

**EXHIBIT C**

Copy of the Proposed Draft Package Insert for  
Ceftriaxone for Injection, USP

# CEFTRIAXONE FOR INJECTION, USP

**SMARTPAK<sup>®</sup>**

**PHARMACY BULK PACKAGE**

**NOT FOR DIRECT INFUSION**

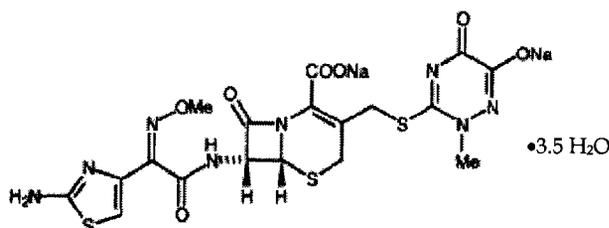
**Rx only**

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

## DESCRIPTION

Ceftriaxone for Injection, USP, is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular 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-methyloxime), disodium salt, sesquaterhydrate.

The chemical formula of ceftriaxone sodium is  $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3.5H_2O$ . It has a calculated molecular weight of 661.59 and the following structural formula:



A Pharmacy Bulk Package is a container of a sterile preparation for parenteral use that contains many single doses. This Pharmacy Bulk Package is for use in a pharmacy admixture service; it provides many single doses of Ceftriaxone. (See DOSAGE AND ADMINISTRATION and DIRECTIONS FOR PROPER USE OF A PHARMACY BULK PACKAGE.)

## CLINICAL PHARMACOLOGY

Average plasma concentrations of ceftriaxone following a single 30-minute intravenous (IV) infusion of a 0.5, 1 or 2 gram dose and intramuscular (IM) administration of a single 0.5 (250 mg/mL or 350 mg/mL concentrations) or 1 gram dose in healthy subjects are presented in Table 1.

**TABLE 1. Ceftriaxone Plasma Concentrations After Single Dose Administration**

Dose/Route	Average Plasma Concentrations ( $\mu\text{g}/\text{mL}$ )								
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	16 hr	24 hr
0.5 gram IV*	82	59	48	37	29	23	15	10	5
0.5 gram IM									
250 mg/mL	22	33	38	35	30	26	16	ND	5
0.5 gram IM									
350 mg/mL	20	32	38	34	31	24	16	ND	5
1 gram IV*	151	111	88	67	53	43	28	18	9
1 gram IM	40	68	76	68	56	44	29	ND	ND
2 grams IV*	257	192	154	117	89	74	46	31	15

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

ND = Not determined.

Ceftriaxone was completely absorbed following IM administration with mean maximum plasma concentrations occurring between 2 and 3 hours post-dosing. Multiple IV or IM doses ranging from 0.5 to 2 grams 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 ( $\mu\text{g}/\text{mL}$ )					
	0-2 hr	2-4 hr	4-8 hr	8-12 hr	12-24 hr	24-48 hr
0.5 gram IV	526	366	142	87	70	15
0.5 gram IM	115	425	308	127	96	28
1 gram IV	995	855	293	147	132	32
1 gram IM	504	628	418	237	ND	ND
2 grams IV	2692	1976	757	274	198	40

ND = Not determined.

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 gram IV dose, average concentrations of ceftriaxone, determined from 1 to 3 hours after dosing, were 581  $\mu\text{g}/\text{mL}$  in the gallbladder bile, 788  $\mu\text{g}/\text{mL}$  in the common duct bile, 898  $\mu\text{g}/\text{mL}$  in the cystic duct bile, 78.2  $\mu\text{g}/\text{gram}$  in the gallbladder wall and 62.1  $\mu\text{g}/\text{mL}$  in the concurrent plasma.

Over a 0.15 to 3 gram 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  $\mu\text{g}/\text{mL}$  to a value of 85% bound at 300  $\mu\text{g}/\text{mL}$ . 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 grams 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.

**Pharmacokinetics in the Middle Ear Fluid:** In one study, total ceftriaxone concentrations (bound and unbound) were measured in middle ear fluid obtained during the insertion of tympanostomy tubes in 42 pediatric patients with otitis media. Sampling times were from 1 to 50 hours after a single intramuscular injection of 50 mg/kg of ceftriaxone. Mean ( $\pm$  SD) ceftriaxone levels in the middle ear reached a peak of 35 ( $\pm 12$ )  $\mu\text{g/mL}$  at 24 hours, and remained at 19 ( $\pm 7$ )  $\mu\text{g/mL}$  at 48 hours. Based on middle ear fluid ceftriaxone concentrations in the 23 to 25 hour and the 46 to 50 hour sampling time intervals, a half-life of 25 hours was calculated. Ceftriaxone is highly

bound to plasma proteins. The extent of binding to proteins in the middle ear fluid is unknown.

