

**CEFTRIAXONE- ceftriaxone sodium injection, powder, for solution**  
**AGILA SPECIALTIES PRIVATE LIMITED**

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**Ceftriaxone for Injection, USP**

**PHARMACY BULK PACKAGE NOT FOR DIRECT INFUSION**

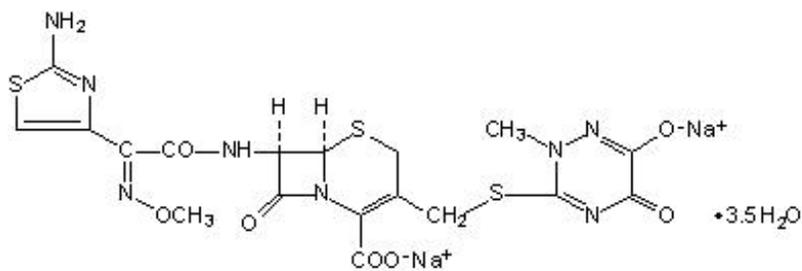
**Rx only**

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, USP is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceftriaxone sodium is (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-*as*-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7<sup>2</sup>-(*Z*)-(O-methyloxime), disodium salt, sesquaterhydrate.

The chemical formula of ceftriaxone sodium is  $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3.5H_2O$ . It has a calculated molecular weight of 661.60 and the following structural formula:



**chemical structure**

Ceftriaxone sodium is white or 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.

Each Pharmacy Bulk Package is supplied as a dry powder in Pharmacy Bulk Package bottles containing sterile ceftriaxone sodium, USP equivalent to 10 g of ceftriaxone and is intended for intravenous infusion only.

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

A Pharmacy Bulk Package is a container of sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted 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 (IV) infusion of a 0.5, 1 or 2 g dose and intramuscular (IM) 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**

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

ND = Not determined

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

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

Ceftriaxone concentrations in urine are shown in Table 2.

**TABLE 2. Urinary Concentrations of Ceftriaxone After Single Dose Administration**

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

ND = Not determined

Thirty-three percent to 67% of a ceftriaxone dose was excreted in the urine as unchanged drug and the remainder was secreted in the bile and ultimately found in the feces as microbiologically inactive compounds. After a 1 g IV dose, average concentrations of ceftriaxone, determined from 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.

Over a 0.15 to 3 g dose range in healthy adult subjects, the values of elimination half-life ranged from 5.8 to 8.7 hours; apparent volume of distribution from 5.78 to 13.5 L; plasma clearance from 0.58 to 1.45 L/hour; and renal clearance from 0.32 to 0.73 L/hour. Ceftriaxone is reversibly bound to human plasma proteins, and the binding decreased from a value of 95% bound at plasma concentrations of <25 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 Concentration (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 to 18.5	1.3 to 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 g per day. Ceftriaxone was not removed to any significant extent from the plasma by hemodialysis. In 6 of 26 dialysis patients, the elimination rate of ceftriaxone was markedly reduced.

**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) Patients With Renal Impairment	8.9	0.83	10.7
Hemodialysis Patients (0 to 5 mL/min)*	14.7	0.65	13.7
Severe (5 to 15 mL/min)	15.7	0.56	12.5
Moderate (16 to 30 mL/min)	11.4	0.72	11.8
Mild (31 to 60 mL/min)	12.4	0.70	13.3
Patients With Liver Disease	8.8	1.1	13.6

\* Creatinine clearance.

The elimination of 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 ( $\pm$ SD) ceftriaxone levels in the middle ear reached a peak of 35 ( $\pm$ 12) mcg/mL at 24 hours, and remained at 19 ( $\pm$ 7) mcg/mL at 48 hours. Based on middle ear fluid 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***

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 g 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**

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.

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 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 resistant to multiple antibiotics, e.g., penicillins, cephalosporins, and aminoglycosides, are susceptible to ceftriaxone.

Aerobic gram-positive microorganisms:

*Staphylococcus aureus* (including penicillinase-producing strains)

*Staphylococcus epidermidis*

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

Viridans group streptococci

NOTE: Methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone. Most

strains of Group D streptococci and enterococci, e.g., *Enterococcus (Streptococcus) faecalis*, are resistant.

