Rofecin®

Ceftriaxone USP

COMPOSITION

Active ingredient: Ceftriaxone in the form of the disodium salt. Vials containing dry substance equivalent to 250 mg, 500 mg, 1 gm and 2 gm ceftriaxone.

Solvent for parenteral use: The solvent ampoule for IM injection contains 1% lidocaine hydrochloride solution, and for IV injection sterile water for injections.

1 ml solvent for IM injection contains 10.66 mg lidocaine hydrochloride monohydrate equivalent to 10 mg anhydrous lidocaine hydrochloride.

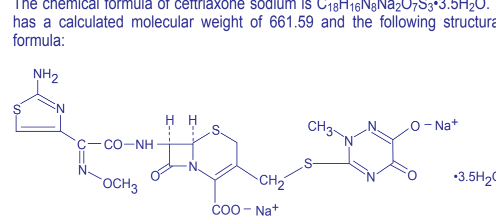
Prescription only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of **Rofecin**® and other antibacterial drugs, **Rofecin**® should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

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

The chemical formula of ceftriaxone sodium is $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3.5H_2O$. It has a calculated molecular weight of 661.59 and the following structural formula:



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

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

CLINICAL PHARMACOLOGY

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

Table 1: Ceftriaxone Plasma Concentrations After Single Dose Administration

Dose/Route	Average Plasma Concentrations (µg/mL)								
	0.5 hr	1hr	2hr	4hr	6hr	8hr	12hr	16hr	24hr
0.5 gm IV*	82	59	48	37	29	23	15	10	5
0.5 gm IM 250 mg/mL	22	33	38	35	30	26	16	ND	5
0.5 gm IM 350 mg/mL	20	32	38	34	31	24	16	ND	5
1 gm IV*	151	111	88	67	53	43	28	18	9
1 gm IM	40	68	76	68	56	44	29	ND	ND
2 gm IV*	257	192	154	117	89	74	46	31	15

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

ND = Not determined.

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

Ceftriaxone concentrations in urine are shown in Table 2.

Table 2: Urinary Concentrations of Ceftriaxone After Single Dose Administration

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

ND = Not determined.

Thirty-three percent to 67% of a ceftriaxone dose was excreted in the urine as unchanged drug and the remainder was secreted in the bile and ultimately found in the feces as microbiologically inactive compounds. After a 1 gm IV dose, average concentrations of ceftriaxone, determined from 1 to 3 hours after dosing, were 581 µg/mL in the gallbladder bile, 788 µg/mL in the common duct bile, 898 µg/mL in the cystic duct bile, 78.2 µg/gm in the gallbladder wall and 62.1 µg/mL in the concurrent plasma.

Over a 0.15 to 3 gm dose range in healthy adult subjects, the values of elimination half-life ranged from 5.8 to 8.7 hours; apparent volume of distribution from 5.78 to 13.5 L; plasma clearance from 0.58 to 1.45 L/hour; and renal clearance from 0.32 to 0.73 L/hour. Ceftriaxone is reversibly bound to human plasma proteins, and the binding decreased from a value of 95% bound at plasma concentrations of <25 µg/mL to a value of 85% bound at 300 µg/mL. Ceftriaxone crosses the blood placenta barrier.

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

Table 3: Average Pharmacokinetic Parameters of Ceftriaxone in Pediatric Patients With Meningitis

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

Compared to that in healthy adult subjects, the pharmacokinetics of ceftriaxone were only minimally altered in elderly subjects and in patients with renal impairment or hepatic dysfunction (Table 4); therefore, dosage adjustments are not necessary for these patients with ceftriaxone dosages up to 2 gm per day. Ceftriaxone was not removed to any significant extent from the plasma by hemodialysis; in six of 26 dialysis patients, the elimination rate of ceftriaxone was markedly reduced.

Table 4: Average Pharmacokinetic Parameters of Ceftriaxone in Humans

Subject Group	Elimination Half-Life (hr)	Plasma Clearance (L/hr)	Volume of Distribution (L)
Healthy Subjects	5.8-8.7	0.58-1.45	5.8-13.5
Elderly Subjects (mean age, 70.5 yr)	8.9	0.83	10.7
Patients With Renal Impairment			
Hemodialysis Patients (0-5 mL/min)*	14.7	0.65	13.7
Severe (5-15 mL/min)	15.7	0.56	12.5
Moderate (16-30 mL/min)	11.4	0.72	11.8
Mild (31-60 mL/min)	12.4	0.70	13.3
Patients With Liver Disease	8.8	1.1	13.6

*Creatinine clearance.

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

Pharmacokinetics in the Middle Ear Fluid: In one study, total ceftriaxone concentrations (bound and unbound) were measured in middle ear fluid obtained during the insertion of tympanostomy tubes in 42 pediatric patients with otitis media. Sampling times were from 1 to 50 hours after a single intramuscular injection of 50 mg/kg of ceftriaxone. Mean (± SD) ceftriaxone levels in the middle ear reached a peak of 35 (± 12) µg/mL at 24 hours, and remained at 19 (± 7) µg/mL at 48 hours. Based on middle ear fluid ceftriaxone concentrations in the 23 to 25 hour and the 46 to 50 hour sampling time intervals, a half-life of 25 hours was calculated. Ceftriaxone is highly bound to plasma proteins. The extent of binding to proteins in the middle ear fluid is unknown.

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

***Microbiology:** Mechanism of Action*

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

Mechanism of Resistance

Resistance to ceftriaxone is primarily through hydrolysis by beta-lactamase, alteration of penicillin-binding proteins (PBPs), and decreased permeability.

Interaction with Other Antimicrobials

In an in vitro study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone.

Ceftriaxone has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE (1) section:

• Gram-negative bacteria

Acinetobacter calcoaceticus
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Neisseria meningitidis
Proteus mirabilis
Proteus vulgaris
Pseudomonas aeruginosa
Serratia marcescens

• Gram-positive bacteria

Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans group streptococci

• Anaerobic bacteria

Bacteroides fragilis
Clostridium species
Peptostreptococcus species

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ceftriaxone. However, the efficacy of ceftriaxone in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

• Gram-negative bacteria

Citrobacter diversus
Citrobacter freundii
Providencia species (including *Providencia rettgeri*)
Salmonella species (including *Salmonella typhi*)
Shigella species

• Gram-positive bacteria

Streptococcus agalactiae

• Anaerobic bacteria

Porphyromonas (Bacteroides) melaninogenicus
Prevotella (Bacteroides) bivius

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method. The MIC values should be interpreted according to criteria provided in Table 5.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method. This procedure uses paper disks impregnated with 30 mcg ceftriaxone to test the susceptibility of microorganisms to ceftriaxone. The disk diffusion interpretive criteria are provided in Table 5.

