PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr cefTRIAXone Sodium for Injection BP

Sterile Powder for Solution, 250 mg, 500 mg, 1 g, 2 g and 10 g ceftriaxone (as ceftriaxone sodium) per vial

Intravenous or Intramuscular

BP

Antibiotic

SteriMax Inc.
2770 Portland Drive,
Oakville, ON
L6H 6R4

Control No. 282633

Date of Initial Authorization:
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RECENT MAJOR LABEL CHANGES
Not Applicable.

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Section or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Ceftriaxone Sodium for Injection BP is indicated for the treatment of the following infections when caused by susceptible strains of the designated micro- organisms:

- Lower Respiratory tract infections caused by *E. coli*, *H. influenzae*, *K. pneumoniae* and species, *Staph. aureus*, *Strep. pneumoniae* and species (excluding enterococci).

- Urinary tract infections (complicated and uncomplicated) caused by *E. coli*, Klebsiella species,
  P. mirabilis and *P. vulgaris*.

- Bacterial Septicemia caused by *E. coli*, *H. influenzae*, *K. pneumoniae*, *Staph. aureus* and *Strep. pneumoniae*, (excluding enterococci).

- Skin and Skin Structure Infections caused by *K. pneumoniae* and species, *P. mirabilis*, *Staph. aureus*, *Staph. epidermidis* and *Streptococcus* species (excluding enterococci).

- Bone and Joint Infections caused by *Staph. aureus*, *Strep. pneumoniae* and *Streptococcus* species (excluding enterococci).

- Intra-Abdominal Infections caused by *E.coli* and *K. pneumoniae*.

- Meningitis caused by *H. influenzae*, *N. meningitidis*, and *Strep. pneumoniae*. Ceftriaxone sodium should not be used for the treatment of meningitis caused by *L. monocytogenes*.
- Uncomplicated Gonorrhea (cervical/urethral, pharyngeal and rectal) caused by *N. gonorrhoeae* (penicillinase and nonpenicillinase producing strains).

Susceptibility Testing: Specimens for bacteriologic culture should be obtained prior to therapy in order to identify the causative organisms and to determine their susceptibilities to ceftriaxone.

Therapy may be instituted before results of susceptibility testing are known. However, modification of the treatment may be required once these results become available.

Prophylaxis: The preoperative administration of a single 1 g dose of ceftriaxone sodium may reduce the incidence of postoperative infections in patients undergoing vaginal or abdominal hysterectomy, coronary artery bypass surgery, or in patients at risk of infection undergoing biliary tract surgery. If signs of post surgical infection should appear, specimens for culture should be obtained for identification of the causative organism(s) so that the appropriate therapy may be instituted.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ceftriaxone Sodium for Injection BP and other antibacterial drugs, Ceftriaxone Sodium for Injection BP should be used only to treat 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.

1.1 Pediatrics

Pediatrics (One Month to 12 Years of Age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Ceftriaxone Sodium for Injection BP in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use [see **DOSAGE AND ADMINISTRATION**].

1.2 Geriatrics

Geriatrics: There is no known evidence to suggest that use in the geriatric population is associated with differences in safety or effectiveness.

2 CONTRAINDICATIONS

Ceftriaxone Sodium for Injection BP is contraindicated in:

- Patients with known hypersensitivity to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container, other cephalosporins, or penicillins (see **WARNINGS AND PRECAUTIONS**). For a complete listing, see **6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

- Hyperbilirubinemic neonates and preterm neonates should not be treated with ceftriaxone. *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 (see **WARNINGS AND PRECAUTIONS**).

- neonates (≤ 28 days old) 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 **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS**, **DOSAGE AND ADMINISTRATION**, **PHARMACEUTICAL INFORMATION**, and **CLINICAL PHARMACOLOGY**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Ceftriaxone Sodium for Injection BP (ceftriaxone sodium) may be administered intravenously or intramuscularly after reconstitution.

Dosage and route of administration should be determined by the severity of infection, susceptibility of the causative organisms, and condition of the patient. The intravenous route is preferable for patients with septicemia or other severe or life-threatening infections.

4.2 Recommended Dose and Dosage Adjustment

Adults

<table>
<tr><th>Type of Infection</th><th>Route</th><th>Dose</th><th>Frequency</th><th>Total Daily Dose</th></tr>
<tr><td rowspan="2">Moderate and Severe Infections</td><td rowspan="2">I.V.
or
I.M.</td><td>1 or 2 g</td><td>q24h</td><td>1 or 2 g</td></tr>
<tr><td>0.5 or 1 g</td><td>q12h</td><td>1 or 2 g</td></tr>
<tr><td colspan="5">There is limited experience with daily doses of 3-4 g administered as a single dose or two equallydivided doses. The total daily dose should not exceed 4 g.</td></tr>
<tr><td>Uncomplicated Gonorrhea</td><td>I.M.</td><td>250 mg</td><td>Single dose</td><td>-</td></tr>
</table>

Infants and Children (One Month to 12 Years of Age)

<table>
<tr><th>Type of Infection</th><th>Route</th><th>Dose</th><th>Frequency</th><th>Total Daily Dose</th></tr>
<tr><td>Serious Miscellaneous Infections</td><td>I.V.
or
I.M.</td><td>25 or
37.5 mg/kg</td><td>q12h</td><td>50 or
75 mg/kg</td></tr>
<tr><td colspan="5">The total daily dose should not exceed 2 g. If body weight is 50 kg or more the adult dose should be used.</td></tr>
<tr><td>Meningitis</td><td>I.V.
or
I.M.</td><td>50 mg/kg*</td><td>q12h</td><td>100 mg/kg</td></tr>
<tr><td colspan="5">With or without a loading dose of 75 mg/kg.
The total daily dose should not exceed 4 g.</td></tr>
</table>

With the exception of gonorrhea, which is treated with a single dose, the administration of Ceftriaxone Sodium for Injection BP (ceftriaxone sodium) should be continued for a minimum of 48 to 72 hours after the patient defervesces or after evidence of bacterial eradication has been obtained, usually 4 to 14 days. In bone and joint infections the average duration of treatment during clinical trials was 6 weeks, with a range of 1 to 13 weeks, depending on the severity of the infection.

When treating infections caused by beta hemolytic streptococcus, it is recommended that therapy be continued for at least 10 days. The average duration of therapy for infections associated with beta hemolytic streptococcus during clinical trials was 2 weeks, with a range of 1 to 5 weeks, depending on the site and severity of the infection.

Prophylaxis (Vaginal or Abdominal Hysterectomy, Coronary Artery Bypass Surgery, Biliary Tract Surgery): For preoperative use as prophylaxis before vaginal or abdominal hysterectomy, coronary artery bypass surgery, or biliary tract surgery in patients at risk of infection, a single dose of 1 g administered 1/2 to 2 hours before surgery is recommended.

Impairment of Renal and/or Hepatic Function: In patients with mild to moderate renal impairment, changes in the dosage regimen are not required, provided liver function is not impaired. In cases of preterminal renal failure (creatinine clearance less than 10 mL/min), periodic monitoring of serum ceftriaxone concentrations is recommended. The daily dosage should be limited to 2 g or less. In patients with liver damage, there is no need for the dosage to be reduced provided renal function is not impaired. In cases of coexistent renal and clinically significant hepatic insufficiency, close monitoring of serum ceftriaxone concentrations, at regular intervals, is recommended. If there is evidence of accumulation, dosage should be decreased accordingly.

4.3 Reconstitution

For Intramuscular Use

Reconstitute Ceftriaxone Sodium for Injection BP powder with the appropriate diluent:

- Sterile Water for Injection
- 0.9% Sodium Chloride Injection
- 5% Dextrose Injection
- Bacteriostatic Water for Injection
- 1% Lidocaine Solution

Reconstitute as follows:

Regular Volume Reconstitution Table (I.M.)

Vial Size	Volume of Diluent to be Added to Vial (mL)	Approximate Available Volume (mL)	Approximate Average Concentration (g/mL)
250 mg	0.9	1.0	0.25
500 mg	1.8	2.0	0.25

Vial Size	Volume of Diluent to be Added to Vial (mL)	Approximate Available Volume (mL)	Approximate Average Concentration (g/mL)
1.0 g 2.0 g	3.3 6.6	4.0 8.0	0.25 0.25

Shake well until dissolved.

Low Volume Reconstitution Table (I.M.)

Vial Size	Volume of Diluent to be Added to Vial (mL)	Approximate Available Volume (mL)	Approximate Average Concentration (g/mL)
250 mg 500 mg	Not recommended for this vial size		
1.0 g 2.0 g	2.2 4.4	2.8 5.6	0.35 0.35

Shake well until dissolved.

NOTE: SOLUTIONS PREPARED FOR INTRAMUSCULAR USE OR ANY SOLUTION CONTAINING LIDOCAINE OR BACTERIOSTATIC WATER FOR INJECTION SHOULD NEVER BE ADMINISTERED INTRAVENOUSLY.

For Intravenous Use

- Reconstitute only with Sterile Water for Injection
- Reconstitute as follows:

Reconstitution Table (I.V.)

Vial Size	Volume to be Added to Vial (mL)	Approximate Available Volume (mL)	Approximate Average Concentration (g/mL)
250 mg 500 mg 1.0 g 2.0 g	2.4 4.8 9.6 19.2	2.5 5.0 10.1 20.5	0.1 0.1 0.1 0.1

Shake well until dissolved. The prepared solution may be further diluted to the desired volume

with any of the “Solutions for I.V. Infusion” listed below.

Solutions for I.V. Infusion

- 0.9% Sodium Chloride Injection
- 5% Dextrose Injection
- Dextrose and Sodium Chloride Injection

Pharmacy Bulk Vial Reconstitution for Preparation of Intravenous Infusion Solutions

The closure of the pharmacy bulk vial shall be penetrated only one time after reconstitution, using a suitable sterile transfer device or dispensing set which allows measured dispensing for the contents.

Reconstituted Table for Bulk Pharmacy Vial

Vial Size	Volume of Diluent to be Added to Vial (mL)	Approximate Available Volume (mL)	Nominal Concentration per mL (g/mL)
10 g	95	101	0.1

Shake well until dissolved. Withdraw the required amount and dilute with one of the “Solutions for I.V. Infusion”. Any unused solution remaining within a period of 8 hours should be discarded.

4.4 Administration

Intramuscular: The reconstituted solution of Ceftriaxone Sodium for Injection BP (ceftriaxone sodium) should be administered by deep intragluteal injection. It is recommended that not more than 1 g be injected at a single site. Pain on intramuscular injection is usually mild and less frequent when Ceftriaxone Sodium for Injection BP is administered in sterile 1% Lidocaine solution.

Intravenous (bolus) Injection: The reconstituted solution should be administered over approximately 5 minutes. If the distal port of an intravenous administration set is used, stop the primary flow, inject the reconstituted Ceftriaxone Sodium for Injection BP solution and then restart the primary flow. This will prevent mixing with the primary fluid and possible incompatibilities.

Short Intravenous Infusion: The further diluted intravenous solution should be given over a period of 10 to 15 minutes in infants and children and 20 to 30 minutes in adults.

NOTE: Ceftriaxone Sodium for Injection BP solution should not be physically mixed with

aminoglycoside antibiotics nor administered at the same site because of possible chemical incompatibility. There have also been literature reports of physical incompatibilities between ceftriaxone and vancomycin, amsacrine, orfluconazole.

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

5 OVERDOSAGE

- Ultrasonographic shadows suggesting precipitation in the kidneys accompanied by calcium ceftriaxone precipitate in the urine was observed in one patient dosed with ceftriaxone sodium at 10 g/day (2.5 times the maximum recommended dose). No other cases of overdosage has been reported to date with ceftriaxone sodium.
- No specific information on symptoms or treatment is available.
- Excessive serum concentration of ceftriaxone cannot be reduced by hemodialysis or peritoneal dialysis. Treatment should be symptomatic.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intravenous or intramuscular	Sterile powder for solution, 250 mg, 500 mg, 1 g, 2 g and 10 g ceftriaxone per vial	None.

Ceftriaxone Sodium for Injection BP vials containing sterile ceftriaxone sodium powder

equivalent to 250 mg, 500 mg, 1 g, and 2 g ceftriaxone. The 250 mg size is available in 10 mL and 15 mL glass vials, the 500 mg size is available in 15 mL glass vials, the 1 g size in 15 mL, 20 mL, and 50 mL glass vials, and the 2 g size in 20 mL and 50 mL glass vials.

Ceftriaxone Sodium for Injection BP Pharmacy Bulk vials containing sterile powder equivalent to 10 g ceftriaxone (not for direct administration). The 10 g size is available in 100 mL glass vial. The availability of the pharmacy bulk vial is restricted to hospitals with a recognized intravenous admixture programme.

All Ceftriaxone Sodium for Injection BP vials are available in cartons containing either 1 vial or 10 vials. The stopper is not made with natural rubber latex.

7 WARNINGS AND PRECAUTIONS

General

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCAR) such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported in association with beta-lactam treatment. When SCAR is suspected, Ceftriaxone Sodium for Injection BP should be discontinued and appropriate therapy and/or measures should be taken.

Clostridium Difficile-Associated Disease

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including ceftriaxone. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be

given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see **ADVERSE REACTIONS**).

