## Ceftriaxone for Injection, USP PHARMACY BULK PACKAGE

R only

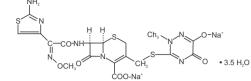
NOT FOR DIRECT INFUSION

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

DESCRIPTION Ceffriaxone for Injection, USP is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceffriaxone sodium is (6R,7R)-712-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[(1,2,5,6+terahydro-2-methyl-5,6-tioxo-as-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic add, 7<sup>2</sup>-(2)-(0-methyloxime), disodium salt, sesquaterhydrate.

The chemical formula of ceftriaxone sodium is C<sub>18</sub>H<sub>18</sub>N<sub>8</sub>Na<sub>2</sub>O<sub>2</sub>S<sub>3</sub>•3.5H<sub>2</sub>O. It has a calculated molecular weight of 661.60 and the following structural formula:



Ceftriaxone sodium is a white to yellowish-orange crystalline powder which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The pH of a 1% aqueous solution is approximately 6.7. The color of Ceftriaxone for Injection, USP solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used

Each Pharmacy Bulk Package is supplied as a dry powder in Pharmacy Bulk Package bottles containing sterile Ceffriaxone sodium, USP equivalent to 10 grams of ceffriaxone and is intended for intravenous infusion only Ceffriaxone sodium, USP equivalent to 10 grams of ceffriaxone and is intended for intravenous infusion only Ceffriaxone sodium contains approximately 83 mg (3.6 mEq) of sodium per gram of ceffriaxone activity.

A Pharmacy Bulk Package is a container of a sterile preparation for parenteral use that contains many single doses. All internated balances of a domainer of a stering preparation for parentiarial data domains and are instructed to the preparation of admixtures for intravenous infusion. FURTHER DILUTION IS REQUIRED BEFORE USE. (See DOSAGE AND ADMINISTRATION, and DIRECTIONS FOR PROPER USE OF PHARMACY BULK PACKAGE.)

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

Table 1. Ceftriaxone Plasma Concentrations After Single Dose Administration

	Average Blasma Concentrations (mag/ml.)								
	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 Intravenous*	82	59	48	37	29	23	15	10	5
0.5 g Intramuscular 250 mg/mL	22	33	38	35	30	26	16	ND	5
0.5 g Intramuscular 350 mg/mL	20	32	38	34	31	24	16	ND	5
1 g Intravenous*	151	111	88	67	53	43	28	18	9
1 g Intramuscular	40	68	76	68	56	44	29	ND	ND
2 g Intravenous*	257	192	154	117	89	74	46	31	15

\* Intravenous doses were infused at a constant rate over 30 minutes. ND = Not determined

ND = Not determined. Ceftriaxone was completely absorbed following intramuscular administration with mean maximum plasma concentrations occurring between 2 and 3 hours post-dose. Multiple intravenous or intramuscular doses ranging from 0.5 to 2 g at 12 to 24-hour intervals resulted in 15% to 36% accumulation of ceftriaxone above single dose values.

Ceftriaxone concentrations in urine are shown in Table 2

### Table 2 Urinary Concentrations of Ceftriaxone 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 Intravenous	526	366	142	87	70	15
0.5 g Intramuscular	115	425	308	127	96	28
1 g Intravenous	995	855	293	147	132	32
1 g Intramuscular	504	628	418	237	ND	ND
2 g Intravenous	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 utimately found in the feces as microbiologically inactive compounds. After a 1 g intravenous dose, average concentrations of ceftriaxone, determined from 1 to 3 hours after dosing, were 581 mcg/mL in the gallbladder bile, 788 mcg/mL in the common duct bile, 898 mcg/mL in the cystic duct bile, 78.2 mcg/g in the gallbladder wall and 62.1 mcg/mL in the concurrent plasma.

Value of 95% bound at plasma concentrations of <25 mcg/mL to a value of 85% bound at 300 mcg/mL. Ceftriaxone concentrations of <25 mcg/mL to a value of 85% bound at 300 mcg/mL. Ceftriaxone concentrations of <25 mcg/mL to a value of 85% bound at 300 mcg/mL. Ceftriaxone concentrations of <25 mcg/mL to a value of 85% bound at 300 mcg/mL.

