

NDA 50-585/S-047

Hoffmann-LaRoche Inc.
Attention: Melanie Bishop
Program Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

AUG 25 2000

Dear Ms. Bishop:

Please refer to your supplemental new drug application dated August 22, 1996, received August 28, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rocephin® (ceftriaxone sodium) for Injection. We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated January 16, 1997, February 1, 2000, February 23, 2000, April 18, 2000, June 27, 2000, and July 26, 2000.

This supplemental new drug application provides for:

1. The addition of the statement "Ceftriaxone crosses the blood placenta barrier" to the CLINICAL PHARMACOLOGY section;
2. Updated Microbiology and Susceptibility Tests subsections of the CLINICAL PHARMACOLOGY section as requested in the Agency's letter dated August 31, 1995, for NDAs 50-585/S-039 and S-043;
3. The addition of an OVERDOSAGE section as requested in the Agency's letter dated August 31, 1995, for NDAs 50-585/S-039 and S-043. This new section reads as follows:

"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."

4. The replacement of "injection site reaction" with "warmth, tightness, or induration" under LOCAL REACTIONS in the ADVERSE REACTIONS section;
5. The addition of "biliary lithiasis, agranulocytosis, renal precipitations, and nephrolithiasis" under MISCELLANEOUS in the ADVERSE REACTIONS section;
6. Addition of a paragraph in the DOSAGE AND ADMINISTRATION section under COMPATIBILITY AND STABILITY, to describe the compatibility of ceftriaxone with metronidazole hydrochloride;
7. Addition of a paragraph in the DOSAGE AND ADMINISTRATION section under COMPATIBILITY AND STABILITY, to describe the incompatibility of ceftriaxone with

vancomycin and fluconazole;

8. Addition of the following notation in the DOSAGE AND ADMINISTRATION section under COMPATIBILITY AND STABILITY:

“Note: Parenteral drug products should be inspected visually for particulate matter before administration.”

9. Updated REFERENCES as requested in the Agency’s letter dated August 31, 1995, for NDAs 50-585/S-039 and S-043;
10. Other minor editorial revisions.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

- In the second table under Anaerobic Techniques in the Microbiology subsection of the CLINICAL PHARMACOLOGY section of the label, the word “Agar” is misspelled.
- In the COMPATIBILITY AND STABILITY subsection of the DOSAGE AND ADMINISTRATION section of the label, the word “stable” is misspelled in the second sentence of the paragraph describing compatibility of ceftriaxone with metronidazole hydrochloride.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted July 26, 2000). These revisions are terms of the approval of this application.

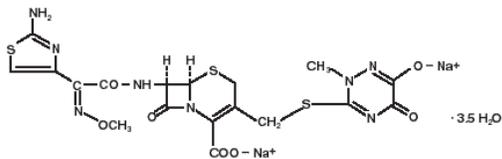
Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDAs (January 1999). For administrative purposes, this submission should be designated “FPL for approved supplement NDA 50-585/S-047.” Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a “Dear Health Care Practitioner” letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

ROCEPHIN[®]
(ceftriaxone sodium)
FOR INJECTION

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, 7²-(*Z*)-(O-methyloxime), disodium salt, sesquaterhydrate.

The chemical formula of ceftriaxone sodium is C₁₈H₁₆N₈Na₂O₇S₃·3.5 H₂O. 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 ($\mu\text{g/mL}$)					
	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 $\mu\text{g/mL}$ in the gallbladder bile, 788 $\mu\text{g/mL}$ in the common duct bile, 898 $\mu\text{g/mL}$ in the cystic duct bile, 78.2 $\mu\text{g/gm}$ in the gallbladder wall and 62.1 $\mu\text{g/mL}$ 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 $<25 \mu\text{g/mL}$ to a value of 85% bound at 300 $\mu\text{g/mL}$. 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 ($\mu\text{g/mL}$)	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 ($\mu\text{g/mL}$)	5.6	6.4
Range ($\mu\text{g/mL}$)	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 (\pm SD) ceftriaxone levels in the middle ear reached a peak of 35 (\pm 12) μ g/mL at 24 hours, and remained at 19 (\pm 7) μ g/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 strain)