Hypersensitivity

Before therapy with Ceftriaxone Sodium for Injection BP (ceftriaxone sodium) is instituted, careful inquiry should be made concerning previous hypersensitivity reactions to ceftriaxone, other cephalosporins, penicillins or other allergens. Ceftriaxone Sodium for Injection BP should only be administered with caution to any patient who has demonstrated any form of allergy particularly to drugs. 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. Ceftriaxone Sodium for Injection BP should be administered with caution to patients with type I hypersensitivity reaction to penicillin. Cross-hypersensitivity among β-lactam antibiotics have been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction occurs, the administration of Ceftriaxone Sodium for Injection BP should be discontinued and appropriate therapy instituted (see CONTRAINDICATIONS and ADVERSE REACTIONS).

Hematologic

Hemolytic Anemia

CEFTRIAXONE SODIUM FOR INJECTION BP SHOULD NOT BE USED IN PATIENTS WITH A HISTORY OF CEPHALOSPORIN-ASSOCIATED HEMOLYTIC ANEMIA SINCE THE RECURRENCE OF HEMOLYSIS IS MUCH MORE SEVERE.

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 in both adults and children. If a patient develops anemia anytime during, or within 2-3 weeks subsequent to the administration of ceftriaxone, the diagnosis of a cephalosporin- associated anemia should be considered and the drug discontinued until the etiology is determined.

Patients who receive prolonged or frequent courses of ceftriaxone may benefit from periodic monitoring for signs and symptoms of hemolytic anemia, including measurement of haematological parameters or drug-induced antibody testing, where appropriate (see ADVERSE REACTIONS).

Renal and Hepatic Impairment
Although transient elevations of BUN and serum creatinine have been observed in clinical studies, there is no other evidence that ceftriaxone sodium, when administered alone, is nephrotoxic.

In severe renal impairment (creatinine clearance of less than 10 mL/min), periodic monitoring of serum ceftriaxone concentrations is recommended. The maximum daily dose should not exceed 2 g. In severe renal impairment associated with clinically significant hepatic impairment, close monitoring of serum ceftriaxone concentrations, at regular intervals, is recommended. If there is evidence of accumulation, dosage should be decreased accordingly.

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing Ceftriaxone Sodium for Injection BP in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

7.1 Special Populations

7.1.1 Pregnant Women

The safety of ceftriaxone sodium in the treatment of infections during pregnancy has not been established. Ceftriaxone Sodium for Injection BP (ceftriaxone sodium) should only be used during pregnancy if the likely benefit outweighs the potential risk to the fetus and/or the mother. Ceftriaxone has been detected in the umbilical cord blood, amniotic fluid and placenta. At parturition, 1 hour after a 2 g I.V. dose of ceftriaxone sodium, average ceftriaxone concentrations in maternal serum, umbilical cord serum, amniotic fluid, and placenta were 106 ± 40 mcg/mL, 19.5 ± 11.5 mcg/mL, 3.8 ± 3.2 mcg/mL and 20.9 ± 4.4 mcg/g.

7.1.2 Breast-feeding

Ceftriaxone is excreted in human milk at low concentrations, (e.g., the peak concentration of total drug in milk ranged between 0.45 to 0.65 mcg/mL, approximately five hours after the administration of 1 g I.V. or I.M.). The clinical significance of this is unknown, therefore, caution should be exercised when ceftriaxone sodium is administered to a nursingmother.

7.1.3 Pediatrics

The safety of ceftriaxone sodium in neonates (birth to 28 days of age) has not been established (see **CLINICAL PHARMACOLOGY**). *In vitro* studies have shown that ceftriaxone can displace bilirubin from serum albumin. Ceftriaxone Sodium for Injection BP (ceftriaxone sodium) should not be used in neonates (especially prematures), at risk of developing bilirubin encephalopathy (see **CONTRAINDICATIONS**).

7.1.4 Geriatrics

The elimination of ceftriaxone may be reduced in elderly patients possibly due to impairment of both renal and hepatic function (see **CLINICAL PHARMACOLOGY**).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most commonly reported adverse reactions are Severe Cutaneous Adverse Reactions, Clostridium Difficile-Associated Disease, Hemolytic Anemia and Renal and Hepatic Impairment (see **WARNINGS AND PRECAUTIONS**).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

During clinical trials and post-marketing experience with ceftriaxone sodium the following adverse reactions have been observed:

Clinical Adverse Experiences

Dermatological: Rash (1.3%); exanthema, allergic dermatitis and pruritis (0.1 - 1.0%); urticaria (post- marketing reports). Isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens Johnson Syndrome, or Lyell's Syndrome/toxic epidermal necrolysis) have also been reported.

Hematological: Anemia (0.1 - 1.0%); auto-immune hemolytic anemia and serum sickness (< 0.1%); immune hemolytic anemia (post-marketing reports – see **WARNINGS AND PRECAUTIONS** for more information on hemolytic anemia); granulocytopenia (post-marketing reports). Isolated cases of agranulocytosis (<500/mm^3) have been reported, most of them after 10 days of treatment and following total doses of 20g or more.

Hepatic: Jaundice, reports (in asymptomatic and symptomatic patients) of ultrasonographic shadows suggesting precipitations in the gallbladder and reports of gallbladder sludge (< 0.1%).

Urogenital: Moniliasis and vaginitis (0.1 - 1.0%); oliguria and nephrolithiasis (post-marketing reports).

Gastrointestinal: Diarrhea (3.3%); nausea, vomiting, dysgeusia and gastric pain (0.1 - 1.0%); abdominal pain, colitis, flatulence, dyspepsia, pseudomembranous colitis and stomatitis (< 0.1%); glossitis (post-marketing reports).

Neurological: Dizziness and headache (0.1 - 1.0%); ataxia and paresthesia (< 0.1%).

Miscellaneous: Fever, chills, diaphoresis, malaise, burning tongue, flushing, edema and

anaphylactic shock (0.1 - 1.0%); bronchospasm, palpitations and epistaxis (< 0.1%); glottic/laryngeal edema (post-marketing reports).

Local Reactions at Injection Site: Pain (9.4%)[a], induration and tenderness (1 - 2%); phlebitic reactions (0.1 - 1.0%); thrombophlebitis (< 0.1%).

[a]Pain on intramuscular injection is usually mild and less frequent when the drug is administered in sterile 1% Lidocaine solution.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Hematologic: Eosinophilia (4.6%), thrombocytosis (5.1%), leukopenia (2.0%); neutropenia, lymphopenia, thrombocytopenia, increase or decrease in hematocrit, prolongation of prothrombin time and decrease in hemoglobin (0.1 - 1.0%); leucocytosis, lymphocytosis, monocytosis, basophilia and decrease in prothrombin time (< 0.1%). (See **WARNINGS AND PRECAUTIONS** for information on alterations in prothrombin time.)

Hepatic: Increase in AST (SGOT) (4.0%)[b] , ALT (SGPT) (4.8%)[b], increase in alkaline phosphatase (1.0%); increase in bilirubin (0.1 - 1.0%).

Urinary: Increase in BUN (1.1%)[c]; increase in creatinine, erythrocyturia, proteinuria and presence of casts in urine (0.1 - 1.0%); glycosuria (< 0.1%).

[b]Incidence is more frequent in patients less than one year old.

[c]Incidence is more frequent in patients less than one year old and over 50 years old.

8.5 Post-Market Adverse Reactions

Post-Market Adverse Drug Reactions

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 sodium and calcium- containing fluids. In some of these cases, the same intravenous infusion line was used for both ceftriaxone sodium 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 sodium 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.

Serious post-market cases of encephalopathy (also reported as altered mental status, delirium, confusion, disturbance of consciousness, disorientation, agitation, hallucinations) have been reported. These cases can be accompanied by myoclonus and other movement disorders (including tremor and choreoathetosis). In the majority of cases, symptoms of neurotoxicity resolved after discontinuation of ceftriaxone. Many cases were reported in

patients with renal impairment. The maximum daily dose in patients with a creatinine clearance less than 10 mL/min should not exceed 2 g.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Interactions between ceftriaxone sodium and other drugs have not been fully evaluated.

9.4 Drug-Drug Interactions

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

Interaction with Calcium-Containing Products

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Ceftriaxone Sodium for Injection BP vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Ceftriaxone Sodium for Injection BP is mixed with calcium-containing solutions in the same IV administration line. Ceftriaxone Sodium for Injection BP 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 Sodium for Injection BP 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 **CONTRAINDICATIONS**, **ADVERSE REACTIONS**, **DOSAGE AND ADMINISTRATION**, and **CLINICAL PHARMACOLOGY**).

Though no reports of intravascular calcium-ceftriaxone precipitates have been reported in other than neonatal patients treated with ceftriaxone and calcium-containing intravenous products, caution is nevertheless warranted during intravenous treatment (see **INCOMPATIBILITY**). There have been reports of sonographic abnormalities in the gallbladder of patients treated with ceftriaxone sodium; 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 sodium and institution of conservative management. Therefore, Ceftriaxone Sodium for Injection BP should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease

and/or the sonographic findings described above. The effect of pre-existing gallbladder disease is not known.

Cases of pancreatitis, possibly of biliary obstruction etiology, have been rarely reported in patients treated with ceftriaxone sodium. Most patients presented with risk factors for biliary stasis and biliary sludge, e.g. preceding major therapy, severe illness and total parenteral nutrition. A trigger or cofactor role of ceftriaxone sodium-related biliary precipitation can not be ruled out.

Ceftriaxone may cause renal lithiasis through precipitation of calcium ceftriaxonate. When using this product in subjects with hypercalciuria or a history of renal lithiasis, benefit must be weighed against risk. Very rare cases of nephrolithiasis (renal precipitation) have been reported, mostly in children older than 3 years and who have been treated with either high daily doses (e.g. ≥80 mg/kg/day) or total doses exceeding 10 grams and presenting other risk factors (e.g. fluid restrictions, confinement to bed, etc.). This event may be symptomatic, may lead torenal insufficiency, and appears to be reversible upon discontinuation of ceftriaxone sodium.

Sonography for biliary sludge or renal lithiasis is recommended in cases of right hypochondrial and/or abdominal pain. Ceftriaxone Sodium for Injection BP treatment should be withdrawn to allow signs and symptoms to resolve.

Alterations in prothrombin time (see **ADVERSE REACTIONS**) and hypoprothrombinemia have occurred rarely in patients treated with ceftriaxone sodium. Patients with impaired vitamin K synthesis or low vitamin K stores (e.g., chronic hepatic disease and malnutrition) may require monitoring of hematology and coagulation parameters during Ceftriaxone Sodium for Injection BP treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during treatment.

Prolonged treatment with ceftriaxone sodium may result in overgrowth of non- susceptible organisms and organisms initially sensitive to the drug. Development of resistant organisms during the administration of ceftriaxone sodium in clinical trials has been observed in 6% of the 94 patients infected with *P. aeruginosa*, in 33% of 3 patients infected with Citrobacter species and in 10% of the 10 patients infected with Enterobacter species. If superinfection occurs, appropriate measures should be taken.

Ceftriaxone Sodium for Injection BP should be administered with caution to individuals with a history of gastrointestinal disease, particularly colitis.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Ceftriaxone may interfere with urine glucose determinations utilizing the copper-reduction test (Clinitest), but not utilizing the glucose-oxidase test (Diastix or Tes Tape). In patients treated with ceftriaxone sodium the Coombs' test may rarely become false-positive; and ceftriaxone sodium, like other antibiotics, may result in false-positive tests for galactosemia.

10 CLINICAL PHARMACOLOGY

10.2 Pharmacodynamics

Animal Pharmacology:
Ceftriaxone, at a maximum dose of 1,000 mg/kg, had no appreciable effect on:

1) the heart, circulation or the autonomic nervous system in anesthetised and unanesthetised dogs, anesthetised cats and conscious spontaneously hypertensive rats;
2) respiration, in unanesthetised dogs, anesthetised cats and conscious rabbits;
3) the gastrointestinal tract in mice;
4) the central nervous system in mice and rats.

In rats (during saline induced diuresis) and in dogs, ceftriaxone, at a maximum dose of 300 mg/kg, had no effect on urinary excretion except for one study where sodium retention in one strain of rat was observed (Na/K ratio 1.1-1.4).

In drug interaction studies in rats, ceftriaxone, given in doses of 200 mg/kg, potentiated the immunosuppressant activity of dexamethasone and cyclophosphamide and antagonised the diuretic effect of furosemide. In mice treated with leptazol, ceftriaxone, given S.C. in doses of 200 mg/kg, significantly decreased the anticonvulsant activity of 6 mg/kg I.P. doses of diazepam but not of 0.75, 1.5 or 3 mg/kg I.P. doses.

Ceftriaxone demonstrated no immunomodulating properties in mice and no antigenic activity in rats and guinea pigs.

Intravenous administration of ceftriaxone to groups of dogs at doses of 150 and 400 mg/kg/day resulted in the formation of some gritty and occasionally clotted concretions in the gallbladder. The concretions consisted mostly of a calcium salt of ceftriaxone.

10.3 Pharmacokinetics

A number of standard abbreviations and terms have been used throughout this section. They

are identified and defined below:

C	-	plasma concentration (max - maximum, min - minimum, ave - average steady state)
AUC	-	area under the plasma concentration - time curve
Cl_p	-	systemic (plasma) clearance
Cl_R	-	renal clearance
V_d(ß)	-	volume of distribution
$t_{1/2}$(ß)	-	half-life of elimination
fu	-	fraction of the dose excreted in the urine
T	-	total drug (bound plus unbound or free drug)
F	-	unbound or free drug
Accumulation (ratio)	-	the ratio of minimum steady state plasma concentration at 12 hours after the last dose to minimum plasma concentration at 12 hours after the first dose
Predicted	-	calculated as a function of t½(ß) accumulation (ratio)
Concentration units	-	mg/L is equivalent to mcg/mL

The pharmacokinetics of ceftriaxone are distinguished by: (1) saturable plasma protein binding within the therapeutic range (the free fraction of ceftriaxone remaining relatively constant at approximately 5 to 10 percent at ceftriaxone plasma concentrations of less than 200 mcg/mL, and increasing to approximately 40 percent at 650 mcg/mL), (2) no active secretion by renal tubules, and (3) approximately 55 percent renal elimination and 45 percent excretion through the bilary pathway.

