

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**50-796**

**LABELING**

# CefTRIaxONE for Injection and Dextrose Injection

**Rx only**

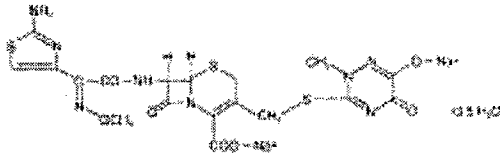
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ceftriaxone for Injection and Dextrose Injection and other antibacterial drugs, Ceftriaxone for Injection and Dextrose Injection should be used only to treat or prevent infections that are proven or strongly suspected 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<sup>2</sup>-(Z)-(O-methylxime), disodium salt, sesquaterhydrate.

Ceftriaxone Sodium has the following structural formula:

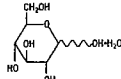


The chemical formula of ceftriaxone sodium is  $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3.5H_2O$ , representing a molecular weight of 661.60.

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 Hydrated 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.

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



The molecular weight of Hydrated 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**

Dose/Route	Average Plasma Concentrations ( $\mu\text{g/mL}$ )								
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	16 hr	24 hr
0.5 g IV*	82	59	48	37	29	23	15	10	5
1 g IV*	151	111	88	67	53	43	28	18	9
2 g 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**

Dose/Route	Average Urinary Concentrations ( $\mu\text{g/mL}$ )					
	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 3 to 3 hours after dosing, were 581  $\mu\text{g/mL}$  in the gallbladder bile, 788  $\mu\text{g/mL}$  in the common bile, 898  $\mu\text{g/mL}$  in the cystic duct bile, 78.2  $\mu\text{g/g}$  in the gallbladder wall and 62.1  $\mu\text{g/mL}$  in the concurrent plasma.

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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 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  $\mu\text{g/mL}$  to a value of 85% bound at 300  $\mu\text{g/mL}$ . 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 ( $\mu\text{g/mL}$ )	216	275
Elimination Half-life (hr)	4.6	4.3
Plasma Clearance ( $\text{mL/hr/kg}$ )	49	60
Volume of Distribution ( $\text{mL/kg}$ )	338	373
CSF Concentration—inflamed meninges ( $\mu\text{g/mL}$ )	5.6	6.4
Range ( $\mu\text{g/mL}$ )	1.3 – 18.5	1.3 – 44
Time after dose (hr)	3.7 ( $\pm$ 1.6)	3.3 ( $\pm$ 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.

## 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.

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.

The following *in vitro* data are available, but their clinical significance is unknown. Ceftriaxone exhibits *in vitro* minimal inhibitory concentrations (MICs) of  $\leq 8 \mu\text{g/mL}$  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*)  
*Sigella* 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.<sup>1</sup> 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<sup>2</sup> for aerobic organisms other than *Haemophilus* spp, *Neisseria gonorrhoeae*, and *Streptococcus* spp, including *Streptococcus pneumoniae*:

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

The following interpretive criteria<sup>2</sup> should be used when testing *Haemophilus* species using Haemophilus Test Media (HTM).

MIC (µg/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<sup>2</sup> should be used when testing *Neisseria gonorrhoeae* when using GC agar base and 1% defined growth supplement.

MIC (µg/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.

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

MIC (µg/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:<sup>2</sup>

Microorganism	ATCC® #	MIC (µg/mL)
<i>Escherichia coli</i>	25922	0.03 – 0.12
<i>Staphylococcus aureus</i>	29213	1 – 8*
<i>Pseudomonas aeruginosa</i>	27853	8 – 32
<i>Haemophilus influenzae</i>	49247	0.06 – 0.25
<i>Neisseria gonorrhoeae</i>	49226	0.004 – 0.015
<i>Streptococcus pneumoniae</i>	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<sup>3</sup> requires the use of standardized inoculum concentrations. This procedure uses paper discs impregnated with 30 µg 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 µg 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<sup>3</sup> should be used when testing *Haemophilus* species when using Haemophilus Test Media (HTM).

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<sup>3</sup> 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<sup>3</sup> 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<sub>2</sub>.

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 µg/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 µg ceftriaxone disc should provide the following zone diameters in these laboratory test quality control strains:<sup>3</sup>

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

### Anaerobic Techniques

For anaerobic bacteria, the susceptibility to ceftriaxone as MICs can be determined by standardized test methods.<sup>4</sup> The MIC values obtained should be interpreted according to the following criteria:

MIC (µg/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<sup>4</sup> testing method:

Method	Microorganism	ATCC®#	MIC (µg/mL)
Agar	<i>Bacteroides fragilis</i>	25285	32 – 128
	<i>Bacteroides thetaiotaomicron</i>	29741	64 – 256
	<i>Bacteroides thetaiotaomicron</i>	29741	32 – 128

ATCC® is a registered trademark of the American Type Culture Collection.

### INDICATIONS AND USAGE

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*.

**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.

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.

## CONTRAINDICATIONS

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

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

## WARNINGS

BEFORE THERAPY WITH CEFTRIAOXONE 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.

**Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftriaxone, and may range in severity 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, appropriate 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 specifically effective against *Clostridium difficile* colitis.

## 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.

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.

### 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 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.

## 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**—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.

**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.

## OVERDOSAGE

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

## DOSAGE AND ADMINISTRATION

Ceftriaxone for Injection and Dextrose Injection is intended for intravenous administration only.

**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.

**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 1 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.

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.

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.

Vancomycin and fluconazole are physically incompatible with ceftriaxone in admixtures. When either of these drugs is 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.

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

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

**Note:** Following reconstitution (activation), product

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.)
- 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 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.

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

NDC	Cat. No.	Dose	Volume
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.

DUPLEX® is a registered trademark of B. Braun Medical Inc.  
U.S. Patent Nos. D388,168, D397,789, D402,366, D407,816, 5,944,709, and 6,165,161; additional patents pending.  
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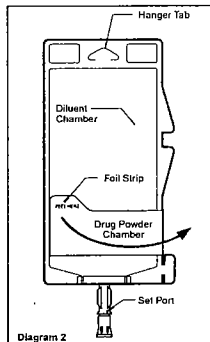
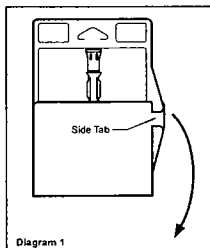


Diagram 3

Side Tab

Diagram 1

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