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

### Table 3 Average Pharmacokinetic Parameters of Ceffriaxone in Pediatric Patients With Meningitis

	50 mg/kg Intravenous	75 mg/kg Intravenous
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) Time after dose (hr)	5.6 1.3 to 18.5 3.7 (± 1.6)	6.4 1.3 to 44 3.3 (± 1.4)

Compared to that in healthy adult subjects, the pharmacokinetics of certriaxone 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 certriaxone dosages up to 2 g per day. Certriaxone was not removed to any significant extent from the plasma by hemodiallysis. In 6 of 26 diallysis patients, the elimination rate of certriaxone was arkedly reduced

### 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 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)* Severe (5 to 15 mL/min) Moderate (16 to 30 mL/min) Mild (31 to 60 mL/min)	14.7 15.7 11.4 12.4	0.65 0.56 0.72 0.70	13.7 12.5 11.8 13.3
Patients With Liver Disease	8.8	1.1	13.6

### \*Creatinine clearance

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

Pharmacokinetics in the Middle Ear Fluid In one study, total ceftriaxone is not altered when ceftriaxone is co-administered with probenecid. 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.

### Interaction with Calcium

Interaction with Calcium Two in vitro studies, one using adult plasma and the other neonatal plasma from umbilical cord blood have been carried out to assess interaction of ceftriaxone and calcium. Ceftriaxone concentrations up to 1 mM (in excess of concentrations achieved in vivo following administration of 2 grams ceftriaxone infused over 30 minutes) were used in combination with calcium concentrations up to 12 mM (48 mg/dL). Recovery of ceftriaxone from plasma was reduced with calcium concentrations of 6 mM (24 mg/dL) or higher in adult plasma or 4 mM (16 mg/dL) or higher in neonatal plasma. This may be reflective of ceftriaxone-calcium precipitation.

Microbiology Mechanism of Action Ceftriaxone is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Ceftriaxone has activity in the presence of some beta-lactamases, both penicillinases and cephalosporinases, of Gram-negative and Gram-positive bacteria.

Mechanism of Resistance Resistance to ceftriaxone 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 ceftriaxone. Ceftriaxone 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 inetobacter calcoaceticus Enterobacter aerogenes
- Enterobacter cloacae Enterobacter cloacae Escherichia coli Haemophilus influenzae Haemophilus parainfluenzae Klebsiella oxytoca Klebsiella oxytoca Moraxella catarrhalis Morganella morganii Neisseria gonorrhoeae Neisseria gonorrhoeae Neisseria meningilidis

- Proteus mirabili Proteus vulgaris
- Pseudomonas aeruginosa Serratia marcescens
- Gram-positive bacteria aphylococcus aureus Staphylococcus epidermidis Streptococcus pneumoniae
- Streptococcus pyogenes /iridans group streptococci Anaerobic bacteria
- Bacteroides fragilis Clostridium species Peptostreptococcus species

# The following *in vitro* data are available, <u>but their clinical significance is unknown</u>. 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 ceftriaxone. However, the efficacy of ceftriaxone in treating clinical infections due to these microorganisms **has not been** established in adequate and well-controlled clinical trials.

- Gram-negative bacteria
- Citrobacter freundii
- Providencia species (including Providencia rettgeri) Salmonella species (including Salmonella typhi) Shigella species
- Gram-positive bacteria
- rentococcus agalactia
- Anaerobic bacteria Porphyromonas (Bacteroides) melaninogenicus Prevotella (Bacteroides) bivius
- Susceptibility Testing

## Susceptionity resulting For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

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 for Injection and To reduce the development of order-esistant bacteria and maintain the effectiveness of centratorie 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

### 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

Acute bacteria of the method o

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

## Skin and Skin Structure infections Caused by Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Viridans group streptococci, Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella enternoriae, Proteus mirabilis, Morganella morgani", 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 gonorrheae, including both penicillinase- and nonpenicillinase-producing strains, and pharyngeal gonorrhea caused by nonpenicillinase-producing strains of Neisseria gonorrheae.

Pelvic Inflammatory Disease Caused by Neisseria gonorrhoeae. Ceftriaxone sodium, like other cephalosporins, has no activity against Chlamydia trachomatis. Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and Chlamydia trachomatis is one of the suspected pathogens, appropriate antichlamydial coverage should be

Bacterial Septicemia Caused by Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae or Klebsiella pneumoniae.

### Bone and Joint Infections occus aureus. Streptococcus pneumoniae. Escherichia coli. Proteus mirabilis. Klebsiella Caused by Staphylococcus aureus 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 for this organism in this organ system was studied in fewer than ten infections

Elicacy to this organism to the organism that of gain system was studied in the well that terminectoris. Surgical Prophylaxis The preoperative administration of a single 1 g 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 calculus cholecystitis in high-risk patients, such as those over 70 years of age, with acute cholecystectomy for chronic calculus 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 for Injection has been shown to have been as effective as cefazolin in the prevention of infection for lowing coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary active threases (integration) following coronary artery bypass surgery.

