PRESCRIBING INFORMATION

CEFTRIAXONE

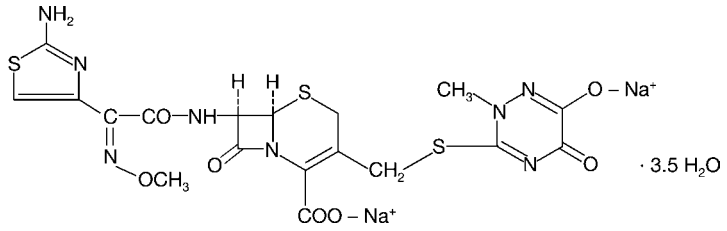
FOR INJECTION, USP

ADD-Vantage® Vials ℞ only

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

DESCRIPTION: Ceftriaxone for Injection 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, 7^2-(*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 661.60 and the following structural formula:



Ceftriaxone sodium is a white to yellowish 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 solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

Ceftriaxone contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone activity.

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

TABLE 1. Ceftriaxone Plasma Concentrations After Single Dose Administration

Dose/Route	Average Plasma Concentrations (mcg/mL)								
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	16 hr	24 hr
0.5 gm IV*	82	59	48	37	29	23	15	10	5
0.5 gm IM 250 mg/mL	22	33	38	35	30	26	16	ND	5
0.5 gm IM 350 mg/mL	20	32	38	34	31	24	16	ND	5
1 gm IV*	151	111	88	67	53	43	28	18	9
1 gm IM	40	68	76	68	56	44	29	ND	ND
2 gm 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 postdosing. Multiple IV or IM doses ranging from 0.5 to 2 gm 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 (mcg/mL)					
	0-2 hr	2-4 hr	4-8 hr	8-12 hr	12-24 hr	24-48 hr
0.5 gm IV	526	366	142	87	70	15
0.5 gm IM	115	425	308	127	96	28
1 gm IV	995	855	293	147	132	32
1 gm IM	504	628	418	237	ND	ND
2 gm IV	2692	1976	757	274	198	40

ND = Not determined.

33% 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 gm IV dose, average concentrations of ceftriaxone, determined from 1 to 3 hours after dosing, were 581 mcg/mL in the gallbladder bile, 788 mcg/mL in the common duct bile, 898 mcg/mL in the cystic duct bile, 78.2 mcg/gm in the gallbladder wall and 62.1 mcg/mL in the concurrent plasma.

Over a 0.15 to 3 gm 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 mcg/mL to a value of 85% bound at 300 mcg/mL. Ceftriaxone crosses the blood placenta barrier.
The average values of maximum plasma concentration, elimination half-life, plasma clearance and volume of distribution after a 50 mg/kg IV dose and after a 75 mg/kg IV dose in pediatric patients suffering from bacterial meningitis are shown in Table 3. Ceftriaxone penetrated the inflamed meninges of infants and pediatric patients; CSF concentrations after a 50 mg/kg IV dose and after a 75 mg/kg IV dose are also shown in Table 3.

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

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

Compared to that in healthy adult subjects, the pharmacokinetics of ceftriaxone were only minimally altered in elderly subjects and in patients with renal impairment or hepatic dysfunction (Table 4); therefore, dosage adjustments are not necessary for these patients with ceftriaxone dosages up to 2 gm 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 (±SD) ceftriaxone levels in the middle ear reached a peak of 35 (±12) mcg/mL at 24 hours, and remained at 19 (±7) mcg/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 ≤8 mcg/mL or less against most strains of the following microorganisms, however, the safety and effectiveness of ceftriaxone in treating clinical infections due to these microorganisms have not been established in adequate and well controlled clinical trials.

Aerobic gram-negative microorganisms:
Citrobacter diversus
Citrobacter freundii
Providencia species (including *Providencia rettgeri*)
Salmonella species (including *Salmonella typhi*)
Shigella species
Aerobic gram-positive microorganisms:
Streptococcus agalactiae
Anaerobic microorganisms:
Prevotella (Bacteroides) bivius
Porphyromonas (Bacteroides) melaninogenicus

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

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

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

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

The absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.
The following interpretive criteria[2] should be used when testing *Neisseria gonorrhoeae* when using GC agar base and 1% defined growth supplement.

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

The absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.
The following interpretive criteria[2] should be used when testing *Streptococcus* spp including *Streptococcus pneumoniae* using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.

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

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the results should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of the drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.
Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standardized ceftriaxone powder should provide the following MIC values:[2]

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

*A bimodal distribution of MICs results at the extremes of the acceptable range should be suspect and control validity should be verified with data from other control strains.
Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[3] requires the use of standardized inoculum concentrations. This procedure uses paper discs impregnated with 30 mcg of ceftriaxone to test the susceptibility of microorganisms to ceftriaxone.