Ceftriaxone plasma protein binding is dependent upon total drug concentration. The free fractions of ceftriaxone at total ceftriaxone concentrations of 4-68, 94-188 and 653 mcg/mL are 4-5, 8 and 42 percent respectively. As a result, the pharmacokinetics of total plasma ceftriaxone are non-linear. This is demonstrated by a less than proportional increase in area under the curve ($AUC^T(0\text{-}\infty)$ with increase in dose and dose dependent increases in volume of distribution (VdT(β)), systemic plasma clearance (Cl^TP) and renal clearance (Cl^TR). In contrast, the pharmacokinetics of free ceftriaxone are linear.

The renal clearance of free ceftriaxone is slightly less than the glomerular filtration rate. Probenecid does not influence the clearance of ceftriaxone. At doses of 500 mg or more, renal clearance based on total ceftriaxone (Cl^TR) decreases with time. In contrast, renal clearance based on free ceftriaxone (Cl^FR) remains relatively constant with time regardless of the dose. This phenomenon is due to increased ceftriaxone protein binding as plasma concentrations decrease during elimination.

Following a single intravenous dose of ^{14}C-ceftriaxone to two male subjects (23 and 27 years old), the following urinary and fecal excretion profile of radioactivity was observed:

Table 2

Time Intervals (hr)	Percent of Total Radioactivity Administered		
	Urine	Feces	Total
0-24	53, 47	29, 14	82, 61
0-48	59, 51	39, 40	98, 91
0-100	61, 52	41, 49	102, 101

Excretion of the radioactivity was complete by 100 hours with 90 percent of the dose being excreted during the first 48 hours. Ninety-two percent of the radioactivity recovered in the urine and approximately ten percent of the radioactivity recovered in the feces was accounted for by unchanged ceftriaxone. Relatively high concentrations of unchanged ceftriaxone are found in the bile. This may suggest that ceftriaxone is inactivated by the intestinal flora rather than by the liver.

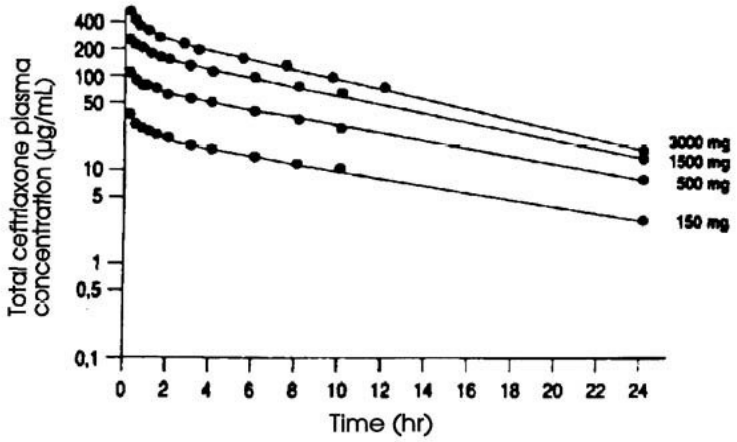
On multiple dosing, the fraction of ceftriaxone excreted unchanged in the urine (fu) and the terminal elimination half-life (t1/2(ß)) remain unchanged regardless of the dose. However, area under the curve (AUC^T) decreases by 12 and 15 percent and volume of distribution (Vd^T(ß)) and systemic plasma clearance (Cl^Tp) increase by 14 and 20 percent and 12 and 15 percent after multiple doses of 1,000 and 2,000 mg at 12-hour intervals, respectively. These parameters are not altered with multiple doses of 500 mg at 12-hour intervals. The changes observed at the higher doses are possibly due to the non- linear plasma protein binding of ceftriaxone.

Intravenous Administration
Bolus Injection Over 5 Minutes:
Single Dose:

Ceftriaxone, reconstituted with saline, was administered as a single dose bolus injection over 5 minutes to six healthy male volunteers (mean age 25 years) in four doses: 150, 500, 1,500 and 3,000 mg. The total ceftriaxone plasma concentration-time profile for each dose, in a single representative subject, is shown in Figure 1. The total drug concentration time profiles could each be described by a biexponential equation.

Figure 1

Total ceftriaxone plasma concentration-time profiles after single dose bolus injections.



Mean urinary recoveries of unchanged drug over 48 or 52 hours were 58.6 ± 6.6, 64.3 ± 7.3, 65.0 ± 4.3 and 66.6 ± 9.0 percent for the 150, 500, 1500 and 3000 mg doses respectively. Mean urinary ceftriaxone concentrations for various collection intervals are shown in Table 3.

Table 3
Urinary concentrations of ceftriaxone after single dose bolus injections

Time Interval (hr)	Mean Urinary Ceftriaxone Concentrations (mcg/mL)*		
	Dose (mg)		
	150	500	1,500
0-2	189 ± 89	894 ± 421	3,483 ± 951
2-4	113 ± 64	453 ± 249	1,530 ± 680
4-6	102 ± 40	360 ± 119	1,093 ± 150
6-8	84 ± 11	329 ± 76	833 ± 263
8-10	47 ± 19	195 ± 66	314 ± 188
10-12	43 ± 20	117 ± 41	323 ± 175
12-24	28 ± 10	82 ± 30	158 ± 50

*Ceftriaxone urinary concentrations for the 3,000 mg dose were not reported.

Various pharmacokinetic parameters were determined and mean values are reported in Table 4.

Table 4
Pharmacokinetics of Ceftriaxone After Single Dose Bolus Injections

Pharmacokinetic Parameters	Dose (mg)			
	150	500	1,500	3,000
AUC^{I}(0-4) (mcg.hr/mL)	268 ± 52	846 ± 179	1,980 ± 376	2,725 ± 293
AUC^{F}(0-4) (mcg.hr/mL)	10.1 ± 2.0	35.6 ± 8.5	106 ± 16.0	196.6 ± 22.7
Cl^{T}_{P}(mL/min)*	9.7 ± 2	10.2 ± 21	13.0 ± 2.6	18.5 ± 2.1

Cl^{F}_{P}(mL/min)*	262 ± 47	253 ± 52	249 ± 36	258 ± 31
Cl^{T}_{R}(mL/min)**	6.5 ± 1.3	8.2 ± 1.1	13.2 ± 1.1	33.0 ± 2.6
Cl^{F}_{R}(mL/min)**	169 ± 29	174 ± 33	165 ± 28	189 ± 48
Vd^{T}(ß) (L)	7.0 ± 0.5	6.7 ± 1.1	8.6 ± 0.8	12.7 ± 0.9
t^{T}1/2(ß) (hour)*	8.6 ± 1.7	7.7 ± 1.2	7.8 ± 1.0	8.0 ± 0.7
t^{F}1/2(ß) (hour)*	8.6 ± 1.6	7.6 ± 1.2	7.6 ± 1.0	7.8 ± 0.3

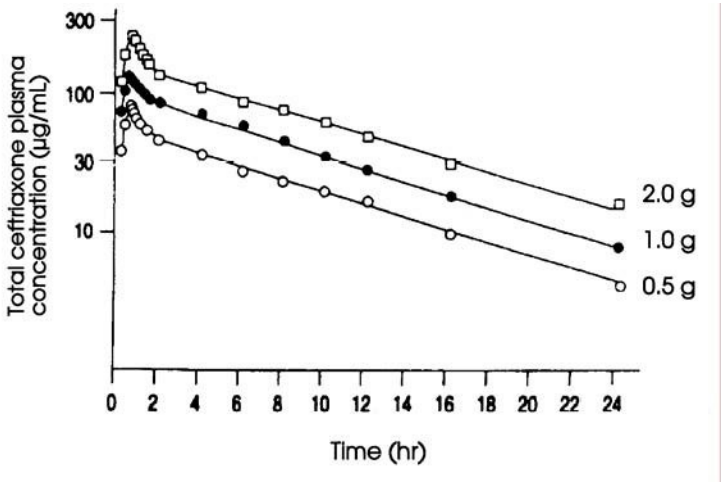
* 0-48 hr for 150, 500, 1,500 mg doses and 0-52 hr for the 3,000 mg dose

** 0-2 hr for 150, 500, 1,500 mg doses and 0-1 hr for the 3,000 mg dose

Infusion Over 30 Minutes:
Single Dose:

Ceftriaxone, in 100 mL of saline, was administered as a single dose infusion at a constant rate over 30 minutes to twelve normal volunteers (ten males and two females, mean age 35 years) in three doses: 500, 1,000 and 2,000 mg. The mean total ceftriaxone plasma concentration-time profile for each dose is shown in Figure 2. The total drug concentration-time profiles were biphasic and were fitted to a linear two compartment model.

Figure 2 -Mean total ceftriaxone plasma concentration-time profiles after single dose infusions.



Mean urinary recoveries of unchanged drug over 48 hours were 41 ± 8, 39 ± 5 and 43 ± 10 percent for the 500, 1,000 and 2,000 mg doses respectively. Mean urinary ceftriaxone concentrations for various collection intervals are shown in Table 5.

Table 5
Urinary Concentrations of Ceftriaxone After Single Dose Infusions

	Mean Urinary Ceftriaxone Concentrations (mcg/mL)

Time Interval (hr)	Dose (mg)		
	500	1,000	2,000
0-2	526 ± 303	995 ± 734	2,692 ± 1,403
2-4	366 ± 203	855 ± 615	1,976 ± 1,047
4-8	142 ± 63	293 ± 163	757 ± 437
8-12	87 ± 45	147 ± 66	274 ± 119
12-24	70 ± 25	132 ± 47	198 ± 93

A number of pharmacokinetic parameters were determined and the mean values are reported in Table 6.

Table 6
Pharmacokinetics of Ceftriaxone After Single Dose Infusions

Pharmacokinetic Parameters	Dose (mg)		
	500	1,000	2,000
$AUC^T(0\text{-}\infty)$ (mcg.hr/mL)	551 ± 91	1,006 ± 118	1,703 ± 203
Vd^T(ß) (L)	8.8 ± 1.22	9.2 ± 1.05	10.3 ± 1.01
$t^T_{½}$ (ß) (hour)	6.5 ± 0.72	6.2 ± 0.76	5.9 ± 0.69
Cl^T_P(mL/min)	15.5 ± 2.4	16.8 ± 2.1	19.8 ± 2.5
Cl^T_R(mL/min) (0-2 hr)	7.3 ± 1.3	9.0 ± 1.6	15.3 ± 3.9

Multiple Doses:

Seven 500, 1,000 or 2,000 mg doses of ceftriaxone were administered at 12-hour intervals to normal volunteers as constant rate infusions over 30-minute periods. The 500 and 1,000 mg doses were each administered to twelve males (mean ages 29 and 31 years respectively) and the 2,000 mg doses to eleven males and one female (mean age 33 years). Total ceftriaxone plasma Cmax, Cmin and Cave values are reported in Table 7.

Table 7
Total ceftriaxone plasma Cmax, Cmin and Cave values after multiple dose infusions

Dose (mg)		C_{max} (mcg/mL)	C_{min} (mcg/mL)	C_{ave}(mcg/mL)
500	First Dose	79 ± 11.5	15 ± 4.5	—
	Last Dose	101 ± 12.7	20 ± 5.5	41 ± 7
1,000	First Dose	145 ± 11	30 ± 6	—
	Last Dose	168 ± 25	35 ± 9.2	72 ± 13
2,000	First Dose	255 ± 41	45 ± 11	—
	Last Dose	280 ± 39	59 ± 21	118 ± 19

Plasma drug concentrations attained steady state by Day 4. The accumulation of ceftriaxone in plasma after the 500, 1,000 and 2,000 mg doses was 35, 20 and 21 percent respectively. The predicted accumulation was 40 percent.

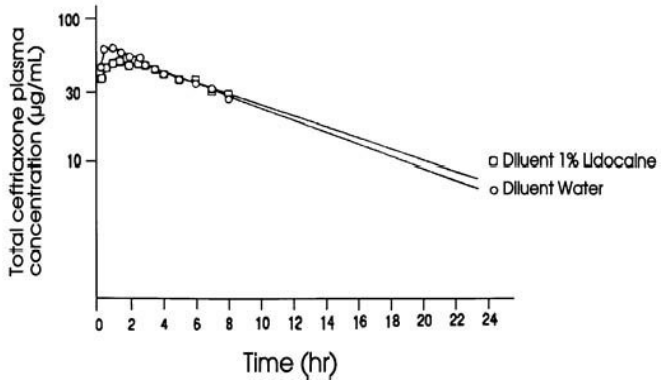
Intramuscular Administration

The bioavailability of ceftriaxone by the intramuscular route is approximately 100 percent.

Single Dose:

Ceftriaxone, reconstituted with either water or 1% lidocaine, was administered intramuscularly in a single 500 mg dose to six normal male volunteers (mean age 36 years). The mean total ceftriaxone plasma concentration-time profile for each diluent is shown in Figure 3.

Figure 3
Mean total ceftriaxone plasma concentration-time profiles after single intramuscular doses



Over 72 hours, 225 ± 40 and 229 ± 26 mg of unchanged ceftriaxone was recovered in the urine after the administration of the water and 1% lidocaine preparations respectively. Mean urinary ceftriaxone concentrations for various collection intervals are shown in Table 8.