Anaerobic techniques:

For anaerobic bacteria, the susceptibility to ceftriaxone as MICs can be determined by a standardized agar test method. The MIC values obtained should be interpreted according to the criteria provided in Table 5.

Table 5: Susceptibility Test Interpretive Criteria for Ceftriaxone

Pathogen	Minimum Inhibitory Concentrations (mcg/ml)			Disk Diffusion Zone Diameters (mm)		
	(S) Susceptible	(I) Intermediate	(R) Resistant	(S) Susceptible	(I) Intermediate	(R) Resistant
Enterobacteriaceae[a]	≤ 1	2	≥4	≥ 23	20-22	≤19
Haemophilus influenzae[b,c]	≤2	-	-	≥26	-	-
Neisseria gonorrhoeae[c]	≤ 0.25	-	-	≥ 35	-	-
Neisseria meningitidis[c]	≤ 0.12	-	-	≥ 34	-	-
Streptococcus pneumoniae[d] meningitis isolates	≤ 0.5	1	≥ 2	-	-	-
Streptococcus pneumoniae[d] non-meningitis isolates	≤1	2	≥4	-	-	-
Streptococcus species beta-hemolytic group[c]	≤0.5	-	-	≥ 24	-	-
Viridans group streptococci	≤ 1	2	≥ 4	≥27	25-26	≤24
Anaerobic bacteria (agar method)	≤ 1	2	≥ 4	-	-	-

a. Susceptibility interpretive criteria for *Enterobacteriaceae* are based on a dose of 1 gram IV q 24h. For isolates with intermediate susceptibility, use a dose of 2 grams IV q 24h in patients with normal renal function.

b. For *Haemophilus influenzae*, susceptibility interpretive criteria are based on a dose of 2 grams IV every 24 hours in patients with normal renal function.

c. The current absence of data on resistant isolates precludes defining any category other than 'Susceptible'. If isolates yield MIC results other than susceptible, they should be submitted to a reference laboratory for additional testing.

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

Susceptibility of staphylococci to ceftriaxone may be deduced from testing only penicillin and either cefoxitin or oxacillin.

A report of *Susceptible* indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration at the site of infection. A report of *Intermediate* indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug d reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control:

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individual performing the test.

Standard ceftriaxone powder should provide the following range of MIC values noted in Table 6. For the diffusion technique using the 30 mcg disk, the criteria in Table 6 should be achieved.

Table 6: Acceptable Quality Control Ranges for Ceftriaxone

QC Strain	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion Zone diameters (mm)
Escherichia coli ATCC 25922	0.03 - 0.12	29 - 35
Staphylococcus aureus ATCC 25923	----------	22 - 28
Staphylococcus aureus ATCC 29213	1 – 8	---------
Haemophilus influenzae ATCC 49247	0.06 - 0.25	31 - 39
Neisseria gonorrhoeae ATCC 49226	0.004 - 0.015	39 - 51
Pseudomonas aeruginosa ATCC 27853	8-64	17-23
Streptococcus pneumoniae ATCC 49619	0.03 - 0.12	30 - 35
Bacteroides fragilis ATCC 25285 (agar method)	32 – 128	---------
Bacteroides thetaiotaomicron ATCC 29741 (agar method)	64 – 256	---------

INDICATIONS AND USAGE

Before instituting treatment with **Rofecin**®, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of **Rofecin**® and other antibacterial drugs, **Rofecin**® should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Rofecin® is indicated for the treatment of the following infections when caused by susceptible organisms:

LOWER RESPIRATORY TRACT INFECTIONS caused by *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Escherichia coli, Enterobacter aerogenes, Proteus mirabilis* or *Serratia marcescens.*

ACUTE BACTERIAL OTITIS MEDIA caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including beta-lactamase producing strains) or *Moraxella catarrhalis* (including beta-lactamase producing strains).

NOTE: In one study lower clinical cure rates were observed with a single dose of ceftriaxone compared to 10 days of oral therapy. In a second study comparable cure rates were observed between single dose ceftriaxone and the comparator. The potentially lower clinical cure rate of ceftriaxone should be balanced against the potential advantages of parenteral therapy .

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes,* Viridans group streptococci, *Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Morganella morganii,* Pseudomonas aeruginosa, Serratia marcescens, Acinetobacter calcoaceticus, Bacteroides fragilis** or *Peptostreptococcus species.*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *Escherichia coli, Proteus mirabilis, Proteus vulgaris, Morganella morganii* or *Klebsiella pneumoniae.*

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase- and nonpenicillinase-producing strains, and pharyngeal gonorrhea caused by nonpenicillinase-producing strains of *Neisseria gonorrhoeae.*

PELVIC INFLAMMATORY DISEASE caused by *Neisseria gonorrhoeae.* **Rofecin**®, like other cephalosporins, has no activity against *Chlamydia trachomatis.* Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and *Chlamydia trachomatis* is one of the suspected pathogens, appropriate antichlamydial coverage should be added.

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

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

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

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

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

SURGICAL PROPHYLAXIS: The preoperative administration of a single 1 gm dose of **Rofecin**® may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (eg, vaginal or abdominal hysterectomy or cholecystectomy for chronic calculous cholecystitis in high-risk patients, such as those over 70 years of age, with acute cholecystitis not requiring therapeutic antimicrobials, obstructive jaundice or common duct bile stones) and in surgical patients for whom infection at the operative site would present serious risk (eg, during coronary artery bypass surgery). Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery.

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

CONTRAINDICATIONS

Hypersensitivity

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

Neonates

Premature neonates: **Rofecin**® is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age).

Hyperbilirubinemic neonates: Hyperbilirubinemic neonates should not be treated with **Rofecin**®. Ceftriaxone can displace bilirubin from its binding to serum albumin, leading to a risk of bilirubin encephalopathy in these patients.