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 ug/mL or less against most strains of the following microorganisms, however, the safety and effectiveness of ceftriaxone in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-negative microorganisms:

Citrobacter diversus

Citrobacter freundii

Providencia species (including *Providencia rettgeri*)

Salmonella species (including *Salmonella typhi*)

Shigella species

Aerobic gram-positive microorganisms:

Streptococcus agalactiae

Anaerobic microorganisms:

Prevotella (Bacteroides) bivia

Porphyromonas (Bacteroides) melaninogenicus

Susceptibility Tests:

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure.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 criteria² 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 criteria² 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 criteria² 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 criteria² 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)
<i>Escherichia coli</i>	25922	0.03 - 0.12
<i>Staphylococcus aureus</i>	29213	1 - 8
<i>Pseudomonas aeruginosa</i>	27853	8 - 32
<i>Haemophilus influenzae</i>	49247	0.06 - 0.25
<i>Neisseria gonorrhoeae</i>	49226	0.004 - 0.015
<i>Streptococcus pneumoniae</i>	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 procedure³ 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—disk 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 criteria³ 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 criteria³ 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 criteria³ should be used when testing *Streptococcus* spp other than *Streptococcus pneumoniae* when using Mueller Hinton agar supplemented with 5% sheep blood incubated in 5% CO₂:

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 disk test with the MIC for ceftriaxone.

Disk diffusion interpretive criteria for ceftriaxone disks 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)
<i>Escherichia coli</i>	25922	29 - 35
<i>Staphylococcus aureus</i>	25923	22 - 28
<i>Pseudomonas aeruginosa</i>	27853	17 - 23
<i>Haemophilus influenzae</i>	49247	31 - 39
<i>Neisseria gonorrhoeae</i>	49226	39 - 51
<i>Streptococcus pneumoniae</i>	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” testing method:

Method	Microorganism	ATCC® #	MIC (µg/mL)
--------	---------------	---------	-------------

Agbar	<i>Bacteroides fragilis</i>	25285	32 - 128
	<i>Bacteroides thetaiotamicron</i>	29741	64 - 256
Broth	<i>Bacteroides thetaiotaomicron</i>	29741	32 - 128

INDICATIONS AND USAGE: 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 *C. 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 *C. 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.

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.

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

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.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS: General: 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.

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 children 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.

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 injection site reaction 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 — (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 leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, gallbladder sludge, glycosuria, hematuria, anaphylaxis, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis.

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 *C. 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 section).

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.

<u>Vial Dosage Size</u>	<u>Amount of Diluent to be Added</u>	
	<u>250 mg/mL</u>	<u>350 mg/mL</u>
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

Intramuscular Convenience Kit: For the 500 mg vial, withdraw 1 mL of diluent, discard the remainder. Inject diluent into vial, shake vial thoroughly to form solution. Withdraw entire contents of vial into syringe to equal approximately 1.4 mL.

For 1 gm vial, withdraw entire contents of diluent (2.1 mL). Inject diluent into vial, shake vial thoroughly to form solution. Withdraw entire contents of vial into syringe to equal approximately 2.8 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 or "piggyback" bottles with an appropriate IV diluent (see COMPATIBILITY AND STABILITY section).

<u>Vial Dosage Size</u>	<u>Amount of Diluent to be Added</u>
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.

<u>Piggyback Bottle Dosage Size</u>	<u>Amount of Diluent to be Added</u>
1 gm	10 mL
2 gm	20 mL

After reconstitution, further dilute to 50 mL or 100 mL volumes with the appropriate IV diluent.