Table 8
Urinary Concentrations of Ceftriaxone After a Single 500 mg Intramuscular Dose

Time Interval (hr)	Mean Urinary Ceftriaxone Concentrations (mcg/mL)	
	Diluent	
	Water	1% Lidocaine
0-2	176 ± 129	176 ± 135
2-4	223 ± 156	215 ± 124
4-6	213 ± 93	298 ± 111
6-8	198 ± 96	216 ± 83
8-24	99 ± 44	111 ± 43

A number of pharmacokinetic parameters were determined and the mean values are reported in Table 9. No significant differences were found between the mean pharmacokinetic parameters of the two preparations.

Table 9
Pharmacokinetics of Ceftriaxone After a Single 500 mg Intramuscular Dose

Pharmacokinetic Parameters	Diluent	
	Water	1% Lidocaine
Cmax (mcg/mL)	67.0 ± 9.7	55.8 ± 4.5
$AUC^T(0\text{-}\infty)$ (mcg.hr/mL)	709 ± 58	728 ± 63
$t^T1/2(ß)$ (hr)	8.5 ± 0.7	8.4 ± 0.5
Cl^TR(0-8 hr) (mL/min)	6.9 ± 0.5	6.6 ± 0.5

Multiple Doses: Seven 500 or 1,000 mg doses of ceftriaxone, reconstituted with 1% lidocaine, were administered intramuscularly at 12-hour intervals to twelve healthy volunteers (ten males and two females, mean age 36 years). Total ceftriaxone plasma Cmax, Cmin and Cave values are reported in Table 10.

Table 10
Total Ceftriaxone Plasma Cmax, Cmin and Cave Values After Multiple Intramuscular Doses

Dose (mg)	C_{max} (mcg/mL)	C_{min} (mcg/mL)	C_{ave} (mcg/mL)
500 First Dose	49 ± 11	16 ± 5	—
Last Dose	65 ± 8	24 ± 6	46 ± 6
1,000 First Dose	81 ± 12	29 ± 7	—
Last Dose	114 ± 16	39 ± 8	70 ± 10

Maximum ceftriaxone plasma concentrations were reached 0.75 to 3 hours (mean 1.7 hours) after drug administration. Steady state plasma concentrations were apparent after the third dose of both dosage regimens, and minimum steady state plasma concentrations were

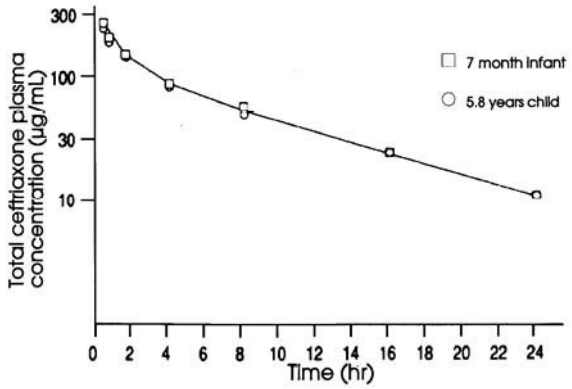
maintained.

The observed mean accumulation ratios were 1.36 and 1.29 after the multiple administration of 500 and 1,000 mg of ceftriaxone respectively. These values were not significantly different from the 1.40 and 1.36 predicted mean accumulation ratios.

Effect of Age on Pharmacokinetics

A representative total ceftriaxone plasma concentration-time profile for an infant (7 months old) and for a child (5.8 years old), each given a single 50 mg/kg dose of ceftriaxone by intravenous injection over 5 minutes, is presented in Figure 4.

Figure 4
Total ceftriaxone plasma concentration-time profiles after single dose intravenous injections in an infant and a child.



A summary of the age-associated changes in ceftriaxone pharmacokinetics is presented in Table 11. Renal and hepatic function was normal for age on the basis of clinical laboratory findings in these subjects. Ceftriaxone sodium was administered intravenously as a bolus over 2 to 5 minutes or as a 30-minute infusion. The age associated changes in half-life appear to result from changes in systemic clearance.

Table 11
Pharmacokinetic Parameters (Mean ± SD) Based on Total Ceftriaxone Plasma Concentration at Various Ages

Subjects and Underlying Condition	N	Mean Ceftriaxone Dosage (mg/kg)	Age	t1/2(ß) (hr)	Vd^T(ß) (L/kg)	Cl^Tp (mL/min/kg)	fu (%)
NEONATES Respiratory distress Syndrome (20)*, Meningitis or Bacteremia (4)*	24	50	1-8 d	18.6 ± 6.9	0.50 ± 0.15	0.34 ± 0.13	72 ± 20
Meningitis or Bacteremia	10	86	9-30 d	9.7 ± 3.9	0.65 ± 0.28	0.93 ± 0.66	75 ± 21
INFANTS Meningitis or Bacteremia (9)*, Viral Infection or Epilepsy (2)*	11	50 (2)* or 95 (9)*	1-12 m	7.2 ± 3.2	0.54 ± 0.25	0.93 ± 0.40	55 ± 20
CHILDREN Viral Infection or Epilepsy	5	50	2-6 y	6.6 ± 0.6	0.40 ± 0.08	0.71 ± 0.15	52 ± 4.7
ADULTS Healthy Volunteers	50	13, 14, 25 or 27	18-49 y	7.3 ± 1.6	0.16 ± 0.03	0.24 ± 0.06	44 ± 9.8
ELDERLY Healthy Volunteers	9	14 or 27	50-74 y	8.3 ± 2.2	0.15 ± 0.02	0.23 ± 0.07	39 ± 11
Healthy Volunteers (1)*, Bronchitis (10)*	11	14 (1)* or 24 (10)*	75-92 y	14.2 ± 2.9	0.15 ± 0.03	0.14 ± 0.04	-

*n

Effect of Renal Impairment on Pharmacokinetics

Twelve functionally anephric patients (six males and six females, mean age 54 years, creatinine clearance ≤ 10 mL/min) received single 150, 500 and 1,500 mg doses of ceftriaxone sodium intravenously over 5 minutes. Ten of the twelve patients had non-renal clearance values of free drug similar to healthy subjects. Pharmaco-kinetic parameters for these ten patients are presented in Table 12. Minor increases were observed in mean elimination half- lives in comparison to normal subjects.

Table 12

Pharmacokinetic Parameters	**150 mg (N = 4)**	**500 mg (N = 2)**	**1,500 mg (N = 4)**
$t^{T}_{½}$ (β) (hr)	12.4 ± 1.8	7.7, 10.3	11.8 ± 2.4
$t^{F}_{½}$ (β) (hr)	12.1 ± 1.8	7.4, 10.0	9.1 ± 1.0
Vd^{T} (β) (L)	9.9 ± 1.9	9.7, 12.6	13.0 ± 2.3
Vd^{F} (β) (L)	115.8 ± 35.2	69.4, 136.9	86.6 ± 17.7
Cl^{T} p (mL/min)	9.3 ± 2.1	14.5, 14.1	12.9 ± 1.8
Cl^{F} p (mL/min)	109.7 ± 22.4	108.1, 158.8	119.7 ± 32.5

Two of the patients exhibited decreased non-renal clearance values indicating an impairment of their biliary elimination pathway which was not obvious from standard liver function tests. Pharmacokinetic parameters for these two patients are presented in Table 13. More severe prolongations of their elimination half-lives were observed as well as decreases in total body clearance.

Table 13

Pharmacokinetic Parameters	**500 mg (N = 2)**
$t^{T}_{½}$ (β) (hr)	20.0, 34.8
$t^{F}_{½}$ (β) (hr)	18.4, 32.0
Vd^{T} (β) (L)	9.5, 13.3
Vd^{F} (β) (L)	79.0, 78.1
Cl^{T} p (mL/min) Cl^{F} p (mL/min)	5.5, 4.4 49.3, 27.9

Peritoneal dialysis did not remove ceftriaxone and hemodialysis was not very efficient at removing the drug.

Effect of Hepatic Dysfunction on Pharmacokinetics

The pharmacokinetics of total ceftriaxone were investigated in eight patients with liver disease (five males and three females, mean age 46 years) after a single 1,000 mg intravenous dose. The half-life of ceftriaxone was within the range for normal subjects regardless of the type of

liver disease. In the two patients suffering from decompensated liver cirrhosis with ascites, area under the curve was decreased and total body clearance and volume of distribution were significantly increased (Table 14). In the remaining six patients, these parameters were similar to normal.

Table 14

Liver Disease (N)	**Fatty Liver (2), Compensated Liver Cirrhosis (2), Liver Fibrosis (1), Liver Damage with Intrahepatic Cholestasis (1)**	**Decompensated Liver Cirrhosis with Ascites (2)**
Pharmacokinetic Parameter AUC^T (0 - ∞) (mcg.hr/mL)	1,160 ± 217	597 ± 49
Cl^Tp (mL/min)	14.9 ± 3.2	28.1 ± 2.3
Vd^T(ß) (L)	10.9 ± 0.8	21.9 ± 3.7
t^T½(ß) (hr)	8.8 ± 2.1	9.0 ± 0.8
fu (%)	61.7 ± 16.9	74.8 ± 3.5

Tissue and Body Fluids Ceftriaxone Concentration

Blister Fluid

Penetration of ceftriaxone into blister fluid is rapid. Pertinent pharmacokinetic parameters, for total ceftriaxone, in plasma and in blister fluid are presented in Table 15. Elimination of ceftriaxone from blister fluid is slightly slower than from plasma.

Table 15
Plasma And Blister Fluid Pharmacokinetic Parameters

Subjects (Healthy Volunteers)			Dosage (mg)	Route	Plasma		Blister Fluid			
N	Sex	Age (yr)			AUC^T (mcg.hr/mL)	t^T ½ (hr)	Cmax (mcg/mL)	Cmin (mcg/mL)	AUC^T (mcg.hr/mL)	t^T ½ (hr)
6	M	21-37	Single Dose 500	I.V.	610 ± 122	8.8 ± 1.7	32.7 ± 7.0	-	569 ± 134	10.4 ± 2.7
12	6M 6F	19-24	Multiple Dose 1000 q 12 h for 5 days.	I.V.						
			First Dose		1,218 ± 301	6.3 ± 1.2	36.0 ± 10.6	13.6 ± 7.5	448 ± 159	8.3 ± 2.9
			Last Dose		1,076 ± 169	6.7 ± 1.1	67.0 ± 22.0	39.8 ± 14.2	513 ± 213	15.0 ± 4.1
			2000 q 24 h for 5 days.							
			First Dose		1,987 ± 280	6.5 ± 0.9	38.6 ± 10.1	14.5 ± 8.3	767 ± 460	11.5 ± 5.7
			Last Dose		1,940 ± 253	7.2 ± 1.0	68.9 ± 19.7	27.1 ± 7.9	1,002 ± 285	12.8 ± 8.0

Cerebrospinal Fluid

Seven infants (4.5 to 15.6 months old) and one child (4.3 years old) received a 50 mg/kg dose of ceftriaxone and eight infants (3.1 to 9.8 months old) received a 75 mg/kg dose, by intravenous injection over five minutes. The pediatric patients had bacterial meningitis or ventriculitis. On average, 3 hours after administration, mean ceftriaxone cerebrospinal fluid concentrations were 4.5 ± 3.5 and 6.0 ± 3.9 mcg/mL after the 50 and 75 mg/kg ceftriaxone doses respectively.

Ceftriaxone sodium was administered as a single intramuscular injection to one hundred and eight patients, presenting with purulent meningitis. The patients were divided into three groups based on dose. The average (± SD) doses administered in the three groups were 21 ± 2.6, 36 ± 2.4 and 52 ± 1.1 mg/kg. Sixty-two patients were between 10 days and 2 years old, eighteen were between 2 and 9 years old, nine were between 10 and 19 years old and nineteen were between 20 and 83 years old. There were sixty-one males and forty-seven females. CSF concentrations of ceftriaxone were lower than serum concentrations. The mean ceftriaxone concentrations at different times are shown in Table 16. A distinction is made between results for purulent meningitis, as a function of whether bacteriology was positive or negative.

At doses equal to or greater than 35 mg/kg, mean spinal ceftriaxone concentrations were consistently higher than 2 mcg/mL for the 24 hours following the single intramuscular injection.

Table 16
Ceftriaxone Concentrations in CSF After Intramuscular Injection in 108 Patients

Culture of CSF	Dose of Ceftriaxone mg/kg (No. of Patients)	Ceftriaxone Concentrations in CSF (mcg/mL) (No. of Assays)			
		Hour 2	Hour 6	Hour 12	Hour 24
Positive	21 ± 2.6 (23)	3.70 ± 1.78 (13)	3.17 ± 1.34 (13)	2.44 ± 1.33 (13)	1.70 ± 1.52 (6)
	36 ± 2.4 (14)	3.36 ± 2.36 (6)	5.72 ± 3.25 (10)	2.68 ± 2.59 (7)	2.25 ± 1.54 (11)
	52 ± 1.1 (49)	5.66 ± 2.60 (16)	6.80 ± 1.76 (26)	5.62 ± 6.48 (4)	2.65 ± 1.67 (18)
Negative	41.7 (22)	2.94 ± 4.48 (5)	3.21 ± 2.25 (10)	4.55 ± 7.35 (5)	1.64 ± 1.45 (18)

Hepatic Bile

Ceftriaxone concentrations were measured in samples of bile obtained from eight patients (five females and three males, mean age 64 years) undergoing surgery for chronic cholecystitis with cholelithiasis (N=5) or other biliary diseases (N=3). Ceftriaxone sodium was administered at a dosage of 500 mg I.V. q 12 h for 7 days. Bile samples were obtained daily through a T-tube at various intervals after dosing. Ceftriaxone was detected in all specimens. Two patients had ceftriaxone bile concentrations consistently < 16 mcg/mL while the remaining six patients had concentrations ranging from 35 to as high as 924 mcg/mL.