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

Hypersensitivity Ceftriaxone for injection is contraindicated in patients with known hypersensitivity to ceftriaxone, any of its excipients or to any other cephalosporin. Patients with previous hypersensitivity reactions to penicillin and other beta lactam antibacterial agents may be at greater risk of hypersensitivity to ceftriaxone (see WARNINGS – Hypersensitivity). Neonates

## Premature neonates

raindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age).

Hyperbilirubinemic neonates Hyperbilirubinemic neonates should not be treated with ceftriaxone for injection. Ceftriaxone can displace bilirubin from its binding to serum albumin, leading to a risk of bilirubin encephalopathy in these patients.

### Neonates Requiring Calcium Containing Intravenous Solutions

Ceftriaxone is contraindicated in neonates (< 28 days) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium (see CLINICAL PHARMACOLOGY, WARNINGS and DOSAGE AND ADMINISTRATION).

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 in some a precipitate was observed in the intravenous infusion line. There have been no similar reports in patients other than neonates.

### Lidocaine

Intravenous administration of ceftriaxone solutions containing lidocaine is contraindicated. Refer to the prescribing information of lidocaine.

### WARNINGS Hypersensitivity Reactions

rial agents

Hemolytic Anemia

PRECAUTIONS

exceed 2 g daily.

Hypersensitivity Reactions Before therapy with ceftriaxone 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-sensitive patients. Antibacterial drugs 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.

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions (i.e., anaphylaxis) have been reported. In case of severe hypersensitivity reactions, treatment with ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated. discontinued immediately and adequate emergency measures must be initiated. Interaction with Calcium-Containing Products Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute ceftriaxone bottles or to further dilute a reconstituted bottle for intravenous administration because a precipitate can form. Precipitation of ceftraxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same intravenous solutions, including continuous calcium-containing solutions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. In vitro studies using adult and neonatel plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftraxone-calcium (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

Clostridium difficile - Associated Diarrhea Clostridium difficile - Associated Diarrhea Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including certificaxone, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to over-growth 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 morbality, 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

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

An immune mediated hemolytic anemia has been observed in patients receiving cephalosporin class antibacterials including ceftriaxone. Severe cases of hemolytic anemia, including fatalities, have been reported during treatment in both adults and children. If a patient develops anemia while on ceftriaxone, the diagnosis of a cephalosporin associated anemia should be considered and ceftriaxone stopped until the etiology is determined.

PRECAUTIONS <u>Development of Drug-resistant Bacteria</u> Prescribing ceftriaxone for injection in the absence of a proven or strongly suspected bacterial infection or a prophylacitic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. 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.

Patients with Renal or Hepatic Impairment 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.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, caution should be exercised and the ceftriaxone dosage should not

Ceftriaxone is not removed by peritoneal- or hemodialysis. In patients undergoing dialysis no additional supplementary dosing is required following the dialysis. In patients with both severe renal and hepatic dysfunction, close clinical monitoring for safety and efficacy is advised.

Effect on Prothrombin Time Alterations in prothrombin times have occurred in patients treated with ceftriaxone. Monitor prothrombin time during Alterations or low vitamin K stores (e.g., chronic hepatic Alterations in promotion and the state occurred in patients areated with centrative motion or four or four or and the centrative of the state of the

Concomitant use of ceftriaxone with Vitamin K antagonists may increase the risk of bleeding. Coagulation parameters should be monitored frequently, and the dose of the anticcagulant adjusted accordingly, both during and after treatment with ceftriaxone (see ADVERSERACTIONS).

dealibladder Pseudolithiasis Ceftriaxone-calcium precipitates in the gallbladder have been observed in patients receiving ceftriaxone. These precipitates 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 probability of such precipitates appears to be greatest in pediatric patients. Patients may be asymptomatic or may develop symptoms of gallbladder disease. The condition appears to be reversible upon discontinuation of ceftriaxone sodium and institution of conservative management. Discontinue ceftriaxone sodium in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above.

Urolithiasis and Post-RenalAcute 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 reversible upon discontinuation of ceftriaxone sodium and institution of 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). Acofactor role of ceftriaxone-related biliary precipitation cannot be ruled out.

### 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., common cold). When ceftriaxone for injection is prescribed to treat a bacterial infection, patients should be told that although it is
- when certraxone for injection is prescribed to treat a bacterial infection, patients should be taken exactly as directed. Skipping doses or not completing the full course of therapy, the medication should be taken exactly as directed. Freatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ceffriaxone 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 Dramlera is a committed process of the autobulk set of an autobulk set of the autobulk

### Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis

Carcinogenesis Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceffriaxone 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 Impairment of reruinty Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 g/day.

