CEFTRIAXONE

DESCRIPTION:
Ceftriaxone for Injection, USP is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceftriaxone sodium is (6R,7R)-7-(2-Amino-4-thiazolyl)glu- 

Glu

OH

N

3-NH2

C6H5

2-NH2

H

N

OH

O

N

OH

H

M.W. 661.59

C6H13N6O6S2·3.5HO

glyoxylylamido)-8-oxo-3-[[1,2,5,6-tetrahydro-2- 
methyl-5,6-dideoxycyclohexa-3,5-dienyl]-5-thia-1- 
azacyclol[4.2.0]oct-2-en-2-carboxylic acid, \( \text{O} \) (0-methylxoyde), disodium salt, sesquihydrate.

The structural formula of ceftriaxone sodium is:

\[ \text{C}_{6}\text{H}_{13}\text{N}_{6}\text{O}_{6}\text{S}_{2}\cdot3.5\text{HO} \]

Ceftriaxone for injection 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 solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluted. Each Pharmacy Bulk Package is supplied by a dry powder in vials containing sterile ceftriaxone sodium equivalent to 10 grams of ceftriaxone and is intended for intravenous infusion only. Ceftriaxone for injection contains approximately 63 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 administration 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 gm dose and intramuscular (IM) administration of a single 0.5 (250 mg/mL) or 360 mg/mL concentrations) or 1 gm dose in healthy subjects are presented in Table 1.

| Table 1: Ceftriaxone Plasma Concentrations After Single Dose Administration |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Dose (Route)    | AUC (mg·h/mL)   | Cmax (mg/mL)    | t1/2 (h)        | A2 (mg·h/mL)   |
| 0.5 gm IV       | 1067            | 7.5             | 1.0             | 16.7           |
| 1 gm IV         | 1530            | 11.6            | 1.1             | 26.0           |
| 2 gm IV         | 2884            | 18.4            | 1.1             | 48.0           |

* Over a 0.15 to 3 gm dose range in healthy adult subjects, the values of maximum plasma concentrations ranged from 4 to 10 mg/mL. Over a 0.15 to 3 gm dose range in healthy adult subjects, 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 are also shown in Table 3.

TABLE 2: Urinary Concentrations of Ceftriaxone After Single Dose Administration

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TABLE 3: Average Pharmacokinetic Parameters of Ceftriaxone in Pediatric Patients with Meningitis

<table>
<thead>
<tr>
<th>Route</th>
<th>AUC (mg·h/mL)</th>
<th>Cmax (mg/mL)</th>
<th>t1/2 (h)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>1530</td>
<td>11.6</td>
<td>1.1</td>
<td>26.0</td>
</tr>
<tr>
<td>IM</td>
<td>1530</td>
<td>11.6</td>
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Compared to that in healthy adult subjects, the pharmacokinetics of ceftriaxone were only minimally altered in elderly subjects and in patients with renal impairment or hepatic dysfunction (Table 4); therefore, dosage adjustments are not necessary for these patients with ceftriaxone dosages up to 2 gm per day.

Ceftriaxone was not removed to any significant value from the plasma by hemodialysis. In six of 26 dialysis patients, the elimination rate of ceftriaxone was markedly reduced.

| Table 4: Average Pharmacokinetic Parameters of Ceftriaxone in Humans |
|-----------------|-----------------|-----------------|-----------------|
| Subject Group   | AUC (mg·h/mL)   | Cmax (mg/mL)    | t1/2 (h)        |
| Healthy Adults   | 1530            | 11.6            | 1.1             |
| Elderly Subjects| 1530            | 11.6            | 1.1             |
| Patients with Renal Impairment| 1530 | 11.6            | 1.1             |

*Creatine clearance

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

Pharmacokinetics in the Middle Ear Fluid
In one study, the 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. Sample 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 2 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 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
The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone has a high affinity for penicillin-binding proteins. Ceftriaxone has a known mechanism of action that involves the reversible binding of ceftriaxone to cell wall synthesis enzymes. The antibiotic causes a rapid and irreversible inhibition of cell wall synthesis. Ceftriaxone is bactericidal due to susceptible organisms throughout the course of therapy.

