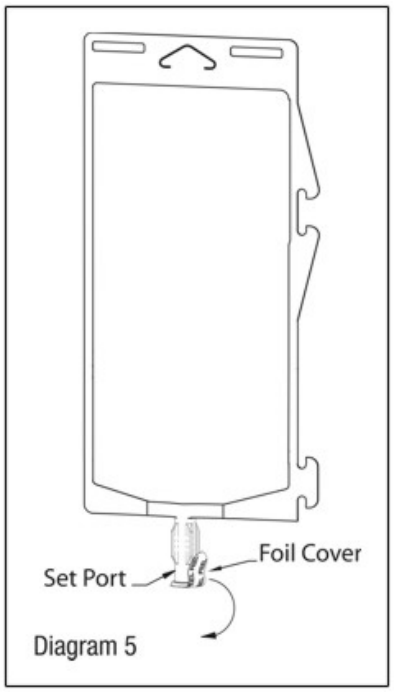


Diagram 5

- Refer to Directions for Use accompanying the administration set.

Precautions

- As with other cephalosporins, reconstituted Ceftriaxone for Injection 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.

ANIMAL PHARMACOLOGY

Concretions consisting of the precipitated calcium salt of ceftriaxone have been found in the gallbladder bile of dogs and baboons treated with ceftriaxone.

These appeared as a gritty sediment in dogs that received 100 mg/kg/day for 4 weeks. A similar phenomenon has been observed in baboons but only after a protracted dosing period (6 months) at higher dose levels (335 mg/kg/day or more). The likelihood of this occurrence in humans is considered to be low, since ceftriaxone has a greater plasma half-life in humans, the calcium salt of ceftriaxone is more soluble in human gallbladder bile and the calcium content of human gallbladder bile is relatively low.

HOW SUPPLIED

Ceftriaxone for Injection 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 ceftriaxone. The diluent chamber contains approximately 50 mL of Dextrose Injection. Dextrose Injection has been adjusted to 3.74% and 2.22% for the 1 g and 2 g doses, respectively, such that the reconstituted solution is iso-osmotic.

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Ceftriaxone for Injection and Dextrose Injection is supplied sterile and nonpyrogenic in the DUPLEX Drug Delivery System containers packaged 24 units per case.

NDC	Cat. No.	Dose	Volume
Ceftriaxone for Injection and Dextrose Injection			
0264-3153-11	3153-11	1 g	50 mL
Ceftriaxone for Injection and Dextrose Injection			
0264-3155-11	3155-11	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. National Committee for Clinical Laboratory Standards, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*; Approved Standard-Fifth Edition. NCCLS document M7-A5 (ISBN 1-56238-309-9). NCCLS, Wayne, PA 19087-1898, 2000.

2. National Committee for Clinical Laboratory Standards, Supplemental Tables. NCCLS document M100-S10(M7) (ISBN 1-56238-309-9). NCCLS, Wayne, PA 19087-1898, 2000.

3. National Committee for Clinical Laboratory Standards, *Performance Standards for Antimicrobial Disk Susceptibility Tests*; Approved Standard-Seventh Edition. NCCLS document M2-A7 (ISBN 1-56238-393-0). NCCLS, Wayne, PA 19087-1898, 2000.

4. National Committee for Clinical Laboratory Standards, *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria*; Approved Standard-Fourth Edition. NCCLS document M11-A4 (ISBN 1-56238-210-1). NCCLS, Wayne, PA 19087-1898, 1997.

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U.S. Patent Nos. D388,168, D397,789, D402,366, D407,816, 5,176,634, 5,944,709, 6,165,161, 6,203,535, 6,846,305, and 6,996,951.

Revised: April 2009

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