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

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

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

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

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

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

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

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

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

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

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

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

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30 mcg ceftriaxone disc should provide the following zone diameters in these laboratory test quality control strains:[3]

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

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

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

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

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

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

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

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ceftriaxone for Injection and 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 compared to 10 days of oral therapy. In a second study comparable cure rates were observed between single dose ceftriaxone and the comparator. The potentially lower clinical cure rate of ceftriaxone 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 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 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 gm dose of ceftriaxone 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 gm dose of ceftriaxone 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.

Neonates (≤28 days)
Hyperbilirubinemic neonates, especially prematures, should not be treated with Ceftriaxone for Injection. In vitro studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.
Ceftriaxone for Injection must not be co-administered with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition, in neonates because of the risk of precipitation of ceftriaxone-calcium salt.
Cases of fatal reactions with ceftriaxone-calcium precipitates in lung and kidneys in neonates have been described. In some cases the infusion lines and the times of administration of ceftriaxone and calcium-containing solutions differed. For information regarding all other patients, see **WARNINGS.**

WARNINGS

Hypersensitivity

BEFORE THERAPY WITH CEFTRIAXONE IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Interaction with Calcium-Containing Products

There are no reports to date of intravascular or pulmonary precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing IV solutions. However, the theoretical possibility exists for an interaction between ceftriaxone and IV calcium-containing solutions in patients other than neonates. Therefore, Ceftriaxone for Injection and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age, even via different infusion lines at different sites. As a further theoretical consideration and based on 5-half-lives of ceftriaxone, Ceftriaxone for Injection and IV calcium-containing solutions should not be administered within 48 hours of each other in any patient (See CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

No data are available on potential interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (IV or oral).

Clostridium difficile

***Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild diarrhea to fatal colitis.**

Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment *C. difficile,* and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS: ***General:*** Prescribing Ceftriaxone for 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 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 gm 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 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 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 for Injection 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 for Injection should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Ceftriaxone for 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 or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

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

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

Impairment of Fertility: Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/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 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 should not be administered to hyperbilirubinemic neonates, especially prematures (see **CONTRAINDICATIONS**).

ADVERSE REACTIONS: Ceftriaxone 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 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 prothrombin time, renal precipitations, seizures, and serum sickness.

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

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 in the ADD-Vantage® Vial is intended for intravenous infusion only, after dilution with appropriate volume of ADD-Vantage diluent solution.
Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Ceftriaxone for Injection. Particulate formation can result. Ceftriaxone for Injection and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age, even via different infusion lines at different sites (see CONTRAINDICATIONS and WARNINGS).

NEONATES: **Hyperbilirubinemic neonates, especially prematures, should not be treated with Ceftriaxone for Injection (see CONTRAINDICATIONS).**
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**). **(The above is for informational purposes only. Ceftriaxone in ADD-Vantage vials is not intended for intramuscular use.)**
For the treatment of serious miscellaneous infections other than meningitis, the recommended total daily dose is 50 to 75 mg/kg, given in divided doses every 12 hours. The total daily dose should not exceed 2 grams.
In the treatment of meningitis, it is recommended that the initial therapeutic dose be 100 mg/kg (not to exceed 4 grams). Thereafter, a total daily dose of 100 mg/kg/day (not to exceed 4 grams daily) is recommended. The daily dose may be administered once a day (or in equally divided doses every 12 hours). The usual duration of therapy is 7 to 14 days.
ADULTS: The usual adult daily dose is 1 to 2 grams given once a day (or in equally divided doses twice a day) depending on the type and severity of infection. The total daily dose should not exceed 4 grams.
If *Chlamydia trachomatis* is a suspected pathogen, appropriate antichlamydial coverage should be added, because ceftriaxone sodium has no activity against this organism.
For 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.
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 USE: Intravenous Administration: Ceftriaxone should be administered intravenously by infusion over a period of 30 minutes.
ADD-Vantage Vials for IV Use Only contain ceftriaxone sodium equivalent to 1 gm or 2 gm ceftriaxone to be used with 50 mL or 100 mL of 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP, in the ADD-Vantage Flexible Diluent Container. (See **Instructions For Use of the ADD-Vantage® System** at the end of this package insert.)
COMPATIBILITY AND STABILITY: Ceftriaxone has been shown to be compatible with Flagyl®* IV (metronidazole hydrochloride). The concentration should not exceed 5 to 7.5 mg/mL metronidazole hydrochloride with ceftriaxone 10 mg/mL as an admixture. The admixture is stable for 24 hours at room temperature only in 0.9% sodium chloride injection or 5% dextrose in water (D5W). No compatibility studies have been conducted with the Flagyl® IV RTU® (metronidazole) formulation or using other diluents. Metronidazole at concentrations greater than 8 mg/mL will precipitate. Do not refrigerate the admixture as precipitation will occur.
* Registered trademark of G.D. Searle & Co.
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.
Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Ceftriaxone for Injection. Particulate formation can result.