Neonates Requiring Calcium Containing IV Solutions

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

Cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving ceftriaxone and calcium-containing fluids.

In some of these cases, the same intravenous infusion line was used for both ceftriaxone and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. There have been no similar reports in patients other than neonates.

Lidocaine

Intravenous administration of ceftriaxone solutions containing lidocaine is contraindicated. When lidocaine solution is used as a solvent with ceftriaxone for intramuscular injection, exclude all contraindications to lidocaine. Refer to the prescribing information of lidocaine.

WARNINGS

Hypersensitivity Reactions

Before therapy with **Rofecin**® is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins and other beta-lactam agentsor other drugs. This product should be given cautiously to penicillin and other beta-lactam agent-sensitive patients. Antibacterial drugs should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions (i.e., anaphylaxis) have been reported. In case of severe hypersensitivity reactions, treatment with ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated.

Methemoglobinemia

Cases of methemoglobinemia have been reported in association with local anesthetic use (e.g. lidocaine). Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.

Signs and symptoms of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue Rocephin Kit and any other oxidizing agents. Depending on the severity of the symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. More severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

Interaction with Calcium-Containing Products

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute **Rofecin**® vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when **Rofecin**® is mixed with calcium-containing solutions in the same IV administration line. **Rofecin**® 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, **Rofecin**® and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. In vitro studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium (see **CLINICAL PHARMACOLOGY, CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION).**

Clostridium difficile -Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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

Hemolytic Anemia

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

PRECAUTIONS

Development of Drug-resistant Bacteria

Prescribing ceftriaxone in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. Prolonged use of **Rofecin**® may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Patients with Renal or Hepatic Impairment

Ceftriaxone is excreted via both biliary and renal excretion (see **CLINICAL PHARMACOLOGY**). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of **Rofecin**® are administered.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, caution should be exercised and the **Rofecin**® dosage should not exceed 2 gm daily.

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

Effect on Prothrombin Time

Alterations in prothrombin times have occurred in patients treated with ceftriaxone. Monitor prothrombin time during **Rofecin**® treatment in patients with impaired vitamin K synthesis or low vitamin K stores (eg, chronic hepatic disease and malnutrition). Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

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

Gallbladder Pseudolithiasis

Ceftriaxone-calcium precipitates in the gallbladder have been observed in patients receiving **Rofecin**®. These precipitates appear on sonography as an echo without acoustical shadowing suggesting sludge or as an echo with acoustical shadowing which may be misinterpreted as gallstones. The probability of such precipitates appears to be greatest in pediatric patients. Patients may be asymptomatic or may develop symptoms of gallbladder disease. The condition appears to be reversible upon discontinuation of ceftriaxone sodium and institution of conservative management. Discontinue ceftriaxone sodium in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above.

Urolithiasis and Post-Renal Acute Renal Failure

Ceftriaxone-calcium precipitates in the urinary tract have been observed in patients receiving ceftriaxone and may be detected as sonographic abnormalities. The probability of such precipitates appears to be greatest in pediatric patients. Patients may be asymptomatic or may develop symptoms of urolithiasis, and ureteral obstruction and post-renal acute renal failure. The condition appears to be reversible upon discontinuation of ceftriaxone sodium and institution of appropriate management. Ensure adequate hydration in patients receiving **Rofecin**®. Discontinue **Rofecin**® in patients who develop signs and symptoms suggestive of urolithiasis, oliguria or renal failure and/or the sonographic findings described above.

Pancreatitis

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

Information for Patients

- Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to stop use and seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue.
- Patients should be counseled that antibacterial drugs including **Rofecin**® should only be used to treat bacterial infections. They do not treat viral infections (eg, common cold).
- When **Rofecin**® is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by **Rofecin**® or other antibacterial drugs in the future.
- Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

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

Nursing Mothers: Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when **Rofecin**® is administered to a nursing woman.

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

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

The pharmacokinetics of ceftriaxone were only minimally altered in geriatric patients compared to healthy adult subjects and dosage adjustments are not necessary for geriatric patients with ceftriaxone dosages up to 2 grams per day provided there is no severe renal and hepatic impairment. (see **CLINICAL PHARMACOLOGY**).

Influence on Diagnostic Tests: In patients treated with **Rofecin**® the Coombs' test may become positive. **Rofecin**®, like other antibacterial drugs, may result in positive test results for galactosemia.

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

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

Drug Interactions: Patients that are administered local anesthetics may be at increased risk of developing methemoglobinemia when concurrently exposed to the following oxidizing agents:

Class	Examples
Nitrates/Nitrites	Nitroglycerin, nitroprusside, nitric oxide, nitrous oxide
Local anesthetics	Benzocaine, lidocaine, bupivacaine, mepivacaine, tetracaine, prilocaine, procaine, articaine
Antineoplastic agents	cyclophosphamide, flutamide, rasburicase, isofamide, hydroxyurea
Antibiotics	dapsone, sulfonamides, nitrofurantoin, para-aminosalicylic acid
Antimalarials	chloroquine, primaquine
Anticonvulsants	phenytoin, sodium valproate, phenobarbital
Other drugs	acetaminophen, metoclopramide, sulfa drugs (i.e.,sulfasalazine), quinine

ADVERSE REACTIONS

Rofecin® is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to ceftriaxone therapy or of uncertain etiology, were observed:

LOCAL REACTIONS —pain, induration and tenderness was 1% overall. Phlebitis was reported in <1% after IV administration. The incidence of warmth, tightness or induration was 17% (3/17) after IM administration of 350 mg/mL and 5% (1/20) after IM administration of 250 mg/mL.

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS—injection site pain (0.6%).

HYPERSENSITIVITY—rash (1.7%). Less frequently reported (<1%) were pruritus, fever or chills.

INFECTIONS AND INFESTATIONS—genital fungal infection (0.1%).

HEMATOLOGIC —eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (<1%) were anemia, hemolytic anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.

BLOOD AND LYMPHATIC DISORDERS—granulocytopenia (0.9%), coagulopathy (0.4%). .

GASTROINTESTINAL—diarrhea/loose stools (2.7%). Less frequently reported (<1%) were nausea or vomiting, and dysgeusia. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment (see **WARNINGS**).

