10084916 **USA**
0705.1072

ROCEPHIN®
(ceftriaxone sodium)
FOR INJECTION

Roche

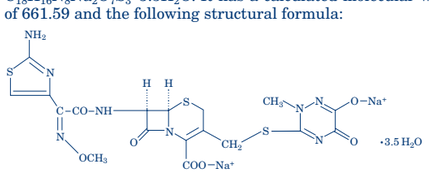
℞ only

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

DESCRIPTION

Rocephin 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:



Rocephin 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 Rocephin solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

Rocephin 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	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	16 hr	24 hr
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 postdosing. 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 high, as shown in Table 2.

Table 2 Urinary Concentrations of Ceftriaxone After Single Dose Administration

Dose/Route	Average Urinary 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 6 of 26 dialysis patients, the elimination rate of ceftriaxone was markedly reduced, suggesting that plasma concentrations of ceftriaxone should be monitored in these patients to determine if dosage adjustments are necessary.

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.

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.

Microbiology: The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria.

Ceftriaxone has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections described in the INDICATIONS AND USAGE section.

Aerobic gram-negative microorganisms:
Acinetobacter calcoaceticus
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae (including ampicillin-resistant and beta-lactamase producing strains)
Haemophilus parainfluenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis (including beta-lactamase producing strains)
Morganella morganii
Neisseria gonorrhoeae (including penicillinase- and nonpenicillinase-producing strains)
Neisseria meningitidis
Proteus mirabilis
Proteus vulgaris
Serratia marcescens

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa.*

NOTE: Many strains of the above organisms that are multiply resistant to other antibiotics, eg, penicillins, cephalosporins, and aminoglycosides, are susceptible to ceftriaxone.

Aerobic gram-positive microorganisms:
Staphylococcus aureus (including penicillinase-producing strains)
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans group streptococci

NOTE: Methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone. Most strains of Group D streptococci and enterococci, eg, *Enterococcus (Streptococcus) faecalis,* are resistant.

Anaerobic microorganisms:
Bacteroides fragilis
Clostridium species
Peptostreptococcus species

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

The following in vitro data are available, **but their clinical significance is unknown.** Ceftriaxone exhibits in vitro minimal inhibitory concentrations (MICs) of ≤8 µg/mL or less against most strains of the following microorganisms, however, the safety and effectiveness of ceftriaxone in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-negative microorganisms:
Citrobacter diversus
Citrobacter freundii
Providencia species (including *Providencia rettgeri*)
Salmonella species (including *Salmonella typhi*)
Shigella species

Aerobic gram-positive microorganisms:
Streptococcus agalactiae

Anaerobic microorganisms:
Prevotella (Bacteroides) bivius
Porphyromonas (Bacteroides) melaninogenicus

Susceptibility Tests:

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure.[1] Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ceftriaxone powder. The MIC values should be interpreted according to the following criteria[2] for aerobic organisms other than *Haemophilus* spp, *Neisseria gonorrhoeae,* and *Streptococcus* spp, including *Streptococcus pneumoniae:*

MIC (µg/mL)	Interpretation
≤8	(S) Susceptible
16–32	(I) Intermediate
≥64	(R) Resistant

The following interpretive criteria[2] should be used when testing *Haemophilus* species using Haemophilus Test Media (HTM).

MIC (µg/mL)	Interpretation
≤2	(S) Susceptible

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

The following interpretive criteria[2] should be used when testing *Neisseria gonorrhoeae* when using GC agar base and 1% defined growth supplement.

MIC (µg/mL)	Interpretation
≤0.25	(S) Susceptible

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

The following interpretive criteria[2] should be used when testing *Streptococcus* spp including *Streptococcus pneumoniae* using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.

MIC (µg/mL)	Interpretation
≤0.5	(S) Susceptible
1	(I) Intermediate
≥2	(R) Resistant

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

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standardized ceftriaxone powder should provide the following MIC values:[2]

Microorganism	ATCC® #	MIC (µg/mL)
Escherichia coli	25922	0.03–0.12
Staphylococcus aureus	29213	1–8*
Pseudomonas aeruginosa	27853	8–32
Haemophilus influenzae	49247	0.06–0.25
Neisseria gonorrhoeae	49226	0.004–0.015
Streptococcus pneumoniae	49619	0.03–0.12

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

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[3] requires the use of standardized inoculum concentrations. This procedure uses paper discs impregnated with 30 µg of ceftriaxone to test the susceptibility of microorganisms to ceftriaxone.

Reports from the laboratory providing results of the standard single-disc susceptibility test with a 30 µg ceftriaxone disc should be interpreted according to the following criteria for aerobic organisms other than *Haemophilus* spp, *Neisseria gonorrhoeae,* and *Streptococcus* spp:

Zone Diameter (mm)	Interpretation
≥21	(S) Susceptible
14–20	(I) Intermediate
≤13	(R) Resistant

The following interpretive criteria[3] should be used when testing *Haemophilus* species when using Haemophilus Test Media (HTM).