Anaerobic microorganisms:

*Bacteroides fragilis*

*Clostridium* species

*Peptostreptococcus* species

NOTE: Most strains of *Clostridium difficile* are resistant.

The following *in vitro* data are available, **but their clinical significance is unknown**. Ceftriaxone exhibits *in vitro* minimal inhibitory concentrations (MICs) of  $\leq 1$  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) bivia*

*Porphyromonas (Bacteroides) melaninogenicus*

### **Susceptibility Tests:**

### **Dilution Techniques**

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure.<sup>1</sup> Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ceftriaxone powder. For details of susceptibility test methodologies, the most recent documents of the Clinical and Laboratory Standards Institute (CLSI) for antimicrobial susceptibility testing<sup>1-3</sup> should be consulted.

The MIC values for aerobic organisms should be interpreted according to following criteria:

For *Enterobacteriaceae*:

<u>MIC (mcg /mL)</u>	<u>Interpretation</u>
$\leq 1$	(S) Susceptible
2	(I) Intermediate
$\geq 4$	(R) Resistant

The following interpretive criteria should be used when testing *Haemophilus* species using

## Haemophilus Test Media (HTM).

<u>MIC (mcg /mL)</u>	<u>Interpretation</u>
≤2	(S) Susceptible

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

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

<u>MIC (mcg /mL)</u>	<u>Interpretation</u>
≤0.25	(S) Susceptible

The following interpretive criteria<sup>4</sup> should be used when testing *Neisseria meningitidis* on Mueller-Hinton agar with 5% defibrinated sheep blood.

<u>MIC (mcg /mL)</u>	<u>Interpretation</u>
≤0.12	(S) Susceptible

The absence of resistant neisserial 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.

When testing *Staphylococcus aureus* (methicillin-susceptible, MSSA) the following interpretive criteria should be applied:

<u>MIC (mcg /mL)</u>	<u>Interpretation</u>
≤4	(S) Susceptible
8	(I) Intermediate
≥16	(R) Resistant

For staphylococcal infections, a daily dose of 2 to 4 g should be administered to achieve >90% target attainment (see **DOSAGE AND ADMINISTRATION**).

The following interpretive criteria should be used when testing *Streptococcus pneumoniae* using Mueller-Hinton broth with 2 to 5% lysed horse blood:

Meningitis:

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

Non-meningitis infections:

<u>MIC (mcg /mL)</u>	<u>Interpretation</u>
≤1	(S) Susceptible
2	(I) Intermediate

≥4	(R) Resistant
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For β-hemolytic streptococci the following interpretive criteria should be used when testing on cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood:

<u>MIC (mcg /mL)</u>	<u>Interpretation</u>
≤0.5	(S) Susceptible

For the Viridians Group streptococci the following interpretive criteria should be applied:

<u>MIC (mcg /mL)</u>	<u>Interpretation</u>
≤1	(S) Susceptible
2	(I) Intermediate
≥4	(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:

<u>Microorganism</u>	<u>ATCC® #</u>	<u>MIC (mcg/mL)</u>
<i>Escherichia coli</i>	25922	0.03 to 0.12
<i>Staphylococcus aureus</i>	29213	1 to 8*
<i>Pseudomonas aeruginosa</i>	27853	8 to 64
<i>Haemophilus influenzae</i>	49247	0.06 to 0.25
<i>Neisseria gonorrhoeae</i>	49226	0.004 to 0.015
<i>Streptococcus pneumoniae</i>	49619	0.03 to 0.12

\* A bimodal distribution of MICs results at the extremes of the acceptable range should be suspect and control validity should be verified with data from other control strains.

## Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure<sup>3</sup> requires the use of standardized inoculum concentrations. This procedure uses paper discs impregnated with 30 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:

For *Enterobacteriaceae*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
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≥23	(S) Susceptible
20 to 22	(I) Intermediate
≤19	(R) Resistant

When testing *Haemophilus influenzae* on Haemophilus Test Media (HTM), the following interpretive criteria should be used:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥26	(S) Susceptible

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

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

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥35	(S) Susceptible

For *Neisseria meningitidis*, the following disc diffusion criteria apply:<sup>5</sup>

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥34	(S) Susceptible

For *Staphylococcus aureus* (methicillin-susceptible, MSSA), the following interpretive criteria apply:

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

The following interpretive criteria should be used when testing β-hemolytic streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO<sub>2</sub>:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥24	(S) Susceptible

For the Viridians Group streptococci the following criteria apply:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥27	(S) Susceptible
25 to 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  $\leq$ 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  $\leq$ 19 mm. The ceftriaxone MIC should be determined for those isolates with oxacillin zone diameters  $\leq$ 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: <sup>3</sup>

<u>Microorganism</u>	<u>ATCC® #</u>	<u>Zone Diameter Ranges (mm)</u>
<i>Escherichia coli</i>	25922	29 to 35
<i>Staphylococcus aureus</i>	29213	22 to 28
<i>Pseudomonas aeruginosa</i>	27853	17 to 23
<i>Haemophilus influenzae</i>	49247	31 to 39
<i>Neisseria gonorrhoeae</i>	49226	39 to 51
<i>Streptococcus pneumoniae</i>	49619	30 to 35

### Anaerobic Susceptibility Testing by Agar Dilution

For anaerobic bacteria, the susceptibility to ceftriaxone as MICs can be determined by standardized test methods.<sup>6</sup> The MIC values obtained should be interpreted according to the following criteria:

<u>MIC (mcg /mL)</u>	<u>Interpretation</u>
$\leq$ 16	(S) Susceptible
32	(I) Intermediate
$\geq$ 64	(R) Resistant

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standardized ceftriaxone powder should provide the following MIC values for the indicated standardized anaerobic dilution<sup>6</sup> testing method:

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

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 and other antibacterial drugs, ceftriaxone for injection, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by 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, USP 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 for injection, USP 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 sodium, like other cephalosporins, has no activity against *Chlamydia trachomatis*. Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and *Chlamydia trachomatis* is one of the suspected pathogens, appropriate antichlamydial coverage should be added.

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

*BONE AND JOINT INFECTIONS* caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae* or *Enterobacter* species.

*INTRA-ABDOMINAL INFECTIONS* caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Bacteroides fragilis*, *Clostridium* species (Note: most strains of *Clostridium difficile* are resistant) or *Peptostreptococcus* species.

*MENINGITIS* caused by *Haemophilus influenzae*, *Neisseria meningitidis* or *Streptococcus pneumoniae*. Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infection caused by *Staphylococcus epidermidis*\* and *Escherichia coli*.\*

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

*SURGICAL PROPHYLAXIS* The preoperative administration of a single 1 g dose of ceftriaxone 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 g dose of

ceftriaxone provides protection from most infections due to susceptible organisms throughout the course of the procedure.

## CONTRAINDICATIONS

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

### Neonates ( $\leq 28$ 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, leading to a possible risk of bilirubin encephalopathy in these patients.

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

A small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving ceftriaxone and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both ceftriaxone and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom ceftriaxone and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.

For information regarding all other patients see **WARNINGS**

## WARNINGS

### Hypersensitivity

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

As with other cephalosporins, anaphylactic reactions with fatal outcome have been reported, even if a patient is not known to be allergic or previously exposed.

### 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 IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Ceftriaxone must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. *In vitro* studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-**

**calcium (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).**

### ***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 of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

### **Hemolytic Anemia**

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**

### **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.

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 exceed 2 g daily.

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 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.

Cases of pancreatitis, possibly secondary to biliary obstruction, have been reported rarely in patients treated with ceftriaxone. Most patients presented with risk factors for biliary stasis and biliary sludge (preceding major therapy, severe illness, total parenteral nutrition). A cofactor role of ceftriaxone-related biliary precipitation cannot be ruled out.

### ***Information for Patients***

Patients should be counseled that antibacterial drugs including ceftriaxone should only be used to treat bacterial infections. They do not treat viral infections (e.g., 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 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 and Impairment of Fertility***

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

#### ***Mutagenesis***

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

#### ***Impairment of Fertility***

Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 g/day.

### ***Pregnancy***

#### ***Teratogenic Effects***

Pregnancy Category B. Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately 3 times the human dose.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during

pregnancy only if clearly needed.