HEPATIC—elevations of aspartate aminotransferase (AST) (3.1%) or alanine aminotransferase (ALT) (3.3%). Less frequently reported (<1%) were elevations of alkaline phosphatase and bilirubin.

RENAL—elevations of the BUN (1.2%). Less frequently reported (<1%) were elevations of creatinine and the presence of casts in the urine.

CENTRAL NERVOUS SYSTEM—headache or dizziness were reported occasionally (<1%).

GENITOURINARY—moniliasis or vaginitis were reported occasionally (<1%).

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (<1%).

INVESTIGATIONS—blood creatinine increased (0.6%).

Other rarely observed adverse reactions (<0.1%) include abdominal pain, agranulocytosis, allergic pneumonitis, anaphylaxis, basophilia, biliary lithiasis, bronchospasm, colitis, dyspepsia, epistaxis, flatulence, gallbladder sludge, glycosuria, hematuria, jaundice, leukocytosis, lymphocytosis, monocytosis, nephrolithiasis, palpitations, a decrease in the prothrombin time, renal precipitations, seizures, and serum sickness.

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

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

GASTROINTESTINAL – pancreatitis, stomatitis and glossitis.

GENITOURINARY – oliguria, ureteric obstruction, post-renal acute renal failure.

DERMATOLOGIC – exanthema, allergic dermatitis, urticaria, edema; acute generalized exanthematous pustulosis (AGEP) and isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens-Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis) have been reported.

HEMATOLOGICAL CHANGES: Isolated cases of agranulocytosis (< 500/mm³) have been reported, most of them after 10 days of treatment and following total doses of 20 g or more.

NERVOUS SYSTEM DISORDERS: Risk of convulsions and involuntary movements.

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

Cephalosporin Class Adverse Reactions

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

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

Altered Laboratory Tests: Positive direct Coombs' test, false-positive test for urinary glucose, and elevated LDH (see **PRECAUTIONS**).

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION**). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Rofecin® may be administered intravenously or intramuscularly. Before administration of ceftriaxone IV injection in body please check the tolerability by giving test dose. Administer ceftriaxone IV injection by two to four minutes .

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute **Rofecin**® vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when **Rofecin**® is mixed with calcium-containing solutions in the same IV administration line. **Rofecin**® 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, **Rofecin**® and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid (see **WARNINGS**).

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

NEONATES: Hyperbilirubinemic neonates, especially prematures, should not be treated with **Rofecin**®. **Rofecin**® is contraindicated in premature neonates (see **CONTRAINDICATIONS**).

Rofecin® is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium (see **CONTRAINDICATIONS**).

Intravenous doses should be given over 60 minutes in neonates to reduce the risk of bilirubin encephalopathy.

PEDIATRIC PATIENTS: For the treatment of skin and skin structure infections, the recommended total daily dose is 50 to 75 mg/kg given once a day (or in equally divided doses twice a day). The total daily dose should not exceed 2 grams.

For the treatment of acute bacterial otitis media, a single intramuscular dose of 50 mg/kg (not to exceed 1 gram) is recommended (see **INDICATIONS AND USAGE**).

For the treatment of serious miscellaneous infections other than meningitis, the recommended total daily dose is 50 to 75 mg/kg, given in divided doses every 12 hours. The total daily dose should not exceed 2 grams.

In the treatment of meningitis, it is recommended that the initial therapeutic dose be 100 mg/kg (not to exceed 4 grams). Thereafter, a total daily dose of 100 mg/kg/day (not to exceed 4 grams daily) is recommended. The daily dose may be administered once a day (or in equally divided doses every 12 hours). The usual duration of therapy is 7 to 14 days.

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

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

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.

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

Generally, **Rofecin**® therapy should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration of therapy is 4 to 14 days; in complicated infections, longer therapy may be required.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least 10 days.

No dosage adjustment is necessary for patients with impairment of renal or hepatic function (see **PRECAUTIONS**).

The dosages recommended for adults require no modification in elderly patients, up to 2 gm per day, provided there is no severe renal and hepatic impairment (see **PRECAUTIONS**).

DIRECTIONS FOR USE: *Intramuscular Administration:* Reconstitute Rofecin® powder with the appropriate diluent (see **COMPATIBILITY AND STABILITY**).

Inject diluent into vial, shake vial thoroughly to form solution. Withdraw entire contents of vial into syringe to equal total labeled dose.

After reconstitution, each 1 mL of solution contains approximately 250 mg or 350 mg equivalent of ceftriaxone according to the amount of diluent indicated below. If required, more dilute solutions could be utilized.

As with all intramuscular preparations, **Rofecin**® should be injected well within the body of a relatively large muscle; aspiration helps to avoid unintentional injection into a blood vessel.

Vial Dosage Size	Amount of Diluent to be Added	
	250 mg/mL	350 mg/mL
500 mg	1.8 mL	1.0 mL
1gm	3.6 mL	2.1 mL

Intravenous Administration: **Rofecin**® should be administered intravenously by infusion over a period of 30 minutes, except in neonates where administration over 60 minutes is recommended to reduce the risk of bilirubin encephalopathy. Concentrations between 10 mg/mL and 40 mg/mL are recommended; however, lower concentrations may be used if desired. Reconstitute vials with an appropriate IV diluent (see **COMPATIBILITY AND STABILITY**).

Vial Dosage Size	Amount of Diluent to be Added
500 mg	4.8 mL
1gm	9.6 mL

After reconstitution, each 1 mL of solution contains approximately 100 mg equivalent of ceftriaxone. Withdraw entire contents and dilute to the desired concentration with the appropriate IV diluent.

COMPATIBILITY AND STABILITY

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute **Rofecin**® vials or to further dilute a reconstituted vial for IV administration. Particulate formation can result.

Ceftriaxone has been shown to be compatible with metronidazole hydrochloride IV. The concentration should not exceed 5 to 7.5 mg/mL metronidazole hydrochloride with ceftriaxone 10 mg/mL as an admixture. The admixture is stable for 24 hours at room temperature only in 0.9% sodium chloride injection or 5% dextrose in water (D5W). No compatibility studies have been conducted with the metronidazole hydrochloride IV RTU formulation or using other diluents. Metronidazole at concentrations greater than 8 mg/mL will precipitate. Do not refrigerate the admixture as precipitation will occur.