Aerobic gram-negative microorganisms:
- Acinetobacter calcoaceticus
- Enterobacter aerogenes
- Enterobacter cloaceae
- Escherichia coli
- Hafnia alvei
- Klebsiella pneumonia
- Moraxella catarrhalis

Aerobic gram-positive microorganisms:
- Staphylococcus aureus
- Streptococcus pneumoniae

Anaerobic microorganisms:
- Bifidobacterium
- Enterococcus faecalis
- Haemophilus aegyptius
- Neisseria gonorrhoeae
- Neisseria meningitidis
- Pasteurella mirabilis
- Proteus vulgaris

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ceftriaxone and other antibacterial drugs, ceftriaxone should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.
strains of Group D streptococci and enterococci, e.g., Enterococcus faecalis, are resistant.  

Antimicrobial Activities:  
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 a broad spectrum of activity against Gram-positive and Gram-negative 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.  

Aerobug gram-negative microorganisms:  
Citrobacter freundii  
Providencia species (including Providencia rettgeri)  
Serratia species (including Salmomella typhi)  
Shigella species  

Aerobic gram-positive microorganisms:  
Staphylococcus epidermidis  
Staphylococcus pneumoniae  
Propionibacterium acnes  
Proteus vulgaris  
Proteus mirabilis  

Anaerobic microorganisms:  
Prevotella (Bacteroides) distasonis  
Prevotella (Bacteroides) melaninigenicus  

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; such procedures are described in CLSI standards.  

The MICs of ceftriaxone for inoculum concentrations of 0.5, 1, 2, or 4 mg/mL should be interpreted according to the following criteria:  

**Susceptible (S)**: An inoculum with an MIC ≤0.06 mg/mL for ceftazidime.  
**Intermediate (I)**: An inoculum with an MIC of 0.12 to 0.5 mg/mL for ceftazidime.  
**Resistant (R)**: An inoculum with an MIC >0.5 mg/mL for ceftazidime.  

For ceftazidime, the MICs are interpreted against the following organisms:  

<table>
<thead>
<tr>
<th>Organism</th>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>≤24</td>
<td>(S) Susceptible</td>
</tr>
<tr>
<td>S. aureus</td>
<td>25 to 26</td>
<td>(I) Intermediate</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>27 to 28</td>
<td>(S) Susceptible</td>
</tr>
</tbody>
</table>

Ceftriaxone for injection has also been used successfully for intravenous infusion only. Ceftriaxone for injection provides protection from most infections including both penicillinase- and non-penicillinase-producing strains of Staphylococcus aureus, Streptococcus faecalis, and Penicillinase-producing strains of Neisseria gonorrhoeae.  

Pulmonary Inflammatory Disease—Chlamydia pneumoniae. Ceftriaxone for injection, like other cephalosporins, has no activity against Chlamydia trachomatis. Therefore, when ceftriaxone is used in the treatment of patients with pelvic inflammatory disease and Chlamydia infection, the presence of the suspected pathogens, appropriate antichlamydial therapy should be added.  

Bacterial Septicemia caused by Streptococcus agalactiae, Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae or Neisseria meningitidis.  

Bone and Joint Infections caused by Staphylococcus aureus, Streptococcus agalactiae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae or Pseudomonas aeruginosa.  

Intra-Abdominal Infections caused by Escherichia coli, Klebsiella pneumoniae, Bacteroides fragilis, Clostridium perfringens, other Clostridium difficile are resistant) or Pseudomonas aeruginosa species.  