The total calcium concentrations in the hepatic bile were also measured. The calculated ionic products of calcium and ceftriaxone ranged from 0.51 to 3.5 x 10^{-6}. The threshold precipitation of the calcium salt of ceftriaxone is 3.16 x 10^{-4}.

Gallbladder Bile

Seven patients (four females and three males, average age 49 ± 16 years) with relatively normal hepatic enzyme levels were given five doses (five patients) or three doses (two patients) of ceftriaxone sodium I.V. at a dosage of 2 g q 12 h. The last injection was given 0.1 to 5.3 (mean 2.7) hours before cholecystectomy. The concentrations of ceftriaxone in the gallbladder bile for all seven patients at the time of the operation ranged from 2,970 to 5,884 mcg/mL. The mean total calcium concentration in the gallbladder bile was 5.1 ± 1.3 mmol/L. The calculated ionic product ranged from 2.4 x 10^{-5} to 6.2 x 10^{-5}.

Interaction of Ceftriaxone and Calcium In Vitro

Two in vitro studies, one using adult plasma and the other neonatal plasma from umbilical cord blood, were carried out to assess the interaction of ceftriaxone and calcium. Ceftriaxone concentrations of 0.1 – 1 mM (55 - 555 mcg/ml) were incubated for 2 hours with calcium concentrations of 2 - 12 mM (80 - 480 mcg/ml). Recovery of ceftriaxone from plasma was statistically significantly reduced at calcium concentrations of 6 mM (240 mcg/ml) or higher in adult plasma and 4 mM (160 mcg/ml) or higher in neonatal plasma. These measures included total free and protein bound ceftriaxone and calcium. The difference observed in the assays may be reflective of ceftriaxone-calcium precipitations.

11 STORAGE, STABILITY AND DISPOSAL

Ceftriaxone Sodium for Injection BP (ceftriaxone sodium) sterile powder should be stored at a controlled room temperature (between 15 and 30 ºC) and protected from light. Ceftriaxone Sodium for Injection BP should be stored in its original packaging.

Reconstituted Solutions - Stability and Storage Recommendations

1. For Intramuscular Use: Solutions should be reconstituted immediately before use. If storage is required, these solutions may be stored under refrigeration and should be used within 48 hours.

2. For I.V. Bolus Injection (without further dilution): Reconstituted solutions should be administered within 24 hours when stored at room temperature and within 72 hours when refrigerated (2-8ºC).

3. For I.V. Infusion:
   Further diluted reconstituted solutions should be administered within 24 hours when

stored at room temperature.

a) Solutions further diluted with 0.9% Sodium Chloride Injection, or with 5% Dextrose Injection should be administered within 72 hours when stored under refrigeration (2- 8ºC).

b) Solutions further diluted with Dextrose and Sodium Chloride Injection as diluent should not be refrigerated. These solutions are not physically compatible when refrigerated.

4. Extended Use of Intravenous Admixtures:

Although intravenous admixtures may often be physically and chemically stable for longer periods, DUE TO MICROBIOLOGICAL CONSIDERATIONS, THEY ARE USUALLY RECOMMENDED FOR USE WITHIN A MAXIMUM OF 24 HOURS AT ROOM TEMPERATURE OR 72 HOURS WHEN REFRIGERATED (2-8ºC). Hospitals and institutions that have recognized admixture programs and use validated aseptic techniques for preparation of intravenous solutions may extend the storage times for ceftriaxone sodium admixtures with 0.9% Sodium Chloride Injection or 5% Dextrose Injection in glass or polyvinyl chloride infusion containers, in concentrations of 3-40 mg/mL, to seven days when stored under refrigeration (2-8ºC).

WARNING: As with all parenteral drug products, intravenous admixtures should be visually inspected prior to administration, whenever solution and container permit. Solutions showing any evidence of haziness or cloudiness, particulate matter, precipitation, discolouration or leakage should not be used.

5. Frozen I.V. Infusion Solutions:

Hospitals and institutions that have recognized admixture programs and use validated aseptic techniques for preparation of intravenous solutions may freeze and store Ceftriaxone Sodium for Injection BP I.V. infusion solutions when prepared in accordance with the following instructions.

I.V. infusion solutions prepared from reconstituted Ceftriaxone Sodium for Injection BP (ceftriaxone sodium) further diluted with 5% Dextrose Injection or 0.9% Sodium Chloride Injection, in flexible polyvinylchloride infusion containers, in concentrations up to 40 mg ceftriaxone per mL, may be stored at -10 to –20ºC for periods up to three months.

The frozen solutions should be thawed in a refrigerator (2-8ºC) overnight and should subsequently be used within 24 hours when stored at room temperature or seven days when stored under refrigeration (2-8ºC).

After thawing, check for leaks by squeezing the bag firmly. If leaks are found, discard the container as sterility may be impaired. Do not use unless the solution is clear and seals/outlet ports are intact. Ceftriaxone solutions range from light yellow to amber in

colour. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever the solution and container permit.

DO NOT REFREEZE the previously frozen ceftriaxone I.V. infusion solutions.

Incompatibility:

Ceftriaxone Sodium for Injection BP should not be added to solutions containing calcium such as Hartmann's solution and Ringer's solution (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Ceftriaxone Sodium for Injection BP should not be physically mixed with other antimicrobial agents, vancomycin, amsacrine, or fluconazole.

Ceftriaxone Sodium for Injection BP should not be added to blood products, protein hydrolysates or amino acids.

12 SPECIAL HANDLING INSTRUCTIONS

Disposal of syringes/sharps

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).
- Keep this container out of the reach of children.
- Placing used sharps containers in the household waste should be avoided.
- Dispose of the full container according to local requirements or as instructed by your healthcare provider.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided. Use established 'collection systems' if available at your location.

PART II: SCIENTIFIC INFORMATION

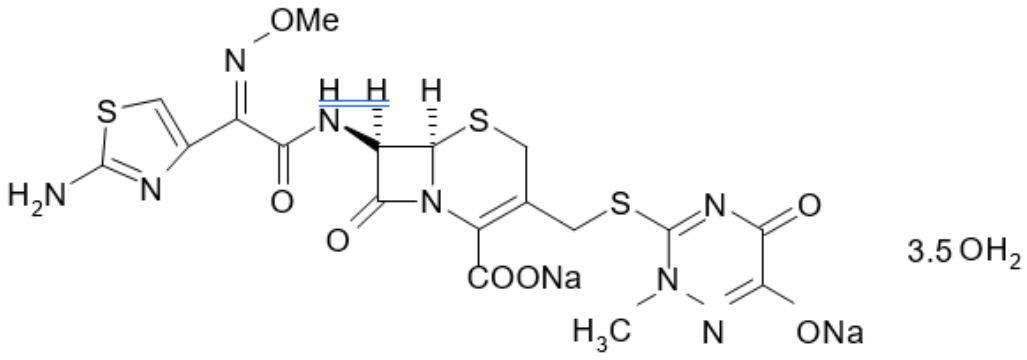
13 PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: ceftriaxone sodium

Chemical Name: (6R,7R)-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-car- boxylic acid, 7^2 -(Z)-(O-methyloxime, disodium salt, ses- quaterhydrate

Structural Formula:



Molecular Formula: $C_{18}H_{16}N_8Na_2O_7S_3$ C $3.5H_20$

Molecular Weight: 662 g/mol

Description: Ceftriaxone sodium is a white to yellowish- orange crystalline powder, soluble in water and sparingly soluble in methanol, very soluble in alcohol.

Melting Range: 220°C - 240°C

Specific optical rotation: - 155° to - 170° in a 1.0% w/v aqueous solution

Product Characteristics:

Composition: Ceftriaxone Sodium for Injection BP vials contain ceftriaxone sodium

(expressed in terms of anhydrous free acid). The sodium content of each gram of Ceftriaxone Sodium for Injection BP is approximately 83 mg (3.6 mEq sodium ion). The pH of freshly reconstituted solutions usually ranges from 6 to 8. Solutions are yellowish in colour.

14 CLINICAL TRIALS

This information is not available for this drug product.

15 MICROBIOLOGY

The *in vitro* activity of ceftriaxone against various gram positive and gram-negative organisms is presented in Table 17.

Table 17
Cumulative Percentage of Clinical Isolates Inhibited at ≤ Indicated Concentrations of Ceftriaxone (mg/L)*

Microorganisms (No. of Isolates)	0.0078	0.016	0.031	0.0625	0.125	0.25	0.50	1.0	2.0	4	8	16	32	64	128
Aerobes Gram Negative															
Acinetobacter anitratum (28)											11	39	96	100	
Acinetobacter calcoaceticus (50)			2				6		12	24	32	66	96	100	
Acinetobacter lwoffi (10)										10		40			50
Citrobacter freundii (21)					5	33	62						67	71	95
Enterobacter aerogenes (17)				24	47	71	82				88	94		100	
Enterobacter cloacae (40)					5	28	50	55	65	75		90		93	
Escherichia coli (47)			6	66	88	94	98	100							
Haemophilus influenzae (16)	86	94		100											
Klebsiella oxytoca (21)							50	90							
Klebsiella species (49)				50	90										
Klebsiella pneumoniae (56)			5	41	86	100									
Neisseria gonorrhea (10)**	90	100													
Neisseria meningitidis (22)**	59	68	77	100											
Proteus inconstans (5)		20	80			100									
Proteus mirabilis (40)	60	95	100												
Proteus morganii (40)	18	43	58	75	85		90	93	98		100				
Proteus rettgeri (12)	42	58	75		92		100								
Proteus vulgaris (29)	3			14	31	52	72	86	90			97		100	
Pseudomonas aeruginosa (64)										5	28	52	73	95	97
Pseudomonas cepacia (7)												14	43	71	100
Pseudomonas fluorescens (8)														25	75
Pseudomonas maltophilia (9)										11	22		67	78	100
Pseudomonas putida (9)												11	33	78	100
Salmonella species (18)				50											
Salmonella typhi (30)**		3	7	43	100										
Shigella (11)**		9		55	73			82	100						

Microorganisms (No. of Isolates)	0.0078	0.016	0.031	0.0625	0.125	0.25	0.50	1.0	2.0	4	8	16	32	64	128
Serratia marcescens (45)						4	20	38	47	58	62	64	78	96	98
Aerobes Gram Positive															
Staphylococcus aureus (34)										15	85	91			97
Staphylococcus epidermidis (22)								9	23	36	50	68	82	95	
Streptococcus agalacticae (25)			48	96	100										
Streptococcus pneumoniae (88)	26	39	55	80	90	100									
Streptococcus pyogenes (15)		100													
Anaerobes Gram Negative															
Bacteroides SP. (56)							2	4	5	13	29	55	71	84	91
Fusobacterium SP. (8)							13			25	38			50	63
Anaerobes Gram Positive															
Clostridium SP. (10)					10	20	50		60	70		80	100		
Peptococcus SP. (15)					33	47	53		66	73	100				
Peptostreptococcus SP. (8)				13			50	88	100						

* The inoculum size ranged from 10^3 to 10^6 cells/mL.

** The inoculum size was not reported.

Methicillin resistant staphylococci and most strains of enterococci, *Streptococcus faecalis*, Group D streptococci, *Clostridium difficile* and *Listeria monocytogenes* are resistant to ceftriaxone.

The MBC/MIC ratio for a selected group of organisms is shown in Table 18.

Table 18
The MBC/MIC Ratio of Ceftriaxone for Randomly Selected Susceptible Isolates

Microorganisms (No. of Strains)	Mean MBC/MIC Ratio
Citrobacter freundii (6)	2.00
Enterobacter cloacae (8)	2.75
Escherichia coli (8)	1.38
Klebsiella pneumoniae (8)	1.13
Proteus mirabilis (8)	2.88
Proteus morganii (5) (*Morganella morganii*)	1.00
Pseudomonas aeruginosa (8)	5.25
Serratia marcescens (8)	1.13

The effect of inoculum size on the activity of ceftriaxone was dependent upon the strain examined. Increases in inocula size from 10^3 to 10^5 CFU/mL had little if any effect on either MIC or MBC for a number of bacterial strains including beta-lactamase producers. However, a 100-fold increase in inocula size from 10^5 to 10^7 CFU/mL resulted in 8 to 533-fold increases in MICs and >32 to 4,267-fold increases in MBCs for *P. aeruginosa*, *S. marcescens* and *P. vulgaris*, and 125 to 8,333-fold increases in MICs and >8 to 8,333-fold increases in MBCs for beta- lactamase producers. A 10-fold increase in inocula size from 10^7 to 10^8 CFU/mL was accompanied by 64 to 1,000-fold increases in MICs for *S. marcescens* and *P. vulgaris*.

The effects of pH in the range of 6 through 8 are shown in Table 19.