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

Rofecin® solutions should not be physically mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, due to possible incompatibility (see WARNINGS).

After reconstitution, protection from normal light is not necessary. The color of solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

Ceftriaxone *intramuscular* solutions remain stable (loss of potency less than 10%) for the following time periods:

Diluent	Concentration mg/ml	Storage	
		Room Temp. (25°C)	Refrigerated (4°C)
Sterile Water for Injection	100	2 days	10 days
	250, 350	24 hours	3 days
0.9% Sodium Chloride Solution	100	2 days	10 days
	250, 350	24 hours	3 days
5% Dextrose Solution	100	2 days	10 days
	250, 350	24 hours	3 days
Bacteriostatic Water + 0.9% Benzyl Alcohol	100	24 hours	10 days
	250, 350	24 hours	3 days
1% Lidocaine Solution (without epinephrine)	100	24 hours	10 days
	250, 350	24 hours	3 days

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

Diluent	Storage	
	Room Temp. (25°C)	Refrigerated (4°C)
Sterile Water	2 days	10 days
0.9% Sodium Chloride Solution	2 days	10 days
5% Dextrose Solution	2 days	10 days
10% Dextrose Solution	2 days	10 days
5% Dextrose + 0.9% Sodium Chloride Solution*	2 days	Incompatible
5% Dextrose + 0.45% Sodium Chloride Solution	2 days	Incompatible

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

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

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

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

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

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

STORAGE

Store **Rofecin**® injection at below 30° C and protect from light.

HOW SUPPLIED

Rofecin® is supplied as a sterile crystalline powder in glass vial. The following packages are available:

For IM injection

250 mg with 1 ampoule containing 2 ml of 1% Lidocaine solution in Blister Pack
500 mg with 1 ampoule containing 2 ml of 1% Lidocaine solution in Blister Pack
1 gm with 1 ampoule containing 3.5 ml of 1% Lidocaine solution in Blister Pack

For IV injection

250 mg with 1 ampoule containing 5 ml of water for injection in Blister Pack
500 mg with 1 ampoule containing 5 ml of water for injection in Blister Pack
1 gm with 1 ampoule containing 10 ml of water for injection in Blister Pack
2 gm with 2 ampoules containing 10 ml of water for injection of each in a plastic tray

NOTE

ADVERSE REACTIONS: Risk of convulsions and involuntary movements.

DOSAGE AND ADMINISTRATION: Before administration of ceftriaxone IV injection in body please check the tolerability by giving test dose. Administer ceftriaxone IV injection by two to four minutes .

Keep out of reach of children

® Registered Trade Mark

RADIANT PHARMACEUTICALS

Manufactured by
Radiant Pharmaceuticals Limited
B-34 & B-46, BSCIC Industrial Estate
Tongi, Gazipur-1710, Bangladesh
at Popular Pharmaceuticals Ltd.
Tongi, Gazipur, Bangladesh

PMR5315 Version: 04

রফেসিন®

সেফট্রায়াক্সন ইউএসপি

কার্যকরী উপাদান ঃ
রফেসিন® এর ভায়ালগুলোতে আছে ২৫০ মিগ্রা, ৫০০ মিগ্রা, ১ গ্রাম ও ২ গ্রাম সমতুল্য শুষ্ক সেফট্রায়াক্সন।

বৈশিষ্ট্য ও গুনাগুন ঃ
সেফট্রায়াক্সন ব্যাকটেরিয়ার কোষ আবরণী সংশ্লেষণ প্রক্রিয়ায় বাধাদানের মাধ্যমে ব্যাকটেরিয়া ধ্বংস করে। সেফট্রায়াক্সন দেহের বাইরে বহুসংখ্যক গ্রাম পজিটিভ ও গ্রাম নেগেটিভ অনুজীবের বিরুদ্ধে কার্যকরী।
সেফট্রায়াক্সন অধিকাংশ বিটাল্যাকটামেজ এনজাইমের উপস্থিতিতেও (যেমন গ্রাম পজিটিভ ও গ্রাম নেগেটিভ ব্যাকটেরিয়ার পেনিসিলিনেজ ও সেফালোসপোরিনেজ এনজাইম) অধিক স্থায়ীভাবে কার্যকরী।
সেফট্রায়াক্সন সাধারণত নিম্নলিখিত অনুজীবের বিরুদ্ধে বিভিন্ন সংক্রমণের ক্ষেত্রে কার্যকরী ঃ

গ্রাম নেগেটিভ বায়ুজীবী অনুজীব ঃ
অ্যাসিনেট্যাব্যাকটর ক্যালকোএসিটিকাস
এন্টারোব্যাকটার এরোজিনেস
এন্টারোব্যাকটার ক্লোয়াসি
শেরিকিয়া কলাই
হেমোফিলাস ইনফ্লুয়েঞ্জা
হেমোফিলাস প্যারাইনফ্লুয়েঞ্জা
ক্লেবসিলা অক্সিটোকা
ক্লেবসিলা নিউমোনি
মোরাক্সেলা কেটারহেলিস
মরগানেলা মরগানি
নাইসেরিয়া গনোরিয়া
নাইসেরিয়া মেনিনজাইটিডিস
প্রোটিয়াস মিরাবিলিস
প্রোটিয়াস ভালগারিস
সিউডোমোনাস অরুজিনোসা
সেরাসিয়া মারসিসেনস

গ্রাম পজেটিভ বায়ুজীবী অনুজীব ঃ
ষ্টেফাইলোকক্কাস অরিয়াস
ষ্টেফাইলোকক্কাস এপিডারমিডিস
ষ্ট্রেপটোকক্কাস নিউমোনি
ষ্ট্রেপটোকক্কাস পায়োজেনস
ভিরিডেনস গ্রুপ স্ট্রেপটোকক্কি

অবায়ুজীবী অনুজীব ঃ
ব্যাকটেরইডস ফ্র্যাজিলিস
ক্লস্ট্রিডিয়াম প্রজাতি
পেপটোষ্ট্রেপটোকক্কাস প্রজাতি