Meningitis caused by Haemophilus influenzae, Neisseria meningitidis or Streptococcus pneumoniae. Ceftriaxone for injection has demonstrated excellent clinical efficacy in vivo 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 clinical trials and the results are not representative.**  

Surgical Prophylaxis: The preoperative administration of a single 1 gm dose of ceftriaxone for injection may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated, i.e., vaginal or abdominal hysterectomy or cholecystectomy, intraperitoneal or transperitoneal cholecystectomy, pelvic inflammatory disease, and cesarean section.  

For the prevention of infection following coronary artery bypass surgery. Although ceftriaxone for injection does not consistently provide effective prophylaxis, it is as effective as cefazolin in the prevention of infection following coronary artery bypass surgery. Well-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery.  

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

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

Neonates (≤ 28 days)  
Hyperbilirubinemic neonates, especially premature, should not be treated with ceftriaxone. In vitro studies have shown that ceftriaxone and other cephalosporins do not have its binding to serum albumin, leading to a possible risk of bilirubin encephalopathy in these neonates.  

Ceftriaxone is contraindicated in neonates if there are signs (or are expected to develop) of calcium-containing IV solutions, including continuous calcium-containing infusions such as enteral nutrition solutions, to prevent precipitation of ceftriaxone-calcium (see CLINICAL PHARMACOLOGY: WARNINGS, PRECAUTIONS, ADMINISTRATION).  

Ceftriaxone is not routinely used in neonates if there are signs (or are expected to develop) of calcium-containing IV solutions, including continuous calcium-containing infusions such as enteral nutrition solutions, to prevent precipitation of ceftriaxone-calcium (see CLINICAL PHARMACOLOGY: WARNINGS, PRECAUTIONS, ADMINISTRATION).  

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

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cephalosporins and other antibacterial drugs, ceftriaxone 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 caused by susceptible organisms:  


URINARY TRACT INFECTIONS caused by Escherichia coli (uncomplicated) is contraindicated in patients with a known allergy to cephalosporin class of antibiotics.  

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 with a single dose of ceftriaxone for injection and the comparator. Therefore, no potentially lower clinical cure rates for injection should be balanced against the potential advantages of parenteral therapy (see CLINICAL STUDIES).  

HHPEs are 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. Prolapse was reported in <1% after IV administration. The incidence of warmth, tightness or induration was 7% (3/47) after IM administration of 250 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 (8%), thrombocytopenia (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 dyspepsia. The onset of pseudomembranous colitis may occur during or after antibiotic treatment (see WARNINGS).

Hepatic – elevations of GGT (>1.5) or SGPT (3.3). Less frequently reported (<1%) were elevations of alkaline phosphatase and bilirubin.

Renal – elevations of 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 was reported occasionally (<1%).

Genitourinary – miosis 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, anaphylactoid reaction, anaphylaxis, anti-thyroid antibodies, asthenia, altitude sickness, allergic reactions, drug fever, serum sickness-like reactions, anemia, aplastic anemia, blood dyscrasias, bruising, cholestatic jaundice, cholestasis, convulsions, cyanosis, deep vein thrombosis, dermatitis, desquamation, dizziness, dysmenorrhea, ecchymosis, edema, edema of face and eyelids, epistaxis, fever, gingivitis, hemorrhage, hyperglycemia, hyperkalemia, hyperuricemia, hypoglycemia, hypoventilation, interstitial nephritis, jaundice, leukocytosis, lymphocytosis, monocyteosis, myocardiitis, nephrotic syndrome, nephrosis, neuropathy, pharyngitis, pruritus, prostatitis, ptosis, pyrexia, Raynaud's phenomenon, respiratory distress, rashes, retroperitoneal fibrosis, skin necrosis, stomach pain, substernal pain, syncope, tetany, toxic psychosis, tachycardia, transfusion reactions, urticaria, urticarial rash, vasculitis, vertigo, vomiting.