### *Nonteratogenic Effects*

In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

### *Nursing Mothers*

Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when ceftriaxone for injection is administered to a nursing woman.

### *Pediatric Use*

Safety and effectiveness of ceftriaxone in neonates, infants and pediatric patients have been established for the dosages described in the **DOSAGE AND ADMINISTRATION** section. *In vitro* studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone for injection should not be administered to hyperbilirubinemic neonates, especially prematures. (see **CONTRAINDICATIONS**.)

### *Geriatric Use*

Of the total number of subjects in clinical studies of ceftriaxone, 32% were 60 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

The pharmacokinetics of ceftriaxone were only minimally altered in geriatric patients compared to healthy adult subjects and dosage adjustments are not necessary for geriatric patients with ceftriaxone dosages up to 2 g per day (see **CLINICAL PHARMACOLOGY**).

## **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 the prothrombin time, renal precipitations, seizures, and serum sickness.

### **Postmarketing Experience**

In addition to the adverse reactions reported during clinical trials, the following adverse experiences have been reported during clinical practice in patients treated with ceftriaxone. Data are generally insufficient to allow an estimate of incidence or to establish causation.

A small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving ceftriaxone and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both ceftriaxone and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom ceftriaxone and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.

**GASTROINTESTINAL**—stomatitis and glossitis.

**GENITOURINARY**—oliguria.

### **DERMATOLOGIC**

Exanthema, allergic dermatitis, urticaria, edema. As with many medications, isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens-Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis) have been reported.

### **Cephalosporin Class Adverse Reactions**

In addition to the adverse reactions listed above which have been observed in patients treated with ceftriaxone, the following adverse reactions and altered laboratory test results have been reported for cephalosporin class antibiotics:

*Adverse Reactions:* Allergic reactions, drug fever, serum sickness-like reaction, renal dysfunction, toxic nephropathy, reversible hyperactivity, 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.

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 Agila Specialties Private Limited at 1-877-244-9825 or go to [www.stridesarco.com](http://www.stridesarco.com) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**

### **OVERDOSAGE**

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

## DOSAGE AND ADMINISTRATION

Ceftriaxone for injection may be administered intravenously or intramuscularly. However, the intent of this Pharmacy Bulk Package is for the preparation of solutions for intravenous infusion only. Ceftriaxone for injection should be administered 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 bottles or to further dilute a reconstituted bottle for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Ceftriaxone must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially 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 and oral calcium-containing products or interactions between intramuscular ceftriaxone and calcium-containing products (IV or oral).

### NEONATES

Hyperbilirubinemic neonates, especially prematures, should not be treated with ceftriaxone for injection (see **CONTRAINDICATIONS**).

Ceftriaxone is contraindicated in neonates if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium (see **CONTRAINDICATIONS**).

### 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 g.

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 g.

In the treatment of meningitis, it is recommended that the initial therapeutic dose be 100 mg/kg (not to exceed 4 g). Thereafter, a total daily dose of 100 mg/kg/day (not to exceed 4 g 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 g given once a day (or in equally divided doses twice a day) depending on the type and severity of infection.

For infections caused by *Staphylococcus aureus* (MSSA), the recommended daily dose is 2 to 4 g, in order to achieve >90% target attainment. The total daily dose should not exceed 4 g.

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 g administered intravenously 1/2 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.

#### **DIRECTIONS FOR PROPER USE OF PHARMACY BULK PACKAGE**

<b>PHARMACY BULK PACKAGE NOT FOR DIRECT INFUSION</b>
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#### **RECONSTITUTED STOCK SOLUTION MUST BE TRANSFERRED AND FURTHER DILUTED FOR I.V. INFUSION**

The 10 g bottle should be reconstituted with 95 mL of an appropriate IV diluent in a suitable work area such as a laminar flow hood. The resulting solution will contain approximately 100 mg/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 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 solutions held longer than the recommended time periods should be discarded.

<b>RECONSTITUTED BULK SOLUTION SHOULD NOT BE USED FOR DIRECT INFUSION</b>
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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/mL and 40 mg/mL are recommended; however, lower concentrations may be used if desired.

