



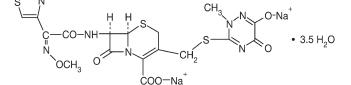
# CEFTRIAXONE FOR INJECTION, USP

Rx only

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

**DESCRIPTION**  
Ceftiraxone for Injection, USP, is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceftiraxone sodium is ( $\text{6R}(\text{Tr})\text{7-2'-2-Amino-4-trichloro-}\text{6-Oxyamido-2-methyl-5,6-dioxo-ss-triazin-3-yl)Methyl-5'-thia-1-azabicyclo[4.2.2]oct-2-ene-2-carboxylic acid, 7''-(Z)-O-methoxime, disodium salt, sesquhydrate.$

The chemical formula of ceftiraxone sodium is  $\text{C}_{14}\text{H}_{14}\text{N}_4\text{Na}_2\text{O}_8 \cdot 3.5\text{H}_2\text{O}$  and the following structural formula:



Ceftiraxone for Injection, USP is a white to yellowish-orange crystalline powder which is rapidly 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 Ceftiraxone for Injection, USP solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

Ceftiraxone for Injection, USP contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftiraxone activity.

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

TABLE 1. Ceftiraxone 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 g IV*	82	59	48	37	29	23	15	10	5		
0.5 g IM 250 mg/mL	22	33	38	35	30	26	16	ND	5		
0.5 g IM 350 mg/mL	20	32	38	34	31	24	16	ND	5		
1 g IV*	151	111	88	67	53	43	28	18	9		
1 g IM	40	68	76	66	56	44	29	ND	ND		
2 g IV*	257	192	154	117	89	74	46	31	15		

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

ND = Not determined.

Ceftiraxone was completely absorbed following IM administration with mean maximum plasma concentrations occurring between 2 and 3 hours post-dose. Multiple IV or IM doses ranging from 0.5 to 2 g at 12- to 24-hour intervals resulted in 15% to 36% accumulation of ceftiraxone above single dose values.

Ceftiraxone concentrations in urine are shown in Table 2.

TABLE 2. Urinary Concentrations of Ceftiraxone After Single Dose Administration

		Average Urinary Concentrations (mcg/mL)					
Dose/Route		0 to 2 hr	2 to 4 hr	4 to 8 hr	8 to 12 hr	12 to 24 hr	24 to 48 hr
0.5 g IV	526	366	142	87	70	15	
0.5 g IM	115	425	308	127	96	28	
1 g IV	995	855	293	147	132	32	
1 g IM	504	628	418	237	ND	ND	
2 g IV	2692	1976	757	274	198	40	

ND = Not determined.

Thirty-three percent to 67% of a ceftiraxone 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 ceftiraxone, determined from 1 to 3 hours after dosing, were 581 mcg/mL in the gallbladder bile, 788 mcg/mL in the common duodenal 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 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. Ceftiraxone 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 Ceftiraxone 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) Range (mcg/mL)	5.6 1.3 to 18.5	6.4 1.3 to 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 ceftiraxone were only minimally altered in elderly subjects and in patients with renal impairment or hepatic dysfunction (Table 4); therefore dosage adjustments are not required for these patients with ceftiraxone dosages up to 2 g per day. Ceftiraxone was not removed to any significant extent from the plasma by hemodialysis; in six of 26 dialysis patients, the elimination rate of ceftiraxone was markedly reduced.

TABLE 4. Average Pharmacokinetic Parameters of Ceftiraxone in Humans

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

\*Creatinine clearance.

The elimination of ceftiraxone is not altered when ceftiraxone is co-administered with probenecid.

**Pharmacokinetics in the Middle Ear Fluid:** In one study, total ceftiraxones 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 ceftiraxone. Mean ( $\pm$  SD) ceftiraxone levels in the middle ear reached a peak of 35 ( $\pm$  12) mcg/mL at 24 hours, and remained at 19 ( $\pm$  7) mcg/mL at 48 hours. Based on middle ear fluid ceftiraxone concentrations in the 23 to 25 hour and the 46 to 50 hour sampling time intervals, a half-life of 25 hours was calculated. Ceftiraxone is highly bound to plasma proteins. The extent of binding to proteins in the middle ear fluid is unknown.

**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 ceftiraxone and calcium. Ceftiraxone concentrations up to 1 mM (in excess of concentrations achieved *in vivo* following administration of 2 grams ceftiraxone infused over 30 minutes) were used in combination with calcium concentrations of 0.5 to 1.5 mM (48 mg/dL). Recovery of ceftiraxone 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 ceftiraxone-calcium precipitation.