Pregnancy and Labor 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 for infection. Data are generally insufficient to allow an estimate of the likelihood of these reactions in patients treated with this drug. They are included to alert health-care professionals to the possibility of their occurrence.

A small number of cases of fetal 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 one fetal death has been reported in a neonate born cephalically, several calcium-containing fluids were administered at different times. A crystalline material was observed in the neonate's lung line 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, urti- caria and edema. As with many other cephalosporin-related cases of severe cutaneous adverse reactions (erythema multiforme, Stevens-Johnson syndrome or Lyell's disease) an epidemic necrolysis have been reported.

Cephalosporin Class Adverse Reactions

In addition to the adverse reactions listed above which have been observed in patients treated with ceftri-axon, the following adverse reactions to cephalosporins in 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, hyperopia, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage, and superinfection.

Alternative Diagnostic 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 increased (see DOSAGE AND ADMINISTRATION). If seizures associate with the administration of ceftriaxone, the drug should be discontinued. Anticonvulsant therapy can be given, if clinically indicated.

OVERDOSAGE

In the case of overdose, drug concentration would not be reduced by hemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdosage should be symptomatic.
DOSE AND ADMINISTRATION: Ceftriaxone for Injection, USP may be administered intramuscularly, subcutaneously, or intravenously. However, the content of this pharmacy bulk package is for the preparation of solutions for intravenous injection only. Ceftriaxone for Injection, USP should be administered intravenously in the following solutions in the same IV administration line. Ceftriaxone for injection 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 for intravenous administration containing sodium chloride may be administered sequentially one of 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 calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (IV or oral).

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

Ceftriaxone for injection is contraindicated in neonates if they are (or are expected to be) treated 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 structure infections, the recommended total daily dose is 50 to 75 mg/kg/day (in divided doses every 12 hours). The usual duration of therapy is 7 to 14 days.

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

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

For preoperative use (surgical prophylaxis), a single dose of ceftriaxone sodium should be given prior to 1 to 2 hours before surgery is recommended.

Generally, Ceftriaxone for Injection, USP therapy should be given for at least 2 days after the signs and symptoms of infection have disappeared. The usual daily dose is 1 gram. For infections involving more virulent organisms or those occurring in debilitated hosts, the total daily dose should be increased. Longer therapy may be required. In compromised situations 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 PACK
The 10 gram vial 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. This closure may be left on the vial for only one time after reconstitution, using a suitable sterile transfer device or dispensing set with a stopcock and containing a sufficient volume (a sterile substance which must be reconstituted prior to use may require a separate closure entry). Use of this procedure to transfer solutions to alternate suitable work areas is a laminar flow hood.

The withdrawal of container contents should be accomplished without delay. However, should this not be the case, 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.

Transfer of solutions held longer than the recommended period times should be discarded.

Reconstituted Bulk Solutions Should Not Be Used for Direct Infusion.

Transfer individual dose to appropriate intravenous solutions in a suitable diluent using a transfer device or dispensing set with a stopcock. Use of equipment containing the correct volume (a sterile substance which must be reconstituted prior to use may require a separate closure entry). Use of this procedure to transfer solutions to alternate suitable work areas is a laminar flow hood.

The withdrawal of container contents should be accomplished without delay. However, should this not be the case, 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.

Transfer of solutions held longer than the recommended period times should be discarded.

COMPATIBILITY AND STABILITY: Ceftriaxone has been shown to be compatible with Flagyl® IV (metronidazole hydrochloride). The concentration should not exceed 5 to 7.5 mg/mL metronidazole hydrochloride with ceftriaxone 10 mg/mL as an admixture. Solutions not used within 48 hours at room temperature only in 0.9% sodium chloride injection or 5% dextrose in water (DDW). No compatibilities studies have been conducted with the Flagyl® IV (metronidazole) formulation or using other diluents. Metronidazole at concentrations greater than 8 mg/mL will precipitate. Do not refilter the admixture as precipitation will occur.