Ceftriaxone solutions should *not* be physically mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, due to the possible incompatibility (see **WARNINGS**).
Ceftriaxone sodium sterile powder should be stored at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature] 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 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.
ADD-Vantage Vials – Ceftriaxone for Injection Units: **See Instructions For Use of the ADD-Vantage® System** at the end of this package insert.

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 is supplied as a sterile, white to yellowish crystalline powder in ADD-Vantage® Vials as follows:
ADD-Vantage Vials containing 1 gm equivalent of ceftriaxone. Box of 10 (NDC 0409-7333-04).
ADD-Vantage Vials containing 2 gm equivalent of ceftriaxone. Box of 10 (NDC 0409-7336-04).

CLINICAL STUDIES: *Clinical Trials in Pediatric Patients With Acute Bacterial Otitis Media:* **(The following is for informational purposes only. Ceftriaxone in ADD-Vantage vials is not intended for intramuscular use.)** 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 - U.S.		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 - U.S.[5]		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:

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

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.
5. 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.

Instructions For Use of the ADD-Vantage® System:
To Open Diluent Container:
Peel overwrap from the corner and remove container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

To Assemble Vial and Flexible Diluent Container (Use Aseptic Technique):
1. Remove the protective covers from the top of the vial and the vial port on the diluent container as follows:
   a. To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down far enough to start the opening (SEE FIGURE 1.), then pull straight up to remove the cap. (SEE FIGURE 2.) NOTE: Do not access vial with syringe.

Fig. 1

Fig. 2

   b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the three tie strings, then pull back to remove the cover. (SEE FIGURE 3.)
2. Screw the vial into the vial port until it will go no further. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. This occurs approximately 1/2 turn (180°) after the first audible click. (SEE FIGURE 4.) The clicking sound does not assure a seal; the vial must be turned as far as it will go. NOTE: Once vial is seated, do not attempt to remove. (SEE FIGURE 4.)
3. Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.
4. Label appropriately.

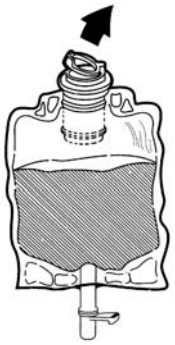


Fig. 3

Fig. 4

To Reconstitute the Drug:
1. Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.
2. With the other hand, push the drug vial down into the container telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container. (SEE FIGURE 5.)
3. Pull the inner cap from the drug vial. (SEE FIGURE 6.) Verify that the rubber stopper has been pulled out, allowing the drug and diluent to mix.
4. Mix container contents thoroughly and use within the specified time.

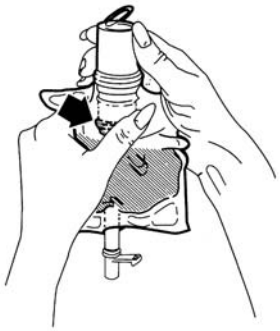


Fig. 5

Fig. 6

Preparation for Administration (Use Aseptic Technique):

1. Confirm the activation and admixture of vial contents.
2. Check for leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.
3. Close flow control clamp of administration set.
4. Remove cover from outlet port at bottom of container.
5. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full directions on administration set carton.
6. Lift the free end of the hanger loop on the bottom of the vial, breaking the two tie strings. Bend the loop outward to lock it in the upright position, then suspend container from hanger.
7. Squeeze and release drip chamber to establish proper fluid level in chamber.
8. Open flow control clamp and clear air from set. Close clamp.
9. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
10. Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible container in series connections.

STABILITY: The ADD-Vantage System is designed to minimize drug waste by allowing the drug and diluent to be mixed at bedside just prior to administration. However, in those rare instances where the admixed unit cannot be administered within the specified time, Ceftriaxone ADD-Vantage units may be safely stored under the following conditions:

		Storage	
		Room Temperature	Refrigeration
Diluent	Concentration	(25°C)	(4°C)
0.9% Sodium Chloride Solution	10 mg/mL to 40 mg/mL	2 days	10 days
5% Dextrose Solution	10 mg/mL to 40 mg/mL	2 days	10 days

Reconstituted ADD-Vantage units should *not* be stored in a frozen state (-20°C).

Hospira

October 2007
EN-1618

Printed in Austria

Manufactured by Sandoz GmbH for Hospira Worldwide, Inc.,
Lake Forest, IL 60045, USA. Made in Kundl, Austria