**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 ceftiraxone and calcium. Ceftiraxone has activity in the presence of some beta-lactamases, both penicillinas and cephalosporinas, of Gram-negative and Gram-positive bacteria.

**Mechanism of Resistance:** Resistance to ceftiraxone is primarily through hydrolysis by beta-lactamase, alteration of penicillin-binding proteins (PBPs), and decreased permeability.

**Interaction with Other Antimicrobials:** In an *in vitro* study antagonistic effects have been observed with the combination of chloramphenicol and ceftiraxone.

**Antibacterial Activity:** Ceftiraxone has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

- **Gram-negative bacteria**
  - *Acinetobacter baumannii*
  - *Enterobacter aerogenes*
  - *Enterobacter cloacae*
  - *Escherichia coli*
  - *Haemophilus influenzae*
  - *Haemophilus parainfluenzae*
  - *Klebsiella oxytoca*
  - *Klebsiella pneumoniae*
  - *Moraxella catarrhalis*
  - *Morganella morganii*
  - *Neisseria gonorrhoeae*
  - *Neisseria meningitidis*
  - *Pseudomonas aeruginosa*
  - *Proteus mirabilis*
  - *Proteus vulgaris*
  - *Pseudomonas aeruginosa*
  - *Serratia marcescens*

- **Gram-positive bacteria**
  - *Staphylococcus aureus*
  - *Staphylococcus epidermidis*
  - *Streptococcus pneumoniae*
  - *Streptococcus pyogenes*
  - *Viridans group streptococci*

- **Anaerobic bacteria**
  - *Bacteroides fragilis*
  - *Clostridium species*
  - *Peptostreptococcus species*

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

- **Gram-negative bacteria**
  - *Citrobacter diversus*
  - *Citrobacter freundii*
  - *Providencia species* (including *Providencia rettgeri*)
  - *Salmonella species* (including *Salmonella typhi*)
  - *Shigella species*

- **Gram-positive bacteria**
  - *Streptococcus agalactiae*

- **Anaerobic bacteria**
  - *Porphyromonas (Bacteroides) melanogenicus*
  - *Prevotella (Bacteroides) blvis*

**Susceptibility Test Methods:** When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

## 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 test method<sup>2,3</sup>. The MIC values should be interpreted according to criteria provided in Table 5.

## Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size is proportional to the concentration of the antimicrobial. The zone size should be determined using a standardized test method<sup>2,3</sup>. This procedure uses paper disks impregnated with 30 mcg ceftiraxone to test the susceptibility of microorganisms to ceftiraxone. The disk diffusion interpretive criteria are provided in Table 5.

## Anaerobic Techniques:

For anaerobic bacteria, the susceptibility to ceftiraxone as MICs can be determined by a standardized agar test method<sup>4</sup>. The MIC values obtained should be interpreted according to the criteria provided in Table 5.