Table 19
Effect of pH on the *In Vitro* Activity of Ceftriaxone

Organism (No. of Strains)	MIC (mg/L) at Indicated pH		
	pH 8	pH 7	pH 6
S. aureus (2)	3.13 - 6.25	3.13	0.78
S. epidermidis (1)	1.56	3.13	1.56
S. pyogenes (1)	0.025	≤0.012	<0.012
E. coli (3)	≤0.012-0.10	0.025 - 0.10	≤0.012 - 0.20
K. pneumoniae (1)	0.05	0.05	0.05
S. typhimurium (2)	0.025-0.100	0.05 - 0.20	0.05 - 0.20
S. marcescens (1)	1.56	0.78	0.20
E. cloacae (1)	1.56	12.5	25.0
P. vulgaris (3)	≤0.012-0.025	≤0.012	≤0.012 - 0.025
P. rettgeri (1)	0.025	0.10	1.56
P. mirabilis (1)	≤0.012	0.025	≤0.012
P. aeruginosa (2)	3.13 - 12.5	3.13 - 12.5	6.25 - 12.5

Heart Infusion Agar Inoculum: 10^6 cells/mL

The MICs of laboratory strains of *S. aureus*, *E.coli*, *P. mirabilis*, *P. vulgaris* and *S. marcescens* were within one dilution of each other when measured in the following media: Nutrient agar, DST agar, antibiotic medium No. 1 and Mueller-Hinton agar. For *P. aeruginosa*, however, ceftriaxone was 2 to 8-fold more active in Nutrient agar than in the other media.

The effect of human serum on the MICs and the MBCs of various bacteria are shown in Table 20.

Table 20
The Effect of Serum on the MIC and MBC of Ceftriaxone (mg/L)

Organism (No. of Strains)	Isosensitest Broth		Isosensitest Broth +25% Human Serum		Isosensitest Broth +75% Human Serum	
	MIC	MBC	MIC	MBC	MIC	MBC
E. coli (2)	0.06	0.06	0.06-0.120	0.06-0.12	0.12-0.25	0.25
K. pneumoniae (2)	0.06	0.06	25	0.25	0.5	0.5
P. mirabilis (1)	0.008	0.015	0.015	0.03	0.06	0.06
P. vulgaris (1)	0.06	0.25	0.25	0.25	0.5	2.0
P. aeruginosa (2)	4.0-32.0	4.0-32.0	4.0-64.0	16.0-64.0	8.0-64.0	64.0-128.0
S. aureus (2)	2.0	4.0	4.0-16.0	8.0-16.0	8.0-16.0	16.0-32.0

The relative rates of hydrolysis of ceftriaxone by various beta-lactamases are shown in Table 21.

Table 21

Beta-Lactamase Source	Type of Beta-Lactamase[1]	Richmond-Sykes Classification	Relative Rate of Hydrolysis[2]
Escherichia coli[3]	Pen	V	0.1
Klebsiella pneumoniae	Cepha	111A	6
Enterobacter cloacae[4]	Cepha	1A	11
Citrobacter freundii[4]	Cepha	-	21
Serratia marcescens	Cepha	1A	0
Morganella morganii[4]	Cepha	1A	10
Proteus vulgaris[4]	Cepha	1C	25
Shigella sonnei[3]	Pen	-	0.2
Pseudomonas aeruginosa[3]	Pen	V	0
Pseudomonas aeruginosa	Cepha	1D	36
Bacteroides fragilis[4]	Cepha	-	128
Staphylococcus aureus[4]	Pen	-	0
Bacillus cereus	Both	-	16

1 - Pen, primarily penicillin substrate; Cepha, primarily cephalosporin substrate; Both, both types.

2 - Rate in relation to cephaloridine (100%), except for *S. aureus* and *B. cereus*, which are

based upon hydrolysis of penicillin G (100%).

3 - Plasmid mediated.

4 - Induced with cephalothin.

Development of Resistance:

The acquisition of resistance to ceftriaxone was studied *in vitro* in eight strains of *E. coli*. MIC values were determined before and after five passages through sublethal doses of ceftriaxone. As shown in Table 22, the increases in resistance to ceftriaxone ranged from 2 to ≥ 1,024-fold.

Table 22
Effect of Five Passages Through Media Containing Ceftriaxone on the Susceptibility of Beta-Lactam Sensitive and Resistant *E. coli* Strains

Strain	MIC (mg/L)		MIC Increase (Fold)	Original susceptibility to Beta-Lactams	
	Pre-transfer	Post-transfer		Cefazolin	Ampicillin
NIHJ	0.1	0.2	2	S[1]	S
IW431	0.025	0.39	16	S	S
IU586	0.05	0.2	4	S	R[2](C)[3]
IW432	0.1	25.0	256	S	R(C)
IW434	0.1	3.13	32	R	R(C)
IV 57	0.2	25.0	128	R	R(C)
IV 84	0.78	100.0	128	R	R(C)
IU581	0.2	>100.0	≥1,024	R	R(R)[4]

1 - S = Sensitive 2 - R = Resistant

3 - (C) = Chromosome-mediated resistance. 4 - (R) = R-plasmid-mediated resistance.

Interaction With Other Antibiotics

Combinations of ceftriaxone with aminoglycosides resulted in synergistic effects (i.e., at least a 4-fold decrease in the MICs of both antibiotics) against many strains of *Pseudomonas aeruginosa* and *Streptococcus faecalis in vitro* (Table 23), even when the organisms were resistant to the individual antibiotics. A combination of ceftriaxone with cefoxitin produced either synergy or antagonism depending on the species and strain (Table 24).

In in vivo studies synergy was very infrequently observed against Pseudomonas aeruginosa with gentamicin (0 of 8 strains at ratios of ceftriaxone:aminoglycoside of 1:1 or 1:8), tobramycin (1 of 8 strains at 1:1 and 0 of 8 at 1:8) and amikacin (0 of 6 strains at 1:1 and 2 of 6 at 1:8). Synergy was not observed against S. faecalis with either gentamicin or amikacin. Antagonism between ceftriaxone and cefoxitin was observed for 5 of 5 strains of Pseudomonas aeruginosa.

Table 23

***In Vitro* Interaction Between Ceftriaxone and Aminoglycosides**

Aminoglycoside	Organism	Sensitivity	No. of Strains	Numbered (%) of Strains at Indicated Ratio of Ceftriaxone: Aminoglycoside	
				Optimum Ratio Synergy	8:1 Ratio Synergy
Gentamicin	***P. aeruginosa***	sens*	20	17(85)	11(55)
	P. aeruginosa	resisa	7	3(43)	1(14)
	P. aeruginosa	resisb	6	3(50)	0
	P. aeruginosa	resisc	3	2(67)	0
	S. faecalis	resisb	1	-	0
	S. faecalis	resisc	9	-	9(100)
	E. coli	sens	3	-	0
	S. typhimurium	sens	2	-	0
	Prot. mirabilis	sens	1	-	0
	Prot. vulgaris	sens	2	-	0
	Prot. morganii	sens	1	-	0
	Prot. rettgeri	sens	1	-	0
	Klebs. pneum.	sens	2	-	0
	Ent. cloacae	sens	1	-	0
	Ent. cloacae	resisa	2	-	0
	S. marcescens	sens	3	-	2(67)
	Staph. aureus	sens	2	-	0
Tobramycin	***P. aeruginosa***	sens	20	15(75)	5(25)
	P. aeruginosa	resisa	10	9(90)	9(20)
	P. aeruginosa	resisb	6	4(67)	0
	S. faecalis	resisb	1	-	0
	S. faecalis	resisc	9	-	9(100)
	E. coli	sens	3	-	0
	S. typhimurium	sens	2	-	0
	Prot. mirabilis	sens	1	-	0
	Prot. vulgaris	sens	1	-	0
	Prot. morganii	sens	1	-	0
	Prot. rettgeri	sens	1	-	0
	Klebs. pneum.	sens	2	-	0
	Ent. cloacae	sens	3	-	0
	S. marcescens	sens	1	-	0
	S. marcescens	resisb	2	-	0
	Staph. aureus	sens	1	-	0
Amikacin	***P. aeruginosa***	sens	23	16(70)	13(57)
	P. aeruginosa	resisa	13	11(85)	6(46)

Aminoglycoside	Organism	Sensitivity	No. of Strains	Numbered (%) of Strains at Indicated Ratio of Ceftriaxone: Aminoglycoside	
				Optimum Ratio Synergy	8:1 Ratio Synergy
	E. coli	sens	3	-	0
	S. typhimurium	sens	2	-	0
	Prot. mirabilis	sens	1	-	0
	Prot. vulgaris	sens	2	-	0
	Prot. morganii	sens	1	-	0
	Prot. rettgeri	sens	1	-	0
	Klebs. pneum.	sens	2	-	0
	Ent. cloacae	sens	1	-	0
	Ent. cloacae	resisa	2	-	0
	S. marcescens	sens	3	-	0
	Staph. aureus	sens	2	-	0

* sens: The organisms were classified as either sensitive or of intermediate sensitivity towards both antibiotics. For ceftriaxone this was ≤ 50 mg/L, for gentamicin ≤ 6.3 mg/L, for tobramycin ≤ 6.3 mg/L and for amikacin ≤ 12.5 mg/L.

a: The organism(s) was (were) resistant to ceftriaxone.

b: The organism(s) was (were) resistant to the aminoglycoside studied.

c: The organism(s) was (were) resistant to ceftriaxone and the aminoglycoside studied.

d: The number of strains does not necessarily match the total number of strains tested. This is because no interaction was observed for some strains.

-: No data.

Table 24
***In Vitro* Interaction Between Ceftriaxone and Cefoxitin**

Organism	No. of Strains	Number* (%) if Strains at Ratio of 1:1	
		Synergy	Antagonism
P. aeruginosa	**12**	**0**	**11(92)**
Enterob. cloacae	**7**	**0**	**4(57)**
P.morganii	**1**	**0**	**1(100)**
S.marcescens	**3**	**0**	**2(67)**
Citr. freundii	**2**	**0**	**2(100)**
Bact. fragilis	**14**	**13(93)**	**0**
Strep. faecalis	**19**	**19(100)**	**0**

***The number of strains does not necessarily match the total number of strains tested. This is because no interaction was observed for some strains.**

Susceptibility Test:

The standard disc susceptibility test (modified Kirby-Bauer method) using the 30 mcg

ceftriaxone sodium disc and dilution susceptibility tests should be interpreted according to the criteria in Table 25.

Table 25

	Zone Diameter (30 mcg Ceftriaxone disc)	Approximate MIC Correlation
Susceptible	≥ 18 mm	≤ 16 mg/L
Moderately susceptible	14 - 17 mm	32 mg/L
Resistant	≤ 13 mm	≥ 64 mg/L

Ceftriaxone has been shown by *in vitro* tests to be active against certain strains found to be resistant when other beta-lactam discs are used. It is therefore recommended that only the ceftriaxone disc (containing 30 mcg ceftriaxone) be used when conducting susceptibility tests. Similarly, the ceftriaxone disc should not be used for testing susceptibility to other cephalosporins.

The zone diameters produced by a 30 mcg ceftriaxone disc and the MICs determined by ceftriaxone dilution susceptibility testing for recommended reference strains are provided in Table 26.

Table 26

Reference Strain	Zone Diameter	MIC
E. coli (ATCC 25922)	29 - 35 mm	0.016 - 0.5 mg/L
S. aureus (ATCC 25923)	22 - 28 mm	1 - 2 mg/L
P. aeruginosa (ATCC 27853)	17 - 23 mm	8 - 64 mg/L

Disc or dilution susceptibility testing may not be appropriate for *Pseudomonas* species because of a 40 and 31 percent incidence of false susceptible results respectively.

16 NON-CLINICAL TOXICOLOGY

Acute Toxicity

The acute toxicity of ceftriaxone was determined in mice, rats and rabbits.

Table 27
Acute Toxicity of Ceftriaxone

Route	Species	Strain	Sex	LD50mg/kg (95% confidence limit)	Signs
	Mice	CFI	M F	1,840 (1,750-1,930) 2,150 (1,940-2,420)	salivation, respiratory depression, tremors
		ICR-SLC	M F	3,000 (2,778-3,240) 2,800 (2,617-2,996)	transient tremor, staggering gait, irregular respiration, accelerated respiration, sedation, systemic convulsions
I.V.	Rats	Sprague Dawley-CD	M,F	2,240 (2,040-2,500)	ataxia, cyanosis, respiratory depression, salivation, Straub reaction, tonic extensor
		Sprague Dawley	M,F	2,175 (2,033-2,327)	systemic stiffness, tonic spasms, dyspnea, staggering gait, irregular respiration, sedation, ataxic walking, cecum enlargement in most animals
	Neonatal Rats*	CD	M,F	1,900 (1,600-3,100)	loss of righting reflex, respiratory depression, cyanosis, gasping, thrashing
	Rabbits	New Zealand White	M,F	240 (69-700)	decreased motor activity, respiratory depression, diarrhea, general debilitated condition, irritation of large intestine, thymus congestion, myocardial pallor or hemorrhage
S.C.	Mice	IRC-SLC	M,F	> 5,000	none reported
	Rats	Sprague Dawley	M,F	> 5,000	sedation, anorexia, ataxia, analgesia, irregular respiration, convulsions, cecum enlargement
	Mice	IRC-SLC	M,F	> 10,000	none reported
P.O.	Rats	Sprague Dawley	M,F	> 10,000	cecum enlargement
I.P.	Neonatal Rats**	CD	M,F	> 2,000	Pallor

* 14 days old
** > 24 hours old

In an intravenous pyramiding dose study in Swiss beagle dogs (one of each sex) daily doses of 100, 200, 400, 800, 1,600, 2 x 1,600 (12 hours between dosing) and 3 x 1,600 mg/kg (8 hours between dosing) of ceftriaxone were administered. The 400 mg/kg dose and higher doses

caused some transient screaming, whimpering, gasping for breath and in one case a few clonic convulsions. The symptoms could be largely avoided by slow I.V. administration. Reversible staggering gait, some dizziness and lassitude were observed at all 1,600 mg/kg doses. Some elevations in SGPT (up to 12- fold in one dog) and alkaline phosphatase were observed. At autopsy the gallbladder of both dogs were vastly contracted but contained no concretion-like material.