Pregnancy Teratogenic Effects

Pergnancy Category Entersor 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

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 Low concentrations of administered to a nursi

Pediatric Use Safety and effectiveness of ceftriaxone in neonates, infants and pediatric patients have been established for the dosages described in the DOSACE 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 hyper-bilirubinemic 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 the total number of subjects in Clinical studies of Certificatorie, 32 is where to an origination to over an uniferences 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 ceftraxone the Coombs' test may become positive. Ceftriaxone, like other antibacterial drugs, may result in positive test results for galactosemia.

Nonenzymatic methods for the glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with ceftriaxone should be done enzymatically.

The presence of ceftriaxone may falsely lower estimated blood glucose values obtained with some blood glucose monitoring systems. Please refer to instructions for use for each system. Alternative testing methods should be used if necessarv

### ADVERSE REACTIONS

Contriacone 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 tendemess was 1% overall. Phlebitis was reported in <1% after intravenous administration. The incidence of warmth, tightness or induration was 17% (3/17) after intramuscular administration of 350 mg/mL and 5% (1/20) after intramuscular administration of 250 mg/mL.

## General Disorders and Administration Site Conditions Injection site pain (0.6%).

Hypersensitivity Rash (1.7%). Less frequently reported (<1%) were pruritus, fever or chills.

## Infections and Infestations Genital fungal infection (0.1%).

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.

Blood and Lymphatic Disorders ia (0.9%), coagulopathy (0.4%) Granulocyto

### Gastrointestinal

Gastrointestinal Diarrhea/loose stools (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 aspartate aminotransferase (AST) (3,1%) or alanine aminotransferase (ALT) (3,3%). Less frequently reported (<1%) were elevations of alkaline phose

Terral 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 (<0.1%) include abdominal pain, agranulocytosis, allergic pneumonitis, anaphylaxis, basophilia, biliary lithiasis, bronchospasm, colitis, dyspepsia, epistaxis, flatulence, galibladder sludge, glycosuria, hematuria, jaundice, leukocytosis, lymphocytosis, monocytosis, nephrolithiasis, palpitations, 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.

C SITUAL TURDER OF CASES OF TATAI OUTCOMES IN which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving ceffriaxone and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both ceffriaxone and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom ceffriaxone 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 dossitis

*Genitourinary* Oliguria, ureteric 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 enidermal 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 q or more.

## Nervous System Disorders

Other, Adverse Reactions Symptomatic precipitation of ceftriaxone calcium salt in the gallbladder, kernicterus, oliguria, and anaphylactic or anaphylactoid reactions.

Cephalosportin 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 cephalosportin class antibiotics:

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

Altered Laboratory Tests Positive direct Coombs' test, false-positive test for urinary glucose, and elevated LDH (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 Piramal Critical Care at 1-888-822-8431 or FDA at 1-800-FDA-1088 or <u>www.fda.gov/medwatch.</u> 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

DOSAGE AND DAMINISTRATION 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 intravenously by infusion over a period of 30 minutes.

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

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

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

Neonates Hyperbilirubinemic neonates, especially prematures, should not be treated with ceftriaxone for injection. Ceftriaxone for injection is contraindicated in premature neonates (see CONTRAINDICATIONS).

Ceftriaxone for injection is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatme with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parente 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 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 dosse very 12 hours). The usual duration of therapy is 7 to 14

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

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

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

Generally, ceftriaxone for injection 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 (see PRECAUTIONS). The dosages recommended for adults require no modification in elderly patients, up to 2 g per day, provided there is no severe renal and hepatic impairment (see **PRECAUTIONS**). DIRECTIONS FOR PROPER USE OF PHARMACY BULK PACKAGE

## PHARMACY BULK PACKAGE NOT FOR DIRECT INFUSION

RECONSTITUTED STOCK SOLUTION MUST BE TRANSFERRED AND FURTHER DILUTED FOR

The 10 gram bottle should be reconstituted with 95 mL of an appropriate intravenous diluent in a suitable work area such as a laminar flow hood. The resulting solution will contain approximately 100 mg per mL of ceftriaxone.

The container closure may be penetrated only one time, utilizing a suitable sterile transfer device or dispensing set which allows measured distribution of the contents. (A sterile substance which must be reconstituted prior to use may require a separate closure entry.) Use of this product is restricted to a suitable work area, such as a laminar flow hood.

The withdrawal of container contents should be accomplished without delay. However, should this not be possible, a maximum time of **4 hours** from initial closure entry is permitted to complete fluid transfer operations. If reconstitution is necessary, this time limit should begin with the introduction of solvent or diluent into the Pharmacy Bulk Package. Unused portions of solution held longer than the recommended time periods should be discarded.