TABLE 5. Susceptibility Test Interpretive Criteria for Ceftiraxone

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion Zone Diameters (mm)
	(S) Susceptible	(I) Intermediate	(R) Resistant	
<i>Enterobacteriaceae*</i>	$\leq 1$	2	$\geq 4$	$\geq 23$
<i>Haemophilus influenzae</i>	$\leq 2$	-	-	$\geq 26$
<i>Neisseria gonorrhoeae</i>	$\leq 0.25$	-	-	$\geq 35$
<i>Neisseria meningitidis</i>	$\leq 0.12$	-	-	$\geq 34$
<i>Streptococcus pneumoniae</i>	$\leq 0.5$	1	$\geq 2$	-
<i>Streptococcus pneumoniae</i> non-meningitis isolates	$\leq 1$	2	$\geq 4$	-
<i>Streptococcus pneumoniae</i> non-meningitis isolates	$\leq 0.5$	-	-	$\geq 24$
<i>Viridans group streptococci</i>	$\leq 1$	2	$\geq 4$	$\geq 27$
Aerobic bacteria (agar method)	$\leq 1$	2	$\geq 4$	-
Susceptibility to staphylococci to ceftiraxone may be deduced from testing only penicillin and either cefotaxime or oxacillin.				
<i>Enterobacteriaceae</i> interpretive criteria for Enterobacteriaceae are based on a dose of 1 g IV q24h. For isolates with intermediate susceptibility, use a dose of 2 grams IV or 24 hr in patients with normal renal function.				
For <i>Haemophilus influenzae</i> , susceptibility interpretive criteria are based on a dose of 1 g IV or 24 hr in patients with normal renal function.				
The current absence of data on certain isolates precludes defining any category other than "Susceptible". If isolates yield MIC results other than susceptible, they should be submitted to a reference laboratory for additional testing.				
Disk diffusion interpretive criteria for ceftiraxone discs against <i>Streptococcus pneumoniae</i> are not available; however, isolates of <i>Streptococcus pneumoniae</i> with oxacillin zone diameters of $\geq 20$ mm are susceptible (MIC $\leq 0.06$ mcg/mL) to penicillin. Susceptible strains of <i>Streptococcus pneumoniae</i> isolates should not be reported as penicillin (edrophonium) resistant or intermediate based solely on an oxacillin zone diameter of $\leq 19$ mm. The ceftiraxone MIC should be determined for those isolates with oxacillin zone diameters $\leq 19$ mm.				
A report of Susceptible indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration at the site of infection that will inhibit susceptible organisms. A report of Resistant indicates that the antimicrobial drug is not fully susceptible; alternative, clinically feasible drugs, should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of Intermediate indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the infection site; other therapeutic drugs should be selected.				
Quality Control:				
Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individual performing the test <sup>1,2,4</sup> .				
Standard ceftiraxone powder should provide the following range of MIC values noted in Table 6. For the diffusion technique using the 20 mcg disk, the criteria in Table 6 should be achieved.				
<b>CONTRAINDICATIONS</b>				
<b>Hypersensitivity:</b> Ceftiraxone is contraindicated in patients with known hypersensitivity to ceftiraxone, any of its excipients or to any other cephalosporins. Patients with previous hypersensitivity reactions to penicillin and other beta-lactam antibiotics may be at greater risk of hypersensitivity to ceftiraxone (see WARNINGS – Hypersensitivity).				
<b>Neonates:</b> Premature neonates: Ceftiraxone is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age).				
Hyperbilirubinemic neonates: Hyperbilirubinemic neonates, should not be treated with ceftiraxone. Ceftiraxone can displace bilirubin from its binding to serum albumin, leading to a risk of bilirubin encephalopathy in these patients.				
<b>Neonates Requiring Calcium Containing IV Solutions:</b> Ceftiraxone is contraindicated in neonates ( $\leq 28$ days) 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 ceftiraxone-calcium (see CLINICAL PHARMACOLOGY, WARNINGS and DOSAGE AND ADMINISTRATION).				
Cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving ceftiraxone and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both ceftiraxone and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. There have been no similar reports in patients other than neonates.				
<b>Lidocaine:</b> Intravenous administration of ceftiraxone solutions containing lidocaine is contraindicated. When lidocaine solution is used as a solvent with ceftiraxone for intramuscular injection, exclude all contraindications to lidocaine. Refer to the prescribing information of lidocaine.				
<b>WARNINGS</b>				
<b>Hypersensitivity Reactions:</b> Before therapy with ceftiraxone is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins and other beta-lactam agents or other drugs. This product should be given cautiously to penicillin and other beta-lactam agent-				

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

**LOWER RESPIRATORY TRACT INFECTIONS** caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Haemophilus parahaemolyticus*, *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter aerogenes*, *Proteus mirabilis* or *Moraxella catarrhalis*.

**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 Ceftiraxone for injection, USP compared to 10 days of oral therapy. In a second study comparable cure rates were observed between single dose Ceftiraxone for injection, USP and the comparator. The potentially lower clinical cure rate of Ceftiraxone for injection, USP 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*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Morganella morganii*, *Pseudomonas aeruginosa*, *Serratia marcescens* (including beta-lactamase-producing strains) or *Peptostreptococcus species*.

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

**UNCOMPLICATED GONORRHEA** (vaginal/urethral/rectal) caused by *Neisseria gonorrhoeae*, including both penicillase- and nonpenicillase-producing strains of *Neisseria gonorrhoeae*.

**PELVIC INFLAMMATORY DISEASE** caused by *Neisseria gonorrhoeae*, *Neisseria meningitidis* or *Haemophilus ducreyi*.

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

disease and/or the sonographic findings described above.