In another intravenous study in four beagle dogs (two/sex), pyramiding doses of 3.6, 12, 36, 120, 360 and 1,200 mg/kg of ceftriaxone were administered at 1 to 2-day intervals. Drug-related signs and symptoms were retching, emesis, head shaking, ear scratching, erythema, edema around the eyes and snout and sporadic panting and licking. Most of these were observed in one animal which may have been atypically responsive to the drug. Following the 1,200 mg/kg dose, SGPT was increased by about 10 and 3.5-fold in two dogs. A grey-white, amorphous, non-gritty, sediment was seen in the gallbladder of three dogs at autopsy, 25 days after the last dose.

Multiple Dose Toxicity Studies

Rats

In a 2-week intravenous administration study, groups of eight male Füllinsdorf rats were administered 0, 25 or 60 mg/kg/day of ceftriaxone. Body weight gain was slightly depressed by 9.2 and 20.1 percent in the 25 and 60 mg/kg/day groups respectively. The average weight of the thyroid glands was increased in the treated groups by 11 to 14 percent in comparison to the control animals. A 50 percent reduction in plasma bilirubin in the treated rats was reported along with a decrease in the number of leucocytes.

In a 4-week intravenous study, groups of twenty-four rats (twelve/sex) were administered 0, 25, 125 or 600 mg/kg/day of ceftriaxone. Local and general tolerance were good except that the rapid injection of 600 mg/kg/day resulted in slight and transient giddiness, apathy, lassitude and deep breathing. Some alopecia was noted in two males and four females in the high-dose group and one male in the middle- dose group. Body weight gain was reduced by about 7 percent in the males of the 600 mg/kg/day group. Compared to control rats urine volumes at week 4 of the study were reduced by 18.5 and 40.0 percent in rats treated with 125 and 600 mg/kg/day respectively. At week 4, one rat of each sex, in the 600 mg/kg/day group developed seizures and convulsions, immediately after injection, and died. At autopsy, all rats in the 125 and 600 mg/kg/day groups showed a marked enlargement of the cecum. There were 18 and 10 percent increases in male and female absolute adrenal gland weights respectively in the high-dose group. The average absolute liver weight was decreased by 10 and 17 percent in males in the 125 and 600 mg/kg/day groups respectively.

Sprague-Dawley rats (sixteen/sex/dose) were administered 0, 100, 350 or 1,225 mg/kg ceftriaxone I.V. daily for 13 weeks after which six rats/sex/dose were observed during a 5-week recovery period. Because of severe damage at the injection site in the 1,225 mg/kg/day group, surviving rats were either sacrificed on day 42 or observed during a 4-week recovery period. In

the high-dose group, transient staggering gait and accelerated respiration were observed. Convulsions and dyspnea followed by death were observed in two females in this group after 31 to 35 days of dosing. Hematology and blood chemistry changes in comparison to control rats were reported in the 1,225 mg/kg/day group only and included: increases in both sexes in MCV and MCH of 12 to 13 and 14 percent respectively and, an increase in serum sodium and decreases in Hb, PCV and RBC count of 2, 2.5, 3.3 and 14 percent respectively in females. All these changes became normal during the recovery period. During autopsy, vascular occlusion at the injection site was observed in the 350 and 1,225 mg/kg/day groups. Cecum enlargement was noted in most treated rats, but returned to normal during the recovery period. In the 1,225 mg/kg/day group, half of the animals (both sexes) exhibited a slight petechial bleeding scattered in the subcapsular parts of the thymus. This was not observed in the recovery group animals.

Dogs

In a 2-week study, male Füllinsdorf beagles (two/group) were administered intravenously 0, 25 or 60 mg/kg/day of ceftriaxone for 2 weeks. The average body weight gains were 8, 4 and 2 percent in the control, low and high-dose groups respectively. Slight dose-related decreases in serum gamma- globulin and potassium along with slight dose-related increases in total bilirubin, serum albumin and albumin/globulin ratio were reported.

In a 4-week study, groups of beagle dogs (two or three/sex/dose) were administered intravenously 0, 25, 150 or 400 mg/kg/day of ceftriaxone. Injection of the drug induced some initial vomiting in one dog in the middle-dose group and in all dogs in the high-dose group. Rectal temperature was slightly raised in the high-dosed dogs at the end of the study. In the treated groups, there was about a 10 percent reduction in lymphocyte count in the middle and high dose groups after four weeks' administration. After four weeks' administration, SGPT was elevated by 4.3, 6.4 and 29-fold and alkaline phosphatase was elevated by 2.7, 1.9 and 3.2-fold in one dog in the middle dose group and two dogs in the high- dose group respectively. At autopsy five of six middle dose dogs and all high-dose dogs had some gritty and occasionally clotted concretions in their gallbladder consisting predominantly of the calcium salt of ceftriaxone. The bile of the high-dose dogs was normal except for an almost doubled content of bile acids and a 50 percent reduction in iron content. Histologically, perivascular hemorrhage, periarteritis or periphlebitis were noted at the injection site. The centrilobular liver cells showed a slightly increased tendency to cloudy swelling and some limited proliferation of pseudo biliary ducts with the higher dose.

In a 4 1/2-week study, groups of four Füllinsdorf beagle dogs (two/sex/group) were administered ceftriaxone intravenously at dosages of 0, 50 mg/kg/day, 50 mg/kg twice daily, 50 mg/kg three times daily or 75 mg/kg three times daily. Changes in some hematological parameters and liver function tests, although statistically significant, were not considered outside the normal ranges or drug-related. At autopsy, gallbladder concrements containing 30-40 percent, of the calcium salt of ceftriaxone were found in two of the four dogs in the 50 mg/kg twice and three times daily groups. This was also found in three of the four dogs in the

75 mg/kg three times daily group. Dogs in the 50 mg/kg/day, as well as one dog in each of the other ceftriaxone treated groups, had flaky, mucous precipitate in the gallbladder containing 3 percent or less of the calcium salt of ceftriaxone. Histologically, some minor centrilobular liver cell swelling was observed and polarising crystals in the lumen of the gallbladder were observed in one dog in the 50 mg/kg three times daily group and in three dogs in the 75 mg/kg three times daily group.

In a 5-week study, groups of eight beagle dogs (four/sex/group) were administered ceftriaxone intravenously at doses of 0, 60, 120, or 240 mg/kg/day. One animal/sex/group was then allowed to recover for 4 weeks. The dogs were fed three times daily. Occasional vomiting was reported in all groups studied including the control animals. In the 120 and 240 mg/kg/day groups, dose independent statistically insignificant decreases in the average platelet counts (27 and 41 percent in males and females respectively) were reported at the end of the 5-week treatment period. Sporadic elevations in alkaline phosphatase and transaminases were observed for some of the treated animals (approximately 1 1/2 to 2-fold). No evidence of precipitation in the gallbladder was reported.

In another 5-week study, ceftriaxone was administered I.V. in doses of 200 or 400 mg/kg/day to groups of two male and two female beagles. Precipitates were found in the bile of three of the four dogs sacrificed at the end of the dosing period, but in none of the four sacrificed after a 5-week recovery period. The one dog having no precipitation after 5 weeks of treatment (with 400 mg/kg/day) had eaten soon after each injection. Analysis showed the precipitate contained ceftriaxone (0.32-0.57 mcmol/mg) and calcium (0.25-0.47 mcmol/mg). The calcium concentrations in the bile were slightly decreased in the treated dogs (0.30-0.37 mg/mL compared with 0.38-0.39 mg/mL in controls).

To investigate the association of precipitate formation with eating habits, ceftriaxone was given as single I.V. doses of 200 or 450 mg/kg to beagles, 3 hours before autopsy. Precipitates in the bile were found in all the dogs given the drug after a 24-hour fast, but in none of those fed just before or just after injection. The bile volume and the calcium concentration in the gallbladder bile were almost twice as high and the concentration of ceftriaxone in the gallbladder bile (excluding the precipitates) was over 5 times higher in the fasting dogs.

In an *in vitro* study, mixing the bile from the fasting dogs with an equal volume of either a 10 or 5 percent solution of ceftriaxone in dog serum at 37°C led to precipitation within 10 or 24 hours respectively. No precipitate formed, however, in the bile from the fed dogs under the same conditions, even at the ceftriaxone concentration of 10 percent.

Further long-term intravenous studies in beagle dogs showed that ceftriaxone doses of 60, 120 or 240 mg/kg/day administered for 5 weeks to dogs (three/sex/dose), fed three times a day, was not associated with bile precipitate. However, when ceftriaxone was administered to dogs for 13 weeks, under the same feeding conditions as in the preceding 5-week study, bile precipitates were observed in three of the three male and two of the three female dogs treated with 240 mg/kg/day. Almost all the precipitate disappeared from the gallbladder after the 5-

week recovery period. No bile precipitate was found in the dogs treated with 120 mg/kg/day or less.

Baboon

In a 29-day toxicity study, groups of four baboons (two/sex/group) were administered intravenously 0, 25, 150 or 400 mg/kg/day of ceftriaxone. Diarrhea was a frequent finding in the treated animals.

Occasional vomiting was observed. Urinary N-acetylglucosaminidase was statistically significantly increased in the 400 mg/kg/day group. Plasma urea concentrations were statistically significantly increased in this high dose group, but remained within normal range. No drug-related histological changes or gallbladder precipitates were observed.

Groups of baboons (three/sex/dose) were given ceftriaxone I.V. in doses of 0, 30, 150, 400 or 700 mg/kg daily for 26 weeks. Early in the study, emesis and soft stools or diarrhea were noted, particularly at doses of 150 mg/kg daily or greater. Late in the study, sclerosis of the veins used for injection was seen in some animals in the 400 and 700 mg/kg/day groups. Other drug-related findings in some animals in the 700 mg/kg/day group were lethargy, decreased activity, pale oral mucosa or facial colour, unthrifty and hunched appearance, sunken eyes, body sores, tremors, weight loss, dehydration and a sweet body odour. Treatment- related haematological changes included decreases in platelet counts particularly in females (up to 51 percent), sporadic increases in reticulocyte counts and transient prolongation of clotting times. The less than 15 percent decreases in haematocrit, haemoglobin and erythrocyte counts found early in the study in the highest dosed group largely returned to normal by the end of the study. The mean SGPT (serum ALT) values were increased by 2 or 3-fold in all treated males at week 4, but were subsequently normal. One male in the highest dose group gradually deteriorated with signs of uremia and was sacrificed at week 20. All other animals were autopsied after 26 weeks of treatment. Increases in absolute kidney weight of 12, 38 and 42 percent were noted in females dosed at 400 mg/kg/day and in males and females dosed at 700 mg/kg/day respectively. Nephropathy was found in the 150, 400 and 700 mg/kg/day groups. In the animals treated with 150 mg/kg/day, it was minimal (greenish-brown granular pigment in regenerative tubular epithelium). At the two highest dose levels, the nephropathy ranged from minimal to moderately severe with necrosis, microliths and regeneration of the renal tubuli. Secondary to the nephropathy there was thymic atrophy in four animals and decreased bone marrow cellularity in two. In the gallbladder, no precipitation was found in the baboons given 30 or 150 mg/kg/day. Soft or granular deposits were found in the gallbladders of some animals treated with 400 or 700 mg/kg/day.

Microscopic choleliths and/or amorphous material were also noted in the lumen in most males of the two highest dose groups.

<u>Fertility and Reproduction Study</u>

Groups of Sprague-Dawley rats (twenty-two/sex/dose) received 0, 100, 350 or 700 mg/kg ceftriaxone I.V. daily. The males were dosed for at least 60 days prior to and during mating and

the females for at least 14 days prior to mating and throughout gestation and lactation. The delivery was natural in twelve females per group and by Cesarian section in the others. Copulation, fertilization and pregnancy were not impaired. There was a tendency to cecal enlargement in all treated groups.

No adverse effects were found on the numbers or relative proportions of corpora lutea and implantations, or on the resorption rate or fetal weight. No visceral or skeletal abnormalities were found in the fetuses from either the control or the treated animals.

In the dams which delivered normally, no adverse effects were seen during lactation or on the numbers of implantation sites and live births. The gestation, viability and lactation indices were not affected and neonatal body weight at birth and throughout lactation were normal. The general appearance, behaviour and sensory function of all the offspring were normal during the suckling period and at autopsy.

Tetratology Studies

Mouse
Groups of thirty female Füllinsdorf albino mice were given 0, 100, 250 or 625 mg/kg ceftriaxone I.V. daily from day 7 to day 16 of gestation. About twenty animals per group were sacrificed on day 19 and the remainder allowed to deliver normally and rear their young.

In the groups that were sacrificed on day 19, the incidence of 14 ribs was much greater (18 fetuses all from one litter) in the high-dose group than in the control group (2 fetuses). In the groups that were permitted to deliver normally, the percentage of resorptions per implantation appeared to increase in a dose-related manner: 6.5, 10.5, 11.1, 17.8 percent at doses of 0, 100, 250, 625 mg/kg/day respectively. The pups showed a uniform increase in body weight during the lactation period. No indications of any embryotoxic or teratogenic effect (except for exencephaly observed in one fetus at the lowest dosage group) of the drug were found.