## RECONSTITUTED BULK SOLUTIONS SHOULD NOT BE USED FOR DIRECT INFUSION.

Transfer individual dose to appropriate intravenous solutions as soon as possible following reconstitution of the bulk package. The stability of the solution that has been transferred into a container varies according to diluent, concentration and temperature (see **Compatibility and Stability**). Concentrations between 10 mg per mL and 40 mg per mL are recommended, however lower concentrations may be used if desired.

Compatibility and Stability Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute ceftriaxone

Ceftriaxone for injection has been shown to be compatible with Flagyl<sup>®</sup> IV (metronidazole hydrochloride). The concentration should not exceed 5 to 7.5 mg per mL metronidazole hydrochloride with ceftriaxone 10 mg per 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 (DSW). No compatibility studies have been conducted with the Flagyl<sup>®</sup> IV RTU<sup>®</sup> (metronidazole) formulation or using other diuents. Metronidazole at concentrations greater than 8 mg per mL will precipitate. Do not refrigerate the admixture as precipitation will occur.

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

Ceftriaxone for injection 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 possible incompatibility (see WARNINGS)

Ceftriaxone for injection sterile powder should be stored at room temperature 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature] 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.

Ceftriaxone intravenous solutions, at concentrations of 10, 20 and 40 mg per 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	2 days	10 days		
5% Dextrose Solution	2 days	10 days		
10% Dextrose Solution	2 days	10 days		
5% Dextrose + 0.9% Sodium Chloride Solution*	2 days	Incompatible		
5% Dextrose + 0.45% Sodium Chloride Solution	2 days	Incompatible		

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

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

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

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.

Ceftriaxone for Injection, USP is available as a sterile crystalline powder in glass bottles as Pharmacy Bulk Package, NOT FOR DIRECT INFUSION as follows:

CLINICAL'S IUDIES Clinical Trials in Pediatric Patients With Acute Bacterial Otitis Media In two adequate and well-controlled US clinical trials a single intramuscular 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

Comparator 10 Days of

Oral Therapy

amoxicillin/clavulanate

82% (247/302)

67% (200/297)

TMP-SMZ

60% (124/206)

45% (93/205)

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

Erad. (%)

32 (84)

28 (85)

12 (80)

Study Day

13 to 15

Analyzed

38

33

15

precipitated calcium salt of ceftriaxone have been found in the gallbladder bile of dogs

Package Factor

Package Factor

25 vials per carton

25 vials per carton

25 vials per carton

Statistical

Outcome

Ceftriaxone is

at study

day 14 and 28.

Ceftriaxone is quivalent to contro at study

at study day 14 and 28.

Erad. (%)

25 (71)

22 (71)

8

9 (60)

Study Day

30+2

Analyzed

35 31

15

wer than control

95%

Confidence

Interval

(-14.4%, -0.5%)

(-17.5%, -1.2%)

(-16.4%, 3.6%)

(-19.9%, 0.0%)

\* Data available for 10 to 40 mg per mL concentrations in this diluent in PVC containers only.

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

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

Ceftriaxone for Injection, USP

10 gram equivalent of ceftriaxone in a Pharmacy Bulk Package Bottle

Ceftriaxone for Injection. USP is also supplied as a sterile crystalline powder in class vials as follows:

P is also supplied as a sterile crystalline **Ceftriaxone for Injection, USP** 250 mg equivalent of ceftriaxone in a Single-Dose Vial 500 mg equivalent of ceftriaxone in a Single-Dose Vial 1 gram equivalent of ceftriaxone in a Single-Dose Vial 2 gram equivalent of ceftriaxone in a Single-Dose Vial

Storage Conditions Store dry powder at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature] or below.

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

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

Ceftriaxone

Single Dose

74% (220/296)

58% (167/288)

54% (113/210)

35% (73/206)

Table 8. Bacteriologic Eradication Rates by Pathogen

Brands listed are the trademarks of their respective owners

ANIMAL PHARMACOLOGY

Concretions consisting of the p and baboons treated with ceftra

HOW SUPPLIED

NDC 66794-215-15

NDC 66794-211-42

66794-212-42

66794-213-42

66794-214-42

Study Day

14

28

Study 1 – U.S.

Study 2 – U.S.

Organism

Streptococcus pneumoniae

Haemophilus influenzae

Moraxella catarrhalis

C Piramal

Revised April 2019

Critical Care Mfg. for: Piramal Critical Care Bethlehem, PA 18017, USA

Made in India ©2019 Piramal Critical Care

CUNICAL STUDIES