এছাড়া নিম্নোক্ত অনুজীবগুলোর বিরুদ্ধে প্রাণীদেহের বাইরে সেফট্রায়াক্সন এর কার্যকারীতা পাওয়া গেছে-

গ্রাম নেগেটিভ বায়ুজীবী অনুজীব ঃ
সাইট্রোব্যাক্টর ডাইভারসাস
সাইট্রোব্যাক্টর ফ্রিআনডি
প্রোভিডেনসিয়া প্রজাতি (প্রোভিডেনসিয়া রিটগেরী সহ)
সালমোনেলা প্রজাতি (সালমোনেলা টাইফি সহ)
সিগেলা প্রজাতি

গ্রাম পজেটিভ বায়ুজীবী অনুজীব ঃ
ষ্ট্রেপটোকক্কাস অ্যাজালাক্টি

অবায়ুজীবী অনুজীব ঃ
পরফাইরোমোনাস (ব্যাকটেরইডস) মেলানিনোজেনিকাস
প্রিভোটেল্লা (ব্যাকটেরইডস) বিভিয়াস

রোগ নির্দেশনা ঃ
রফেসিন® সংবেদনশীল জীবানু ঘটিত নিম্নলিখিত সংক্রমণে নির্দেশিত-

শ্বাসনালীর নিম্নাংশের সংক্রমণ
নাক, কান ও গলার সংক্রমণ
অস্থি, অস্থিসন্ধি, নরমকলা, চর্ম ও ক্ষতের সংক্রমণ
কিডনি ও মূত্রনালীর সংক্রমণ
প্রজনন তন্ত্রের সংক্রমণ (গনোরিয়া সহ)
উদরাবরক ঝিল্লী প্রদাহ, পিত্তনালী ও পরিপাকনালীর সংক্রমণ
সেপসিস (জীবানু দূষণ)
আন্ত্রিক সংক্রমণ
মস্তিষ্ক ঝিল্লী প্রদাহ
অস্ত্রোপচারকালীন সংক্রমণ প্রতিরোধ

প্রয়োগমাত্রা ও প্রয়োগবিধি ঃ
প্রাপ্ত বয়স্কদের ক্ষেত্রে ঃ
সাধারণ নির্দেশিত মাত্রা ১-২ গ্রাম দৈনিক একবার (অথবা দৈনিক দুইবার সমবিভক্ত মাত্রায়) সংক্রমণের প্রকার ও তীব্রতা অনুযায়ী প্রয়োগ করতে হবে। দৈনিক মাত্রা বাড়ানো যেতে পারে, কিন্তু ৪ গ্রামের বেশি হওয়া উচিত নয়।

শিশুদের ক্ষেত্রে ঃ
চর্ম ও নরম কলার সংক্রমণ এর ক্ষেত্রে ৫০-৭৫ মিলিগ্রাম/কেজি মাত্রায় দৈনিক একবার (অথবা দৈনিক দুইবার সমবিভক্ত মাত্রায়) প্রয়োগ করতে হবে। দৈনিক মাত্রা বাড়ানো যেতে পারে, কিন্তু ২ গ্রামের বেশি হওয়া উচিত নয়।
একিউট ব্যাকটেরিয়াল ওটাইটিস মিডিয়া এর ক্ষেত্রে ৫০ মিলিগ্রাম/কেজি (কিন্তু ১ গ্রামের বেশি হওয়া উচিত নয়) একক মাত্রায় ইন্ট্রামাসকুলার হিসাবে নির্দেশিত।
তীব্র সংক্রমণের ক্ষেত্রে মস্তিষ্ক ঝিল্লী প্রদাহ ব্যতীত দৈনিক মোট মাত্রা ৫০-৭৫ মিলিগ্রাম/কেজি (দৈনিক দুইবার ১২ ঘন্টা অন্তর সমবিভক্ত মাত্রায়), কিন্তু ২ গ্রামের বেশি হওয়া উচিত নয়।

বয়স্ক রোগীদের ক্ষেত্রে ঃ
বয়স্ক রোগীদের ক্ষেত্রে প্রাপ্তবয়স্কদের অনুরূপ মাত্রা প্রয়োগ করতে হবে।

চিকিৎসার মেয়াদকাল ঃ
রফেসিন® দ্বারা চিকিৎসার মেয়াদ রোগের স্থিতিকালের উপর নির্ভর করে। অন্যান্য এন্টিবায়োটিক দ্বারা চিকিৎসার মতই জ্বর কমে যাওয়ার বা সংক্রমণ সৃষ্টিকারী ব্যাকটেরিয়ার নির্মূলের লক্ষণ প্রকাশ পাওয়ার পর, কমপক্ষে ২ দিন পর্যন্ত **রফেসিন**® প্রয়োগ বজায় রাখতে হবে।

বিশেষ বিশেষ ক্ষেত্রে প্রয়োগ মাত্রা এবং প্রয়োগ বিধি ঃ
মস্তিষ্ক ঝিল্লী প্রদাহ ঃ
শিশুদের ব্যাকটেরিয়া ঘটিত মস্তিষ্ক ঝিল্লীপ্রদাহের চিকিৎসায় প্রাথমিকভাবে দৈনিক একবার ১০০ মিলিগ্রাম/কেজি (৪ গ্রামের বেশী হওয়া উচিত নয়) মাত্রা দিয়ে শুরু করতে হবে। পরবর্তীতে সর্বমোট ১০০ মিলিগ্রাম/কেজি দেহ ওজনে (৪ গ্রাম এর বেশী নয়) দৈনিক (অথবা দৈনিক দুইবার সমবিভক্ত মাত্রায়) নির্দেশিত। মস্তিষ্ক ঝিল্লীপ্রদাহের ক্ষেত্রে সাধারণত চিকিৎসাকাল ৭ থেকে ১৪ দিন।

গনোরিয়া ঃ
গনোরিয়া চিকিৎসায় (পেনিসিলিনেজ ও ননপেনিসিলিনেজ উৎপন্নকারী জীবানু দ্বারা সৃষ্ট) **রফেসিন**® এর ২৫০ মিলিগ্রাম একক মাত্রা পেশীপথে প্রয়োগ করতে হবে।