Zone Diameter (mm)	Interpretation
≥26	(S) Susceptible

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

The following interpretive criteria[3] should be used when testing *Neisseria gonorrhoeae* when using GC agar base and 1% defined growth supplement.

Zone Diameter (mm)	Interpretation
≥35	(S) Susceptible

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

The following interpretive criteria[3] should be used when testing *Streptococcus* spp other than *Streptococcus pneumoniae* when using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

Zone Diameter (mm)	Interpretation
≥27	(S) Susceptible
25–26	(I) Intermediate
≤24	(R) Resistant

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disc test with the MIC for ceftriaxone.

Disc diffusion interpretive criteria for ceftriaxone discs against *Streptococcus pneumoniae* are not available, however, isolates of pneumococci with oxacillin zone diameters of >20 mm are susceptible (MIC ≤0.06 µg/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.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30 µg ceftriaxone disc should provide the following zone diameters in these laboratory test quality control strains:[3]

Microorganism	ATCC® #	Zone Diameter Ranges (mm)
Escherichia coli	25922	29–35
Staphylococcus aureus	25923	22–28
Pseudomonas aeruginosa	27853	17–23
Haemophilus influenzae	49247	31–39
Neisseria gonorrhoeae	49226	39–51
Streptococcus pneumoniae	49619	30–35

Anaerobic Techniques: For anaerobic bacteria, the susceptibility to ceftriaxone as MICs can be determined by standardized test methods.[4] The MIC values obtained should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
≤16	(S) Susceptible
32	(I) Intermediate
≥64	(R) Resistant

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standardized ceftriaxone powder should provide the following MIC values for the indicated standardized anaerobic dilution[4] testing method:

Method	Microorganism	ATCC® #	MIC (µg/mL)
Agar	*Bacteroides fragilis*	25285	32–128
	Bacteroides thetaiotaomicron	29741	64–256
Broth	*Bacteroides thetaiotaomicron*	29741	32–128

ATCC® is a registered trademark of the American Type Culture Collection.

INDICATIONS AND USAGE

Before instituting treatment with Rocephin, 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 Rocephin and other antibacterial drugs, Rocephin 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.

Rocephin 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 Rocephin compared to 10 days of oral therapy. In a second study comparable cure rates were observed between single dose Rocephin and the comparator. The potentially lower clinical cure rate of Rocephin should be balanced against the potential advantages of parenteral therapy (see **CLINICAL STUDIES**).

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

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

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

PELVIC INFLAMMATORY DISEASE caused by *Neisseria gonorrhoeae.* Rocephin, 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.* Rocephin 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 Rocephin 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 Rocephin 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 Rocephin provides protection from most infections due to susceptible organisms throughout the course of the procedure.

CONTRAINDICATIONS

Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

Hyperbilirubinemic neonates, especially prematures, should not be treated with Rocephin. In vitro studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.

Rocephin should not be administered concurrently with calcium-containing solutions or products in newborns because of the risk of precipitation of ceftriaxone-calcium salt (see **WARNINGS**).

WARNINGS

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

Ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines.

Calcium-containing solutions or products must not be administered within 48 hours of last administration of ceftriaxone.

Cases of fatal reactions with calcium-ceftriaxone precipitates in lung and kidneys in both term and premature neonates have been described. In some cases the infusion lines and times of administration of ceftriaxone and calcium-containing solutions differed (see CONTRAINDICATIONS and ADVERSE REACTIONS).

Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Rocephin, 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 *C. difficile,* and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General: Prescribing Rocephin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins.

Ceftriaxone is excreted via both biliary and renal excretion (see **CLINICAL PHARMACOLOGY**). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin. Patients with impaired vitamin K synthesis or low vitamin K stores (eg, chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

There have been reports of sonographic abnormalities in the gallbladder of patients treated with Rocephin; 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 Rocephin and institution of conservative management.** Therefore, Rocephin should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above.

Information for Patients: Patients should be counseled that antibacterial drugs including Rocephin should only be used to treat bacterial infections. They do not treat viral infections (eg, common cold). When Rocephin 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 Rocephin 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 Rocephin is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of Rocephin 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. Rocephin should not be administered to hyperbilirubinemic neonates, especially prematures (see **CONTRAINDICATIONS**).

ADVERSE REACTIONS

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

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

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

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

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

HEPATIC – elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (<1%) were elevations of alkaline phosphatase and bilirubin.

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

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

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

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

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

Cases of fatal reactions with calcium-ceftriaxone precipitates in lung and kidneys in both term and premature neonates have been described. In some cases the infusion lines and times of administration of ceftriaxone and calcium-containing solutions differed.