#### Urolithiasis and Post-Renal Acute Renal Failure

Ceftriaxone-calcium precipitates in the urinary tract have been observed in patients receiving ceftriaxone and may be detected as sonographic abnormalities. The probability of such precipitates appears to be greatest in pediatric patients. Patients may be asymptomatic or may develop symptoms of urolithiasis, and ureteral obstruction and post-renal acute renal failure. The condition appears to be dose related and may be avoided by discontinuing ceftriaxone if appropriate management. Ensure adequate hydration in patients receiving ceftriaxone. Discontinue ceftriaxone in patients who develop signs and symptoms suggestive of urolithiasis, oliguria or renal failure and/or the sonographic findings described above.

#### Pancreatitis

Cases of pancreatitis, possibly secondary to biliary obstruction, have been reported in patients treated with ceftriaxone. 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.

#### 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., the common cold).
- When ceftriaxone 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.
- 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 toxicity studies was 20 times the recommended clinical dose of 2 g/day.

**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 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 is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness of ceftriaxone in neonates, infants and pediatric patients have been established for the dosage 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 should not be administered to hyperbilirubinemic neonates, especially prematures (see CONTRAINDICATIONS).

**Geriatric Use:** Of the total number of subjects in clinical studies of ceftriaxone, 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 provided there is no severe renal and hepatic impairment (see CLINICAL PHARMACOLOGY).

**Influence on Diagnostic Tests:** In patients treated with ceftriaxone the Coombs' test, positive direct Coombs' test, false-positive test for urinary glucose, and elevated LDH (see PRECAUTIONS).

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

**DOSAGE AND ADMINISTRATION**  
Ceftriaxone may be administered intravenously or intramuscularly.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line.

Ceftriaxone should not be administered simultaneously with calcium-containing IV solutions, including parenteral calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially if one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid (see WARNINGS).

There have been no reports of an interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (IV or oral).

**NEONATES:** Hyperbilirubinemic neonates, especially prematures, should not be treated with ceftriaxone. Ceftriaxone is contraindicated in premature neonates (see CONTRAINDICATIONS).

Ceftriaxone is contraindicated in neonates ( $\leq 28$  days) 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 CONTRAINDICATIONS).

Intravenous doses should be given over 60 minutes in neonates to reduce the risk of bilirubin encephalopathy.

**PEDIATRIC PATIENTS:** 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 acute bacterial 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

#### BLOOD AND LYMPHATIC DISORDERS

— granulocytopenia (0.9%), coagulopathy (0.4%).

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

**HEPATIC** — elevations of aspartate aminotransferase (AST) (3.1%) or alanine aminotransferase (ALT) (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%).

#### INVESTIGATIONS

— blood creatinine increased (0.6%).

Other rarely observed adverse reactions (<1%) include abdominal pain, agranulocytosis, allergic pneumonitis, anaphylaxis, basophilia, biliary lithiasis, bronchospasm, colitis, dyspepsia, epistaxis, fistulization, gallbladder sludge, glucosuria, hematuria, jaundice, leukocytosis, lymphocytosis, monocytosis, nephrothiasis, papillitis, a decrease in the prothrombin time, renal precipitations, seizures, and serum sickness.

**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. 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 and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both ceftriaxone and calcium-containing fluids and/or a precipitate was observed in the intravenous infusion line. At least one mortality has been reported in which ceftriaxone 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 — pancreatitis, stomatitis and glossitis.

**GENITOURINARY** — oliguria, ureteral obstruction, post-renal acute renal failure.

**DERMATOLOGIC** — exanthema, allergic dermatitis, urticaria, edema; acute generalized exanthematous pustulosis (AGEP) and isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens-Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis) have been reported.

**HEMATOLOGICAL CHANGES:** Isolated cases of agranulocytosis (< 500/mm<sup>3</sup>) have been reported, most of them after 10 days of treatment and following total doses of 20 g or more.

#### NERVOUS SYSTEM DISORDERS:

convulsion

#### OTHER Adverse Reactions:

symptomatic precipitation of ceftriaxone calcium salt in the gallbladder, kennicterus, oliguria, and anaphylactic or anaphylactoid reactions.

#### 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, hypertension, 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 (see PRECAUTIONS).

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.

**To report SUSPECTED ADVERSE REACTIONS, contact Sagent Pharmaceuticals, Inc. at 1-866-625-1618 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

#### OVERDOSAGE

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

#### Ceftriaxone

may be administered intravenously or intramuscularly.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line.

Ceftriaxone should not be administered simultaneously with calcium-containing IV solutions, including parenteral calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially if one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid (see WARNINGS).