Registered trademark of G.D. Searle & Co. Vancomycin, gentamicin, amphotericin B, and fluconazole are physically incompatible with ceftriaxone in admixture. When any of these drugs are to be administered concurrently 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 vials to further dilute a reconstituted vial for IV administration because calcium precipitation of ceftriaxone-calcium can also occur when ceftriaxone is administered using these solutions in the same IV administration line. Ceftriaxone for injection 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 for intravenous administration containing calcium chloride may be administered sequentially one of another if the infusion lines are thoroughly flushed between infusions with a compatible fluid (see WARNINGS).

Clinical Efficiency in Evaluation Population

Clinical Study: Ceftriaxone for Injection, USP sterile powder should be stored at 20 to 25°C (68° to 77°F) [see USES Controlled Room Temperature], and protected from light. Frozen Ceftriaxone for Injection, USP should be stored at or below -20°C (-4°F).

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

Critical Care

<table>
<thead>
<tr>
<th>Study</th>
<th>Ceftriaxone</th>
<th>Oral Therapy</th>
<th>Statistical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>74%</td>
<td>70%</td>
<td>1.14 (0.66 - 2.05)</td>
</tr>
<tr>
<td>28</td>
<td>70%</td>
<td>67%</td>
<td>1.05 (0.65 - 1.77)</td>
</tr>
<tr>
<td>35</td>
<td>76%</td>
<td>73%</td>
<td>1.04 (0.65 - 1.68)</td>
</tr>
<tr>
<td>54%</td>
<td>50%</td>
<td>46%</td>
<td>1.10 (0.68 - 1.77)</td>
</tr>
<tr>
<td>28</td>
<td>72%</td>
<td>68%</td>
<td>1.05 (0.65 - 1.68)</td>
</tr>
<tr>
<td>35</td>
<td>76%</td>
<td>73%</td>
<td>1.04 (0.65 - 1.68)</td>
</tr>
</tbody>
</table>

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 follow: WBC and ESR and Fever and Erythema Necrosis Rates in the Per Protocol Analysis in the Roche Bacteriologic Study by pathogen:

**REFERENCES:**

**ANIMAL PHARMACOLOGY:**
Concrections consisting of the precipitated calcium salt of ceftriaxone have been found in the gallbladder bile of dogs and bunnies treated with ceftriaxone. These appeared as a gritty sediment in dogs that received 100 mg/kg/day for 4 weeks. A similar phe- nomenon has been observed in bunnies but only after a protracted dosing period (30 weeks) at higher dose levels (335 mg/kg/day or more). The likelihood of this occurrence in humans appears to be low, since ceftriaxone has a greater plasma half-life in humans, the calcium content 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 a Pharmacy Bulk Package. NOTES FOR DIRECT ADMINISTRATION, containing 10 gram equivalent of ceftriaxone is available as:

**PRODUCT NDC**

<table>
<thead>
<tr>
<th>strength</th>
<th>304410</th>
<th>304310</th>
<th>304320</th>
</tr>
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<tbody>
<tr>
<td>250 mg</td>
<td>100 mL</td>
<td>100 mL</td>
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<tr>
<td>500 mg</td>
<td>100 mL</td>
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<tr>
<td>1 g</td>
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<tr>
<td>2 g</td>
<td>100 mL</td>
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Vial stoppers do not contain natural rubber latex.

Ceftriaxone for Injection, USP is also supplied as a sterile crystalline powder in glass vials:

**Product NDC**

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<tr>
<td>2 g</td>
<td>10 mL</td>
<td>10 mL</td>
<td>10 mL</td>
</tr>
</tbody>
</table>

**NOTE:** Ceftriaxone for Injection, USP sterile powder should be stored at 20 to 25°C (68° to 77°F) [see USES Controlled Room Temperature], and protected from light. Frozen Ceftriaxone for Injection, USP should be stored at or below -20°C (-4°F).