অস্ত্রোপচারকালীন সংক্রমণ প্রতিরোধ ঃ
অস্ত্রোপচারকালীন সংক্রমণের সম্ভাব্যতার উপর ভিত্তি করে ১-২ গ্রাম **রফেসিন**® অস্ত্রোপচারের ৩০- ১২০ মিনিট পূর্বে শিরাপথে প্রয়োগ করতে হবে।

কিডনি ও যকৃতের গোলযোগ ঃ
কিডনির গোলযোগের রোগীদের ক্ষেত্রে যদি যকৃতের কার্যকারিতা ঠিক থাকে তবে **রফেসিন**® এর মাত্রা কমানোর কোন প্রয়োজন নেই। একইভাবে যকৃতের কার্যহীনতার রোগীদের ক্ষেত্রে যদি কিডনির কার্যকারিতা ঠিক থাকে তবে **রফেসিন**® প্রয়োগের মাত্রা কমানোর কোন প্রয়োজন নেই। তবে যে সকল রোগীদের কিডনি ও যকৃত উভয়ের জটিলতা রয়েছে, তাদের ক্ষেত্রে সর্তকতা অবলম্বন করা উচিত এবং দৈনিক মাত্রা ২ গ্রামের বেশী হওয়া উচিত নয়।
যে সকল রোগী রক্তের ডায়ালাইসিস করান তাদের ক্ষেত্রে ডায়ালাইসিস এর পর কোন সম্পূরক মাত্রা দেয়ার প্রয়োজন নেই। তাদের ক্ষেত্রে যেহেতু যকৃত ও কিডনি দ্বারা বর্জ নিঃসরনের পরিমান কমে যায় সে ক্ষেত্রে **রফেসিন**® প্রয়োগের মাত্রা পুনঃ নির্ধারনের জন্য রক্তরসে এর ঘনত্ব নিয়মিতভাবে পর্যবেক্ষন করতে হবে।

প্রয়োগবিধি ঃ
সাধারন ক্ষেত্রে **রফেসিন**® এর দ্রবণ তৈরীর সঙ্গে সঙ্গেই ব্যবহার করা উচিত। ঘনত্ব ও সংরক্ষণের সময়কালের উপর ভিত্তিকরে **রফেসিন**® এর বর্ণ হালকা হলুদ থেকে অ্যাম্বার-এ পরিবর্তিত হতে পারে।
সেফট্রায়াক্সন ইন্ট্রাভেনাস ইনজেকশন রোগীর শরীরে প্রবেশের পূর্বে টেস্ট ডোজ দিয়ে সহনীয়তা পরীক্ষা করতে হবে।

ইন্ট্রামাসকুলার ইনজেকশন ঃ
২৫০ মিগ্রা অথবা ৫০০ মিগ্রা **রফেসিন**® ২ মিলিলিটার এবং ১ গ্রাম **রফেসিন**® ৩.৫ মিলিলিটার ১% লিডোকেইনে দ্রবীভূত করতে হবে। **রফেসিন**® এর দ্রবণটি গভীর মাংসপেশীতে প্রয়োগ করতে হবে। লিডোকেইনে **রফেসিন**® এর এই দ্রবণ কখনোই শিরাপথে প্রয়োগ করা উচিত নয়।

ইন্ট্রাভেনাস ইনজেকশন ঃ
শিরাপথে প্রয়োগের জন্য ২৫০ মিগ্রা অথবা ৫০০ মিগ্রা **রফেসিন**® ৫ মিলিলিটার, ১ গ্রাম **রফেসিন**® ১০ মিলিলিটার এবং ২ গ্রাম **রফেসিন**® ২০ মিলিলিটার স্টেরাইল ওয়াটার ফর ইনজেকশনে দ্রবীভূত করতে হবে। এই দ্রবণটি শিরাপথে দুই থেকে চার মিনিট ধরে প্রয়োগ করতে হবে।

ইন্ট্রাভেনাস ইনফিউশন ঃ
রফেসিন® ইনফিউশন কমপক্ষে ৩০ মিনিট ধরে প্রয়োগ করতে হবে।

প্রতি নির্দেশনা ঃ
সেফালোসপোরিন এন্টিবায়োটিকের প্রতি অতি সংবেদনশীল রোগীদের **রফেসিন**® প্রয়োগ করা উচিত নয়। পেনিসিলিনের প্রতি অতিসংবেদনশীল রোগীদের ক্ষেত্রে সেফট্রায়াক্সনের প্রতি অতি সংবেদনশীল হওয়ার অধিক ঝুঁকি থাকে।
হাইপারবিলুরোবিনামিক সদ্য প্রসূত ও সময়পূর্ব প্রসূত শিশুদের সেফট্রায়াক্সন ব্যবহার করা যাবে না।
এ ছাড়াও সদ্য প্রসূত শিশুদের ক্যালসিয়াম চিকিৎসার একই সাথে সেফট্রায়াক্সন ব্যবহার করা যাবে না।

সতর্কতা ঃ
অতি সংবেদনশীলতা, মিথেমোগ্লোবিনেমিয়া, ক্যালসিয়াম সমৃদ্ধ ঔষুধের বা দ্রবণের সাথে প্রতিক্রিয়া, *ক্লস্ট্রিডিয়াম ডিফিসাইল-* সম্পর্কিত ডায়রিয়া এবং হেমোলাইটিক এনিমিয়া ইত্যাদি ক্ষেত্রে সতর্কতা অবলম্বন করতে হবে।
এছাড়াও ঔষধ প্রতিরোধী ব্যকটেরিয়া সৃষ্টি, কিডনি ও যকৃতের গোলযোগে আক্রান্ত রোগীদের ক্ষেত্রে, প্রোথম্বিন সময় পরিবর্তন, পিত্তথলির স্যুডোলিথিয়াসিস, ইউরোলিথিয়াসিস ও পোস্ট রেনাল তীব্র কিডনি অকার্যকারিতা এবং প্যানক্রিয়াটাইটিস এর বিষয়ে সতর্কতা অবলম্বন করা উচিত।