**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  $\leq 8$   $\mu\text{g}/\text{mL}$  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) bivia*

*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*:

<u>MIC (<math>\mu\text{g}/\text{mL}</math>)</u>	<u>Interpretation</u>
$\leq 8$	(S) Susceptible
16-32	(I) Intermediate
$\geq 64$	(R) Resistant

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

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 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.

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 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.

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 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>

<u>Microorganism</u>	<u>ATCC® #</u>	<u>MIC (µg/mL)</u>
<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, including *Streptococcus pneumoniae*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 21	(S) Susceptible
14-20	(I) Intermediate
≤ 13	(R) Resistant

The following interpretive criteria<sup>3</sup> should be used when testing *Haemophilus* species using *Haemophilus* Test Media (HTM).

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 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.

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 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* using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO<sub>2</sub>.

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 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 interpretative 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 of ≤ 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>

<u>Microorganism</u>	<u>ATCC® #</u>	<u>Zone Diameter Ranges (mm)</u>
<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:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 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:

<u>Method</u>	<u>Microorganism</u>	<u>ATCC® #</u>	<u>MIC (µg/mL)</u>
Agar	<i>Bacteroides fragilis</i>	25285	32 - 128
	<i>Bacteroides thetaiotamicron</i>	29741	64 - 256
Broth	<i>Bacteroides thetaiotamicron</i>	29741	32 - 128

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

## INDICATIONS AND USAGE

Before instituting treatment with Ceftriaxone for 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 and other antibacterial drugs, Ceftriaxone for 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 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*

ACUTE BACTERIAL OTITIS MEDIA caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including beta-lactamase producing strains) or *Moraxella catarrhalis* (including beta-lactamase producing strains).

NOTE: In one study lower clinical cure rates were observed with a single dose of Ceftriaxone for Injection compared to 10 days of oral therapy. In a second study, comparable cure rates were observed between single dose Ceftriaxone for Injection and the comparator. The potentially lower clinical cure rate of Ceftriaxone for Injection should be balanced against the potential advantages of parenteral therapy (see CLINICAL STUDIES).

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*.

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase- and nonpenicillinase-producing strains, and pharyngeal gonorrhea caused by nonpenicillinase- producing strains of *Neisseria gonorrhoeae*.

PELVIC INFLAMMATORY DISEASE caused by *Neisseria gonorrhoeae*. Ceftriaxone, like other cephalosporins, has no activity against *Chlamydia trachomatis*. Therefore, when cephalosporins are used in the treatment of 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 for Injection has also been used successfully in a limited

number of cases of meningitis and shunt infection caused by *Staphylococcus epidermidis*\* and *Escherichia coli*.\*

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

**SURGICAL PROPHYLAXIS:** The preoperative administration of a single 1 gram dose of Ceftriaxone for 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 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 gram dose of Ceftriaxone for Injection provides protection from most infections due to susceptible organisms throughout the course of the procedure.

## **CONTRAINDICATIONS**

Ceftriaxone is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

## **WARNINGS**

BEFORE THERAPY WITH CEFTRIAZONE 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 clinically effective against *Clostridium difficile* colitis.

## **PRECAUTIONS**

### ***General***

Prescribing Ceftriaxone 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 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 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 dosage should not exceed 2 grams daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients treated with Ceftriaxone. 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 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 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 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; 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 and institution of conservative management.** Therefore, Ceftriaxone should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above.

#### *Information for Patients*

Patients should be counseled that antibacterial drugs, including Ceftriaxone, should only be used to treat bacterial infections. They do not treat viral infections (e.g., common cold). When Ceftriaxone for Injection, USP, 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 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 grams/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 is administered to a nursing woman.

*Pediatric Use:* Safety and effectiveness of Ceftriaxone 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 should not be administered to hyperbilirubinemic neonates, especially prematures.

#### **ADVERSE REACTIONS**

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

*LOCAL REACTIONS* - pain, induration and tenderness was 1% overall. Phlebitis was reported in < 1% after IV administration. The incidence of warmth, tightness or induration was 17% (3/17) after IM administration of 350 mg/mL and 5% (1/20) after IM administration of 250 mg/mL.

*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 treatments (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 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 may be administered intravenously or intramuscularly. However, the intent of this Pharmacy Bulk Package is for the preparation of solutions for intravenous infusion only. Ceftriaxone for Injection should be administered by intravenous infusion over a period of 30 minutes.

*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 the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.