Rat
Groups of thirty female Sprague-Dawley rats were given 0, 100, 350 or 700 mg/kg ceftriaxone I.V. daily from day 7 to day 17 of gestation. Twenty animals per group were sacrificed on day 21 and the remaining ten were allowed to deliver normally.

No dams died during gestation or lactation. There were no drug-related differences in average litter size, resorption rate or fetal body weight between the control and treated groups. The drug produced no external, visceral or skeletal abnormalities in the fetuses.

Rabbit
Groups of seven to twelve rabbits were given 0, 20 or 100 mg/kg ceftriaxone I.V. daily from day 7 to day 19 of gestation. The drug was poorly tolerated by the dams, death occurring in 50 and 30 percent of the dams in the high and low-dose groups respectively. Diarrhea was seen in most of the dams (heavy in all high-dose animals). All animals in the high-dose group

experienced vaginal bleeding.

The number of resorptions was significantly increased: 100 percent of implantations at the high dose and 50.6 percent at the low dose. Examination of surviving fetuses (low-dose group) provided no evidence of any teratogenic effect of the drug.

Monkey
Ceftriaxone was given I.V. in a dose of 100 mg/kg/day to ten Cynomolgus monkeys (group A) from day 21 to day 31 of gestation and to nine (group B) from day 32 to day 45 of gestation. A control group (nine animals) received the vehicle from day 21 to day 45 of gestation. Fetuses were delivered by Cesarian section on day 100 ± 1 of gestation and immediately examined for abnormalities.

Abortion occurred in two control monkeys, one in group A and two in group B. Mild diarrhea occurred in two animals in each of the treatment groups. The body weights of the fetuses from group B (average of approximately 99 grams) were decreased in comparison to controls (average of approximately 108 grams). All other findings were normal and there were no fetal malformations.

Perinatal and Postnatal Study
Groups of twenty female Sprague-Dawley rats were given ceftriaxone I.V. in doses of 0, 100, 350 and 700 mg/kg/day from day 17 of gestation and throughout lactation. All were allowed to give birth naturally.

No maternal deaths occurred. Body weight gain and food intake were slightly diminished in all treated dams during gestation but not during lactation. Parturition occurred normally. At autopsy, cecal enlargement was seen in all treated dams. The average numbers of implantations and of live and dead births were similar in all groups. Neonatal viability, body weight, appearance, behaviour and sensory function were not affected by the drug. No notable external, visceral or skeletal anomalies were seen.

During the 8-week observation period after weaning, no notable effects were seen on mean body weight, emotional behaviour, learning ability, fertility or reproductive performance of the F1 rats.

Mutagenicity Studies In the Ames test, ceftriaxone did not induce mutations in various Salmonella typhimurium strains at concentrations up to 100 ng/plate either with or without activation by a rat liver homogenate fraction. Higher concentrations were bactericidal to these strains.

In the micronucleus test, groups of three mice/sex/dose were given 18, 84.0 or 420.0 mg/kg ceftriaxone I.V. 30 and 6 hours before sacrifice. No drug-related increases in micronuclei were found. Hence, under the conditions used, the drug does not induce chromosome breaks or

mitotic non-disjunctions in mouse bone marrow cells.

In a third study, lymphoblasts obtained from human peripheral blood lymphocytes were exposed *in vitro* to ceftriaxone at a concentration of 0.2, 2 or 20 mg/mL culture medium for 24 hours. No increase in chromosome aberrations was observed with the first two concentrations. The highest concentration could not be evaluated since it was toxic to the cells.

Other Studies Tolerance Studies

Intramuscular route
Female albino rats were given 0.2 mL of freshly prepared injections of ceftriaxone in water into the rectus femoris muscle of a hind leg. The increases in SGOT levels 24 hours after administration were 44 and 58 percent for 119 and 289 mg/mL solutions of ceftriaxone respectively.

New Zealand white rabbits received 0.1 or 1.0 mL injections of a low concentration (10 mg/mL) or a high concentration (600 mg added to 1.7 mL) of ceftriaxone in water, or distilled water into the sacrospinalis muscle. While 0.1 mL of the low concentration was not more irritating than the vehicle, 0.1 mL of the high concentration and 1.0 mL of both concentrations produced significant muscle irritation estimated in terms of swelling, edema, hemorrhage and necrosis. The irritation appeared to be dependent upon both volume and dose.

Intramuscular injection of a 100 mg/mL solution of ceftriaxone in a dose of 100 mg/kg caused a 4-fold rise in plasma SGOT in one dog and a 47 percent increase in another. Slight pain occurred during injection in both animals.

Intravenous route
An aqueous solution containing 100 mg/mL ceftriaxone was diluted 1, 3 or 7-fold with normal saline solution and incubated with citrated whole canine blood for 5 minutes. No hemolysis occurred.

Injection of 0.5 mL of ceftriaxone disodium aqueous solution (100 mg/mL) into the rabbit ear vein was well tolerated.

A 10 mg/mL solution of ceftriaxone in water was administered I.V. to dogs (0.4 mL/kg) at a rate of 1.25 mL/min. Analysis of plasma for hemoglobin just before and 1 minute after infusion did not reveal any detectable hemolysis. Gross examination of the injection sites 24 hours later did not reveal any venous irritation. In another study in dogs, a 40 mg/mL solution of ceftriaxone in 5% dextrose solution was infused I.V. at the same rate to achieve a dose of 16 mg/kg (0.4 mL/kg). No appreciable hemolysis and no venous irritation were found.

Intrathecal route
Cerebrospinal fluid (3 mL in one dog and 2 mL in seven dogs) was withdrawn from Swiss beagle dogs (four males and four females) anaesthetised with pentobarbital and replaced by

ceftriaxone solution (100 mg/mL) or isotonic saline. The 3 mL replacement dose was too toxic. Injection of ceftriaxone (2 mL) immediately resulted in depression of breathing followed by temporary apnea (2-3 minutes), significant tachycardia, opisthotonus and tetanic convulsions. After 24 hours, convulsions and central nervous disorders were still present and the CSF contained increased protein and mono- and polynucleated cells. At autopsy, the brain was normal, but the subarachnoid space was dilated with infiltration of polymorphonuclear leucocytes and edema. No abnormal findings were observed in control dogs given saline.

Nephrotoxicity Male rabbits (three/dose) were administered single S.C. injections of 100, 200 or 400 mg/kg ceftriaxone. No drug-related renal changes were reported but a 4-5 percent loss of body weight was observed.

Another study was carried out comparing ceftriaxone, cephaloridine and cefoxitin at single doses of 30, 300 or 1,000 mg/kg in rabbits. Slight to moderate focal or multi-focal necrosis of kidney tubular epithelium was observed in rabbits dosed with 1,000 mg/kg of ceftriaxone.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Rocephin®, Powder for Solution, 250 mg and 1 g, submission control 134328, Product Monograph, Hoffman-La Roche Limited. February 09, 2010

2. CEFTRIAXONE SODIUM FOR INJECTION, Powder for Solution, 1 g and 10 g, submission control 246728, Product Monograph, Teva Canada Limited. May 26, 2021

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]cefTRIAXone Sodium for Injection BP
Ceftriaxone Sodium for Injection

Read this carefully before you start taking Ceftriaxone Sodium for Injection BP and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Ceftriaxone Sodium for Injection BP.

What is Ceftriaxone Sodium for Injection BP used for?

Ceftriaxone Sodium for Injection BP is used to treat infections of the:

- brain (meningitis)
- lungs
- abdomen and abdominal wall (peritonitis)
- urinary tract including kidneys
- bones and joints
- skin or soft tissues
- blood
- heart

It is also used:

- to treat gonorrhea which is a sexually transmitted infection
- to treat bronchitis which is an infection of the chest
- to prevent infections during surgery

Antibacterial drugs like Ceftriaxone Sodium for Injection BP treat only bacterial infections. They do not treat viral infections such as the common cold.

How does Ceftriaxone Sodium for Injection BP work?
Ceftriaxone Sodium for Injection BP is an antibiotic. It belongs to a group of antibiotics called cephalosporins. It works by killing bacteria that cause infections. It does this by preventing them from making their cell walls.

What are the ingredients in Ceftriaxone Sodium for Injection BP
Medicinal ingredients: ceftriaxone sodium
Non-medicinal ingredients: none

Ceftriaxone Sodium for Injection BP comes in the following dosage forms:

- Powder for solution; 250 mg, 500 mg, 1 g, 2 g and 10 g ceftriaxone (as ceftriaxone

sodium) per vial.

Do not use Ceftriaxone Sodium for Injection BP if:

- You are allergic to ceftriaxone sodium or any component of the container, other cephalosporins or penicillins.

- Ceftriaxone Sodium for Injection BP should not be given to newborn babies with certain health conditions.

- Ceftriaxone Sodium for Injection BP should not be given along with intravenous (into a vein) solutions that contain calcium.

Talk to your doctor or nurse before you are given Ceftriaxone Sodium for Injection BP if you:

- have had an allergic reaction in the past, including to a medicine
- have or have had asthma
- have had a condition called hemolytic anemia (loss of red blood cells) after taking an antibiotic
- have kidney problems
- have liver problems
- have or have had gastrointestinal disease (diseases of the stomach or bowels) including colitis (inflammation of the bowels)
- are on a low sodium diet
- are pregnant
- are breastfeeding

Other warnings you should know about:

Secondary infections
If you develop new symptoms while you are receiving Ceftriaxone Sodium for Injection BP, talk to your healthcare professional since you may have a second infection.

Other medicines and your kidneys
Tell your healthcare professional if you are taking any other medicines before you receive Ceftriaxone Sodium for Injection BP. It can interact with other medicines that have an effect on your kidneys.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Ceftriaxone Sodium for Injection BP:

- Ceftriaxone Sodium for Injection BP will be given to you by a healthcare professional

- It will be given in one of the following ways:

- as a slow injection into a vein
- as an infusion through a small tube into one of your veins
- as an injection into a large muscle (such as the muscle in your arm)

- Although you may feel better early in treatment, Ceftriaxone Sodium for Injection BP should be used exactly as directed.

- Misuse or overuse of Ceftriaxone Sodium for Injection BP could lead to the growth of bacteria that will not be killed by Ceftriaxone Sodium for Injection BP (resistance). This means that Ceftriaxone Sodium for Injection BP may not work for you in the future.

- Do not share your medicine.

Usual Dose:

- Your healthcare professional will decide how much Ceftriaxone Sodium for Injection BP you will receive and for how long you will receive it.

Overdose:

If you think you, or a person you are caring for, have taken too much Ceftriaxone Sodium for Injection BP, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using Ceftriaxone Sodium for Injection BP?

These are not all the possible side effects you may feel when taking Ceftriaxone Sodium for Injection BP. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

Common:
- diarrhea
- pain or tenderness at the injection site

Uncommon:
- nausea
- vomiting
- altered sense of taste
- dizziness
- headache
- sweating

- malaise
- hot flashes
- swelling of the hands or feet
- tingling, prickling or numbness of the hands or feet
- impaired coordination

Rare

- stomach pain and cramps
- passing gas
- heartburn
- burning tongue
- nose bleed

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Anaphylactic reactions (allergic reactions): difficulty breathing, fever, hives, itching, rash, swelling of your tongue or throat.			√
Anemia (decreased red blood cells): dizziness, fatigue, loss of energy, shortness of breath, weakness.		√	
Oral candidiasis (yeast infection of the mouth): bad taste in the mouth, creamy white bumps on the tongue, cheeks, gums or throat that bleed when scrapped, pain, trouble swallowing.		√	
Fever or chills		√	
Phlebitis (swelling of a vein): pain, tenderness, redness or swelling of a body area.		√	
Skin reaction: Severe skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforma: blistering, hives, itching blistering, inflamed, peeling, red and dying skin and severe rash.		√	
Infection of the vagina, including yeast infection: burning during intercourse or urination, discharge, pain, redness, swelling, vaginal itching.		√	
RARE			

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Neutropenia (decreased white blood cells): aches, bleeding gums, feeling tired, fever, flu-like symptoms, infections, sore mouth and gums, mouth ulcer, rash.			√
Clostridium difficile colitis (bowel inflammation): severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness.			√
Kidney problems: abdominal or back pain, changes in your urine, confusion, fatigue, irregular heartbeat, nausea, shortness of breath, swelling, weakness.		√	
Liver problems: abdominal pain, dark urine, fatigue, loss of appetite, nausea, vomiting, yellowing of the skin or eyes (jaundice).		√	
Palpitations		√	
Mouth sores		√	
Thrombocytopenia (decreased platelets in the blood); bleeding, bruising, fatigue, weakness.		√	
Severe Cutaneous Adverse Reactions (SCAR) (severe skin reactions that may also affect other organs: • Skin peeling, scaling, or blistering (with or without pus) which may also affect your eyes, mouth, nose or genitals, itching, severe rash, bumps under the skin, skin pain, skin colour changes (redness, yellowing, purplish) • Swelling and redness of eyes or face • Flu-like feeling, fever, chills, body aches, swollen glands, cough • Shortness of breath, chest pain or discomfort			√
Encephalopathy (brain dysfunction): agitation, change in mental state, confusion, difficulty thinking,			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
disorientation, going in and out of consciousness, hallucinations, sudden involuntary muscle jerks, tremors or twitches			

If you have troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or

- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature (between 15 and 30 ºC) and protect from light.

Keep out of reach and sight of children.

If you want more information about Ceftriaxone Sodium for Injection BP:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.sterimax.com; or by calling 1-800-881-3550.

This leaflet was prepared by:

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