পার্শ্ব প্রতিক্রিয়া ঃ
রফেসিন® সাধারনত সুসহনীয়। **রফেসিন**® ব্যবহারের ফলে নিম্নলিখিত পার্শ্বপ্রতিক্রিয়া দেখা যায়-
স্থানীয় পার্শ্ব প্রতিক্রিয়া - ব্যথা, ইনডিউরেশন এবং টেন্ডারনেস।
সাধারণ জটিলতা এবং প্রয়োগ স্থানের অবস্থা- ব্যথা।
সংবেদনশীলতা- চুলকানি, ফুসকুড়ি, জ্বর বা ঠান্ডা।
সংক্রমণ ও উপদ্রব- ছত্রাক সংক্রমণ।
হেমাটোলজিক- ইউসিনোফিলিয়া, থ্রম্বোসাইটোসিস, লিউকোপিনিয়া, এনিমিয়া, হেমোলাইটিক এনিমিয়া এবং থ্রম্বোসাইটোপেনিয়া।
রক্ত ও লসিকা সম্পর্কিত জটিলতা- গ্রানুলোসাইটোপেনিয়া ও কোয়াগুলোপ্যাথি।
আন্ত্রিক- পাতলা পায়খানা, ডায়রিয়া, বমি বমি ভাব, বমি ও ডিসজেউসিয়া।
যকৃতের জটিলতা- অ্যাসপারটেট অ্যামিনোট্রান্সফারেজ ও অ্যালানিন অ্যামিনোট্রান্সফারেজ এর মাত্রা বৃদ্ধি।
রেনাল জটিলতা- বিইউএন ও ক্রিয়েটিনিনের মাত্রা বৃদ্ধি।
কেন্দ্রীয় স্নায়ুতন্ত্রের জটিলতা- মাথা ব্যথা ও ঘুমঘুম ভাব।
প্রজননতন্ত্রের জটিলতা- ছত্রাক সংক্রমণ।
অন্যান্য- ডায়াফোরেসিস এবং ফ্লাশিং।
বিরল পার্শ্ব প্রতিক্রিয়া- পেটে ব্যাথা, অ্যাগ্রানুলোসাইটোসিস ইত্যাদি।

বিপণন পরবর্তী অভিজ্ঞতায় বিভিন্ন আন্ত্রিক, প্রজননতান্ত্রিক, ত্বক সম্পর্কিত, হেমাটোলজিক্যাল, কেন্দ্রীয় স্নায়ুতন্ত্রের জটিলতা যেমন- খিঁচুনি ও অনৈচ্ছিক নড়াচড়া ইত্যাদি লক্ষ্য করা গেছে। বিস্তারিত তথ্যের জন্য ইংরেজী অংশ দেখুন।

অন্যান্য ঔষধের সাথে বিক্রিয়া ঃ
স্থানিক অনুভূতিনাশক প্রয়োগের সাথে একই সময়ে অক্সিডাইজিং এজেন্ট ব্যবহারে মিথেমোগ্লোবিনেমিয়া হওয়ার ঝুঁকি বৃদ্ধি পেতে পারে।

গর্ভাবস্থায় এবং স্তন্যদানকালে ব্যবহার ঃ
পরীক্ষাগারে প্রাণীদের ক্ষেত্রে গর্ভাবস্থায় গর্ভস্থ প্রাণীর বৃদ্ধির উপর সেফট্রায়াক্সন এর কোন বিরুপ প্রতিক্রিয়া পাওয়া যায়নি কিন্তু গর্ভাবস্থায় মানবদেহে এর নিরাপত্তা এখনো প্রমাণিত হয়নি। সুতরাং চরম ভাবে নির্দেশিত না হলে গর্ভাবস্থায় এর ব্যবহার নিষিদ্ধ।

যেহেতু মাতৃদুগ্ধে সেফট্রায়াক্সন এর নিঃসরন হয় সুতরাং স্তন্যদানকারী মায়েদের ক্ষেত্রে **রফেসিন**® সাবধানতা ও সতর্কতার সাথে ব্যবহার করা উচিত।

উপযোগিতা ও স্থায়িত্ব ঃ
বিস্তারিত তথ্যের জন্য ইংরেজী অংশ দেখুন।

সংরক্ষণ ঃ
৩০° সেঃ এর কম তাপমাত্রায় সংরক্ষণ করুন। সকল প্রকার ওষুধ শিশুদের নাগালের বাইরে রাখুন।

সরবরাহ ঃ
রফেসিন® *ইন্ট্রামাসকুলার ইনজেকশন ঃ*
প্রতিটি বাক্সে একটি ভায়াল ও একটি অ্যাম্পুল আছে। প্রতিটি ভায়ালে ২৫০ মিগ্রা, ৫০০ মিগ্রা বা ১ গ্রাম সমতুল্য শুষ্ক সেফট্রায়াক্সন আছে এবং প্রতিটি এ্যাম্পুলে ২ মিলিলিটার বা ৩.৫ মিলিলিটার ১ % লিডোকেইন দ্রবণ আছে।

রফেসিন® *ইন্ট্রাভেনাস ইনজেকশন ঃ*
প্রতিটি বাক্সে একটি ভায়াল ও একটি অ্যাম্পুল আছে। প্রতিটি ভায়ালে ২৫০ মিগ্রা, ৫০০ মিগ্রা, ১ গ্রাম বা ২ গ্রাম সমতুল্য শুষ্ক সেফট্রায়াক্সন আছে এবং প্রতিটি এ্যাম্পুলে ৫ মিলিলিটার বা ১০ মিলিলিটার স্টেরাইল ওয়াটার ফর ইনজেকশন আছে।

দ্রষ্টব্য ঃ

পার্শ্ব প্রতিক্রিয়া ঃ খিঁচুনি ও অনৈচ্ছিক নড়াচড়ার ঝুঁকি।
প্রয়োগবিধি ঃ সেফট্রায়াক্সন ইন্ট্রাভেনাস ইনজেকশন রোগীর শরীরে প্রবেশের পূর্বে টেস্ট ডোজ দিয়ে সহনীয়তা পরীক্ষা করতে হবে এবং এই দ্রবণটি শিরাপথে দুই থেকে চার মিনিট ধরে প্রয়োগ করতে হবে।

বিস্তারিত তথ্যের জন্য ইংরেজী অংশ দেখুন।

® রেজিস্ট্রার্ড ট্রেডমার্ক

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পপুলার ফার্মাসিউটিক্যালস লিমিটেড
টঙ্গী, গাজীপুর, বাংলাদেশ-এ প্রস্তুতকৃত