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

Rocephin may be administered intravenously or intramuscularly.

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.

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.

Generally, Rocephin 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; however, blood levels should be monitored in patients with severe renal impairment (eg, dialysis patients) and in patients with both renal and hepatic dysfunctions.

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

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Rocephin. Particulate formation can result.

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. **A 350 mg/mL concentration is not recommended for the 250 mg vial since it may not be possible to withdraw the entire contents.**

As with all intramuscular preparations, Rocephin 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
250 mg	0.9 mL	–
500 mg	1.8 mL	1.0 mL
1 gm	3.6 mL	2.1 mL
2 gm	7.2 mL	4.2 mL

Intravenous Administration: Rocephin should be administered intravenously by infusion over a period of 30 minutes. 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
250 mg	2.4 mL
500 mg	4.8 mL
1 gm	9.6 mL
2 gm	19.2 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: Rocephin sterile powder should be stored at room temperature – 77 °F (25 °C) – or below and protected from light. After reconstitution, protection from normal light is not necessary. The color of solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

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

Diluent	Concentration mg/ml	Storage Room Temp. (25 °C)	Storage 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

Rocephin *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)	Storage 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* Rocephin 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).

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

*Registered trademark of G.D. Searle & Co.

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

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Rocephin. Particulate formation can result.

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.

Rocephin 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 Rocephin, should be thawed at room temperature before use. After thawing, unused portions should be discarded. **DO NOT REFREEZE.**

Rocephin 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**).

ANIMAL PHARMACOLOGY

Concretions consisting of the precipitated calcium salt of ceftriaxone have been found in the gallbladder bile of dogs and baboons treated with ceftriaxone.

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

HOW SUPPLIED

Rocephin is supplied as a sterile crystalline powder in glass vials. The following packages are available:

Vials containing 250 mg equivalent of ceftriaxone. Box of 1 (NDC 0004-1962-02) and box of 10 (NDC 0004-1962-01).

Vials containing 500 mg equivalent of ceftriaxone. Box of 1 (NDC 0004-1963-02) and box of 10 (NDC 0004-1963-01).

Vials containing 1 gm equivalent of ceftriaxone. Box of 1 (NDC 0004-1964-04) and box of 10 (NDC 0004-1964-01).

Vials containing 2 gm equivalent of ceftriaxone. Box of 10 (NDC 0004-1965-01).

Bulk pharmacy containers, containing 10 gm equivalent of ceftriaxone. Box of 1 (NDC 0004-1971-01). NOT FOR DIRECT ADMINISTRATION.

NOTE: Rocephin sterile powder should be stored at room temperature, 77 °F (25 °C) or below, and protected from light.

CLINICAL STUDIES

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

Clinical Efficacy in Evaluable Population

Study Day	Ceftriaxone Single Dose	Comparator – 10 Days of Oral Therapy	95% Confidence Interval	Statistical Outcome
Study 1 – US		amoxicillin/clavulanate		
14	74% (220/296)	82% (247/302)	(–14.4%, –0.5%)	Ceftriaxone is lower than control at study day 14 and 28.
28	58% (167/288)	67% (200/297)	(–17.5%, –1.2%)	
Study 2 – US[5]		TMP-SMZ		
14	54% (113/210)	60% (124/206)	(–16.4%, 3.6%)	Ceftriaxone is equivalent to control at study day 14 and 28.
28	35% (73/206)	45% (93/205)	(–19.9%, 0.0%)	

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

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

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

REFERENCES

1. National Committee for Clinical Laboratory Standards, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically;* Approved Standard-Fifth Edition. NCCLS document M7-A5 (ISBN 1-56238-309-9). NCCLS, Wayne, PA 19087-1898, 2000.
2. National Committee for Clinical Laboratory Standards, Supplemental Tables. NCCLS document M100-S10(M7) (ISBN 1-56238-309-9). NCCLS, Wayne, PA 19087-1898, 2000.
3. National Committee for Clinical Laboratory Standards, *Performance Standards for Antimicrobial Disk Susceptibility Tests;* Approved Standard-Seventh Edition. NCCLS document M2-A7 (ISBN 1-56238-393-0). NCCLS, Wayne, PA 19087-1898, 2000.
4. National Committee for Clinical Laboratory Standards, *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria;* Approved Standard-Fourth Edition. NCCLS document M11-A4 (ISBN 1-56238-210-1). NCCLS, Wayne, PA 19087-1898, 1997.
5. Barnett ED, Teele DW, Klein JO, et al. *Comparison of Ceftriaxone and Trimethoprim-Sulfamethoxazole for Acute Otitis Media.* Pediatrics. Vol. 99, No. 1, January 1997.

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Revised: May 2007

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