#### **COMPATIBILITY AND STABILITY**

Ceftriaxone has been shown to be compatible with Flagyl<sup>®</sup>\* 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<sup>®</sup>\* IV RTU<sup>®</sup> (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, ampicillin, aminoglycosides, and fluconazole are physically 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.

**Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute ceftriaxone for injection or to further dilute a reconstituted pharmacy bulk package bottle for IV administration. Particulate formation can result.**

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 20° to 25°C (68° to 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.

Ceftriaxone *intravenous* solutions, at concentrations of 10, 20 and 40 mg/mL, remain stable (loss of potency less than 10%) for the following time periods stored in glass or PVC containers:

Diluent	Storage	
	Room Temp. (25°C)	Refrigerated (4°C)
Sterile Water for Injection	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

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

The following *intravenous* ceftriaxone solutions are stable at room temperature (25°C) for 24 hours, at concentrations between 10 mg/mL and 40 mg/mL: Sodium Lactate (PVC container), 10% Invert Sugar (glass container), 5% Sodium Bicarbonate (glass container), 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).

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

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

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

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

## 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 gritty sediment in dogs that received 100 mg/kg/day for 4 weeks. A similar phenomenon has been observed in baboons but only after a protracted dosing period (6 months) at higher dose levels (335 mg/kg/day or more). The likelihood of this occurrence in humans is considered to be low, since ceftriaxone has a greater plasma half-life in humans, the calcium salt of ceftriaxone is more soluble in human gallbladder bile and the calcium content of human gallbladder bile is relatively low.

## HOW SUPPLIED

Ceftriaxone for Injection, USP in Pharmacy Bulk Package is supplied as a sterile crystalline powder in glass bottles containing ceftriaxone sodium equivalent to 10g ceftriaxone. Box of 1 (NDC 76126-007-

10)

NOTE: Ceftriaxone for Injection, USP sterile powder should be stored at 20° to 25°C (68° to 77°F)[See USP Controlled Room Temperature], and protected from light.

## CLINICAL STUDIES

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

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		Ceftriaxone is lower than control at study day 14 and 28.
14	74% (220/296)	82% (247/302)	(-14.4%, -0.5%)	
28	58% (167/288)	67% (200/297)	(-17.5%, -1.2%)	
Study 2–U.S. <sup>7</sup>		TMP-SMZ		Ceftriaxone is equivalent to control at study day 14 and 28.
14	54% (113/210)	60% (124/206)	(-16.4%, 3.6%)	
28	35% (73/206)	45% (93/205)	(-19.9%, 0.0%)	

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

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

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

## REFERENCES

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4. Burgess DS, Frei CR, Lewis II JS, et al. The contribution of pharmacokinetic-pharmacodynamic modeling with Monte Carlo simulation to the development of susceptibility breakpoints for *Neisseria*

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5. Jorgensen JH, Crawford SA, Fulcher LC, et al. Multilaboratory evaluation of disk diffusion antimicrobial susceptibility testing of *Neisseria meningitidis* isolates. J Clin Microbiol. 2006;44(5):1744-1754.
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7. 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.