There have been no reports of an interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (IV or oral).

**NEONATES:** Hyperbilirubinemic neonates, especially prematures, should not be treated with ceftriaxone. Ceftriaxone is contraindicated in premature neonates (see CONTRAINDICATIONS).

Ceftriaxone is contraindicated in neonates ( $\leq 28$  days) 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 CONTRAINDICATIONS).

Intravenous doses should be given over 60 minutes in neonates to reduce the risk of bilirubin encephalopathy.

**PEDIATRIC PATIENTS:** 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 acute bacterial 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.

**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 antimicrobial 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 100 mg/mL concentrations in this diluent in PVC containers only.

The following intravenous ceftriaxone solutions are stable at room temperature (25°C) for 24 hours, at concentrations between 10 mg/mL and 40 mg/mL: Sodium Lactate (PVC container), 10% Invert Sugar (glass container), 5% Sodium Bicarbonate (glass container), Freedamine III (glass container), Normosol-M in 5% Dextrose (glass and PVC containers), Ionsolos-B in 5% Dextrose (glass container), 5% Mannitol (glass container), 10% Mannitol (glass container).

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

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

Ceftriaxone reconstituted with 5% Dextrose or 0.9% Sodium Chloride solution at concentrations between 10 mg/mL and 40 mg/mL, and then stored in frozen state (-20°C) in PVC or polyolefin containers, remains stable for 26 weeks.

Frozen solutions of ceftriaxone should be thawed at room temperature before use. After thawing, unused portions should be discarded. **DO NOT REFREEZE.**

#### ANIMAL PHARMACOLOGY

Concrecions 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 (months) at higher dose levels (335 mg/kg/day or more). The mechanism 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 supplied as a sterile crystalline powder in glass vials as follows:

NDC	Ceftriaxone for Injection, USP	Package Factor
25021-105-10	500 mg equivalent of ceftriaxone in a Single-Dose Vial	25 vials per carton
25021-106-10	1 g equivalent of ceftriaxone in a Single-Dose Vial	25 vials per carton
25021-107-20	2 g equivalent of ceftriaxone in a Single-Dose Vial	25 vials per carton

Ceftriaxone for Injection, USP is also supplied as a sterile crystalline powder in a Pharmacy Bulk Package as follows:

NDC	Ceftriaxone for Injection, USP	Package Factor
25021-108-99	10 g equivalent of ceftriaxone in a Pharmacy Bulk Package – NOT FOR DIRECT INFUSION	1 bottle per carton

**Storage Conditions**  
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

#### Protect from light.

**Sterile, Nonpyrogenic, Preservative-free.**  
The container closure is not made with natural rubber latex.

#### CLINICAL STUDIES

**Acute Bacterial Otitis Media:** In two adequate and well-controlled U.S. 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:

TABLE 7. Clinical Efficacy in Pediatric Patients with Acute Bacterial Otitis Media

Study Day	Clinical Efficacy in Evaluable Population		
	Ceftriaxone Single Dose	Comparator – 10 Days of Oral Therapy	95% Confidence Interval
14	74% (220/296)	82% (247/302)	(-14.4%, -0.5%)
28	58% (167/288)	67% (200/297)	(-17.5%, -1.2%)
Study 2 – U.S. <sup>a</sup>		TMP-SMZ	
14	54% (113/210)	60% (124/206)	(-16.4%, 3.6%)
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:

TABLE 8. Bacteriologic Eradication Rates 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)

Ceftriaxone for Injection intravenous solutions, at concentrations of 10, 20 and

40 mg/mL, remain stable (loss of potency less than 10%) for the following time periods stored in glass or PVC containers:

#### Storage

Diluent

Room Temp. (25°C)

Refrigerated (4°C)

Sterile Water

2 days

10 days

0.9% Sodium Chloride Solution

250, 350

24 hours

3 days

100

2 days

10 days

5% Dextrose Solution

250, 350

24 hours

3 days

100

2 days

10 days

Bacteriostatic Water + 0.9% Benzyl Alcohol

250, 350

24 hours

3 days

100

24 hours

10 days

1% Lidocaine Solution (without epinephrine)

250, 350

24 hours

3 days

100

24 hours

10 days

For the treatment of acute bacterial 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

#### REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI), Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically: Approved Standard - Tenth Edition. CLSI document M07-A10, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

2. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk Diffusion Susceptibility Testing: Twenty-fifth Information Supplement. CLSI document M2-A25, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.