For preoperative use (surgical prophylaxis), a single dose of 1 gram administered intravenously ½ to 2 hours before surgery is recommended.

*PEDIATRIC PATIENTS:* For the treatment of skin and skin structure infections, the recommended 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 acute otitis media, a single intramuscular dose of 50 mg/kg (not to exceed 1 gram) is recommended (see INDICATIONS AND USAGE).

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 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.

*DIRECTIONS FOR PROPER USE OF PHARMACY BULK PACKAGE:* The 100 gram SmartPak<sup>®</sup> bag should be reconstituted with 950 mL of Sterile Water for Injection, USP in a suitable work area such as a laminar flow hood. The resulting solution will contain approximately 100 mg/mL of ceftriaxone. CAUTION: THE 100 GRAM SMARTPAK<sup>®</sup> BAGS ARE NOT INTENDED FOR DIRECT INFUSION. The SmartPak<sup>®</sup> package is for use in a pharmacy admixture service only under a laminar flow hood. Entry into the bag must be made with a sterile transfer set or other sterile dispensing device, which allows measured dispensing of contents and the contents dispensed in aliquots using aseptic technique. The use of syringe and needle is not recommended as they may cause leakage.

After reconstitution of the Pharmacy Bulk Package, unused solutions should be discarded within 24 hours of initial entry. Unused portions of the solution held longer than the recommended time periods should be discarded.

## Reconstituted Bulk Solutions Should Not Be Used For Direct Infusion

*COMPATIBILITY AND STABILITY:* Ceftriaxone for Injection sterile powder should be stored at room temperature - 77°F (25°C) - or below and protected from light. After reconstitution, protection from normal light is not necessary. The color of solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

After reconstitution as directed (concentration of 100 mg/mL), solutions are stable (loss of potency of less than 10%) for 2 days at room temperature (25°C) and for 10 days under refrigerated conditions (4°C).

Solutions of Ceftriaxone for Injection should *not* be physically mixed or piggybacked into solutions containing other antimicrobial drugs due to possible incompatibility.

### **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, USP is a sterile powder supplied in SmartPak<sup>®</sup>, 100-gram equivalent of Ceftriaxone, plastic bag with foil outer wrap Pharmacy Bulk Package NDC 66288-6100-1.

NOTE: Ceftriaxone for Injection should be stored at room temperature, 77°F (25°C) or below and protected from light.

### **CLINICAL STUDIES**

*Clinical Trials in Pediatric Patients With Acute Bacterial Otitis Media:* In two adequate and well-controlled US clinical trials, a single IM dose of ceftriaxone was compared with a 10 day course of oral antibiotic in pediatric patients between the ages of 3 months and 6 years. The clinical cure rates and statistical outcome appear in the table below:

Clinical Efficacy in Evaluable Population				
Study Day	Ceftriaxone Single Dose	Comparator - 10 Days of Oral Therapy	95% Confidence Interval	Statistical Outcome
Study 1 - US		Amoxicillin/Clavulanate		
14	74% (220/296)	82% (247/302)	(-14.4%, -0.5%)	Ceftriaxone is lower than control at study day 14 and 28.
28	58% (167/288)	67% (200/297)	(-17.5%, -1.2%)	
Study 2 - US <sup>5</sup>		TMP-SMZ		
14	54% (113/210)	60% (124/206)	(-16.4%, 3.6%)	Ceftriaxone is equivalent to control at study day 14 and 28.
28	35% (73/206)	45% (93/205)	(-19.9%, 0.0%)	

An open-label bacteriologic study of ceftriaxone without a comparator enrolled 108 pediatric patients, 79 of whom had positive baseline cultures for one or more of the common pathogens. The results of this study are tabulated as follows:

Week 2 and 4 Bacteriologic Eradication Rates in the Per Protocol Analysis in the Roche Bacteriologic Study by pathogen:

Organism	Study Day 13-15		Study Day 30+2	
	No. Analyzed	No. Erad. (%)	No. Analyzed	No. Erad. (%)
<i>Streptococcus pneumoniae</i>	38	32 (84)	35	25 (71)
<i>Haemophilus influenzae</i>	33	28 (85)	31	22 (71)
<i>Moraxella catarrhalis</i>	15	12 (80)	15	9 (60)

## REFERENCES

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<sup>1</sup> 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.

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

<sup>3</sup> 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.

<sup>4</sup> 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.

<sup>5</sup> Barnett, ED, Teele DW, Klein JO, et al. *Comparison of Ceftriaxone and Trimethoprim-Sulfamethoxazole for Acute Otitis Media*. Pediatrics. Vol. 99, No.1, January 1997.

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