**Manufactured by:**

Agila Specialties Private Limited

Bangalore –560076, India

Revised: 09-2012

**PACKAGE LABEL.PRINCIPAL DISPLAY PANEL**

<p style="text-align: center;">NDC 76126-007-10</p> <p style="text-align: center;"><b>Ceftriaxone for Injection, USP</b></p> <div style="border: 1px solid red; padding: 2px; text-align: center; color: red; font-weight: bold;">             PHARMACY BULK PACKAGE NOT FOR DIRECT INFUSION         </div> <div style="background-color: red; color: white; padding: 5px; text-align: center; font-weight: bold; margin: 5px 0;"> <b>10 grams</b> per Pharmacy Bulk Package         </div> <p style="text-align: center; font-weight: bold;">For Intravenous Use</p> <p style="text-align: center;">℞ only</p> <p style="text-align: center; color: red; font-weight: bold;">NOT TO BE DISPENSED AS A UNIT</p> <p style="text-align: center;">1x10g Pharmacy Bulk Package</p> <p style="text-align: center; font-size: 1.5em; font-weight: bold;">agila</p>	<p>Each Pharmacy Bulk Package contains sterile ceftriaxone sodium equivalent to 10 grams of ceftriaxone. The sodium content is approximately 83 mg (3.6 mEq) per gram of ceftriaxone activity.</p> <p><b>Dosage and administration:</b> See package insert for dosage, administration and proper use of the Pharmacy Bulk Package. Reconstitute with 95 mL of a suitable diluent as listed in the package insert. Each 1 mL of solution contains approximately 100 mg equivalent of ceftriaxone.</p> <p>This Pharmacy Bulk Package is intended for use in a Pharmacy Admixture Service. Utilizing a sterile transfer device penetrate container (PBP) one time only under a laminar flow hood. Transfer individual doses to appropriate intravenous infusion solutions. Use of a syringe with needle is not recommended. ONCE THE CONTAINER CLOSURE HAS BEEN PUNCTURED WITHDRAWAL OF THE CONTAINER CONTENTS SHOULD BE COMPLETED WITHOUT DELAY. DISCARD THE CONTENTS NO LATER THAN <b>4 HOURS</b> AFTER INITIAL CLOSURE PUNCTURE. FURTHER DILUTION IS REQUIRED BEFORE USE.</p>	<p style="text-align: center;">NDC 76126-007-10</p> <p style="text-align: center;"><b>Ceftriaxone for Injection, USP</b></p> <div style="border: 1px solid red; padding: 2px; text-align: center; color: red; font-weight: bold;">             PHARMACY BULK PACKAGE NOT FOR DIRECT INFUSION         </div> <div style="background-color: red; color: white; padding: 5px; text-align: center; font-weight: bold; margin: 5px 0;"> <b>10 grams</b> per Pharmacy Bulk Package         </div> <p style="text-align: center; font-weight: bold;">For Intravenous Use</p> <p style="text-align: center;">℞ only</p> <p style="text-align: center; color: red; font-weight: bold;">NOT TO BE DISPENSED AS A UNIT</p> <p style="text-align: center;">1x10g Pharmacy Bulk Package</p> <p style="text-align: center; font-size: 1.5em; font-weight: bold;">agila</p>	<div style="border: 1px solid black; padding: 5px; text-align: center; font-weight: bold; margin-bottom: 10px;">             RECONSTITUTED BULK SOLUTION SHOULD NOT BE USED FOR DIRECT INFUSION         </div> <p><b>Storage Prior to Reconstitution:</b> Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].</p> <p><b>Protect from light.</b></p> <p><b>Storage After Reconstitution:</b> See package insert.</p> <p>Date Entered.....</p> <p>Time of Entry.....</p> <p><b>Manufactured by:</b> <b>Agila Specialties Pvt. Ltd.</b> Bangalore, India.</p> <p>Code: KR/DRUGS/KTK/28/384/2009 Revision: 08/12</p> <div style="text-align: center;">  <p style="font-size: 0.8em;">N 3 7 6 1 2 6 1 0 0 7 1 0 1 1</p> </div>
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**carton-label-10g**

<b>CEFTRIAXONE</b>			
ceftriaxone sodium injection, powder, for solution			
<b>Product Information</b>			
<b>Product Type</b>	HUMAN PRESCRIPTION DRUG LABEL	<b>Item Code (Source)</b>	NDC:76 126-007
<b>Route of Administration</b>	INTRAVENOUS	<b>DEA Schedule</b>	
<b>Active Ingredient/Active Moiety</b>			

Ingredient Name	Basis of Strength	Strength
CEFTRIAZONE SODIUM (CEFTRIAZONE)	CEFTRIAZONE	10 g in 100 mL

### Product Characteristics

Color	WHITE (White or Yellowish)	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:76126-007-10	1 in 1 CARTON		
1		100 mL in 1 VIAL, PHARMACY BULK PACKAGE		

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091068	01/07/2013	

**Labeler** - AGILA SPECIALTIES PRIVATE LIMITED (650548014)

**Registrant** - AGILA SPECIALTIES PRIVATE LIMITED (650548014)

Revised: 1/2013

AGILA SPECIALTIES PRIVATE LIMITED