COMPATIBILITY AND STABILITY: Rocephin sterile powder should be stored at room temperature — 77°F (25°C) — 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	Storage		
	Concentration mg/mL	Room Temp. (25°C)	Refrigerated (4°C)
Sterile Water for Injection	100	3 days	10 days
	250, 350	24 hours	3 days
0.9% Sodium Chloride Solution	100	3 days	10 days
	250, 350	24 hours	3 days
5% Dextrose Solution	100	3 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)	Refrigerated (4°C)
Sterile Water	3 days	10 days
0.9% Sodium Chloride Solution	3 days	10 days
5% Dextrose Solution	3 days	10 days
10% Dextrose Solution	3 days	10 days
5% Dextrose + 0.9% Sodium Chloride Solution*	3 days	Incompatible
5% Dextrose + 0.45% Sodium Chloride Solution	3 days	Incompatible

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

Similarly, Rocephin *intravenous* solutions, at concentrations of 100 mg/mL, remain stable in the IV piggyback glass containers for the above specified time periods.

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).

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

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 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.

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 and piggyback bottles. 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).

Piggyback bottles containing 1 gm equivalent of ceftriaxone. Box of 1 (NDC 0004-1964-02).

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

Piggyback bottles containing 2 gm equivalent of ceftriaxone. Box of 1 (NDC 0004-1965-02).

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

Rocephin is also supplied in an Intramuscular Convenience Kit, available in two strengths, consisting of a vial of ceftriaxone sodium as a sterile crystalline powder and a vial of Xylocaine®-MPF 1% (lidocaine HCl Injection, USP).

The following strengths are available:

Kit containing 1 vial of 500 mg equivalent of ceftriaxone, plus 1 vial of 2.1 mL Xylocaine (NDC 0004-2014-92).

Kit containing 1 vial of 1 gm equivalent of ceftriaxone, plus 1 vial of 2.1 mL Xylocaine (NDC 0004-2013-92).

Xylocaine®-MPF 1% (lidocaine HCl Injection, USP) is manufactured for Roche Laboratories Inc. by Astra USA, Inc., Westborough, MA 01581.

Rocephin is also supplied as a sterile crystalline powder in ADD-Vantage®* Vials as follows:

ADD-Vantage Vials containing 1 gm equivalent of ceftriaxone. Box of 10 (NDC 0004-1964-05).

ADD-Vantage Vials containing 2 gm equivalent of ceftriaxone. Box of 10 (NDC 0004-1965-05).

Rocephin (ceftriaxone sodium injection), also supplied premixed as a frozen, iso-osmotic, sterile, nonpyrogenic solution of ceftriaxone sodium in 50 mL single dose Galaxy®# containers (PL 2040 plastic), is manufactured for Roche Laboratories Inc., by Baxter Healthcare Corporation, Deerfield, Illinois 60015. The following strengths are available:

1 gm equivalent of ceftriaxone, iso-osmotic with approximately 1.9 gm Dextrose Hydrous, USP, added (NDC 0004-2002-78).

2 gm equivalent of ceftriaxone, iso-osmotic with approximately 1.2 gm Dextrose Hydrous, USP, added (NDC 0004-2003-78).

NOTE: Store Rocephin in the frozen state at or below -20°C/-4°F.

*Registered trademark of Abbott Laboratories, Inc.

#Registered trademark of Baxter International Inc.

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 14	74% (220/296)	amoxicillin/clavulanate 82% (247/302)	(-14.4%, -0.5%)	Ceftriaxone is lower

28	58% (167/288)	67% (200/297)	(-17.5%, -1.2%)	than control at study day 14 and 28.
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		Study Day 30+2	
	No. Analyzed	No. Erad. (%)	No. Analyzed	No. Erad. (%)
<i>Streptococcus pneumoniae</i>	38	32 (84)	35	25 (71)
<i>Haemophilus influenzae</i>	33	28 (85)	31	22 (71)
<i>Moraxella catarrhalis</i>	15	12 (80)	15	9 (60)

Roche Pharmaceutical
Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Revised: July 2000