

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

Approval Package for:

APPLICATION NUMBER:

65-125

Generic Name: Ceftriaxone for Injection USP,
250mg/vial, 500mg/vial, 1g/vial, and
2g/vial

Sponsor: Lupin Limited

Approval Date: September 30, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
65-125**

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**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-125

APPROVAL LETTER

ANDA 65-125

SEP 30 2003

Lupin Limited
Attention: Vinita Gupta
Harborplace Tower
111 South Calvert Street, 21st Floor
Baltimore, MD 21202

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 28, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ceftriaxone for Injection USP, 250 mg/vial, 500 mg/vial, 1 g/vial, and 2 g/vial. We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendments dated August 22, and August 25, 2003.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Ceftriaxone for Injection USP, 250 mg, 500 mg, 1 g and 2 g/vial to be bioequivalent and therapeutically equivalent to the listed drug (Rocephin[®] for Injection, 250 mg, 500 mg, 1 g, and 2 g/vial, respectively, of HLR Technology).

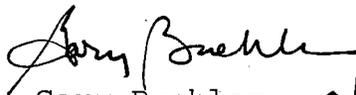
Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,



Gary Buehler 9/30/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

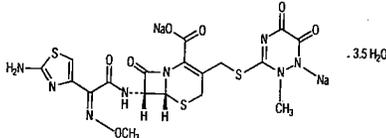
65-125

FINAL PRINTED LABELING(S)

CEFTRIAXONE FOR INJECTION USP
250 mg, 500 mg, 1 g and 2 g
Rx only

DESCRIPTION: Ceftriaxone for injection is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceftriaxone sodium is (6R,7R)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[1-(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo- α -triazin-3- γ)thio]methyl]-5-thia-1-azabicyclo [4.2.1]oct-2-ene-2-carboxylic acid, 7 β -(2)-(D-methylxime), disodium salt, sesquahydrate.

The molecular formula of ceftriaxone sodium is $C_{18}H_{16}N_6Na_2O_5S_3 \cdot 3.5 H_2O$. It has a calculated molecular weight of 661.60 and the following structural formula:



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

Ceftriaxone for injection 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 g dose and intramuscular (IM) administration of a single 0.5 (250 mg/mL) or 350 mg/mL concentrations or 1 g dose in healthy subjects are presented in Table 1.

TABLE 1 Ceftriaxone Plasma Concentrations After Single Dose Administration

Dose/Route	Average Plasma Concentrations (mcg/mL)									
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	16 hr	24 hr	48 hr
0.5 g IV*	82	59	48	37	29	23	15	10	5	
0.5 g IM	22	33	38	35	30	26	16	ND	5	
0.5 g IM 250 mg/mL	20	32	38	34	31	24	16	ND	5	
0.5 g IM 350 mg/mL	20	32	38	34	31	24	16	ND	5	
1 g IV*	151	111	88	67	53	43	28	18	9	
1 g IM	40	68	76	68	56	44	29	ND	ND	
2 g 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 g 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 (mcg/mL)					
	0-2 hr	2-4 hr	4-8 hr	8-12 hr	12-24 hr	24-48 hr
0.5 g IV	526	366	142	87	70	15
0.5 g IM	115	425	308	127	96	28
1 g IV	995	855	293	147	132	32
1 g IM	504	628	418	237	ND	ND
2 g 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 g IV dose, average concentrations of ceftriaxone, determined from 1 to 3 hours after dosing, were 581 mcg/mL in the gallbladder bile, 788 mcg/mL in the common duct bile, 896 mcg/mL in the cystic duct bile, 78.2 mcg/g in the gallbladder wall and 62.1 mcg/mL in the concurrent plasma.

Over a 0.15 to 3 g 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 mcg/mL to a value of 85% bound at 300 mcg/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

	With Meningitis	
	50 mg/kg IV	75 mg/kg IV
Maximum Plasma Concentrations (mcg/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 (mcg/mL)	5.6	6.4
Range (mcg/mL)	1.3 - 18.5	1.3 - 44
Time after dose (hr)	3.7 (\pm 1.6)	3.3 (\pm 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 g 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) mcg/mL at 24 hours, and remained at 19 (\pm 7) mcg/mL at 48 hours. Based on middle ear fluid ceftriaxone concentrations in the 23 to 25 hour and the 46 to 50 hour sampling time intervals, a half-life of 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 californica (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, e.g., 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, e.g., *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 mcg/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. 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 (mcg/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 (mcg/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 (mcg/mL)	Interpretation
≤ 0.25	(S) Susceptible

The absence of resistant strains precludes defining any categories other than

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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, e.g., 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, e.g., *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 mcg/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 procedure¹. 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 (mcg/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 (mcg/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 (mcg/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 (mcg/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 (mcg/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.

Dilution 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 mcg 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 mcg 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 "Non-susceptible" 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 "Non-susceptible" 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 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.

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 mcg 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 (mcg/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 dilution⁴ testing method.

Method	Microorganism	ATCC [®] #	MIC (mcg/mL)
Agar	<i>Bacteroides fragilis</i>	25285	32 - 128
	<i>Bacteroides thetaiotaomicron</i>	29741	64 - 256
Broth	<i>Bacteroides thetaiotaomicron</i>	29741	32 - 128

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

INDICATIONS AND USAGE: Ceftriaxone for injection 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 for injection compared to 10 days of oral therapy. In a second study comparable cure rates were observed between single dose ceftriaxone for injection and the comparator. The potentially lower clinical cure rate of ceftriaxone for injection 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*. Ceftriaxone for injection, 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 for injection 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 g dose of ceftriaxone for injection may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e.g., 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 (e.g., during coronary artery bypass surgery). Although ceftriaxone for injection 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 g dose of ceftriaxone for injection provides protection from most infections due to susceptible organisms throughout the course of the procedure.

Before instituting treatment with ceftriaxone for injection, 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: Ceftriaxone for injection is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS: BEFORE THERAPY WITH CEFTRIAZONE FOR INJECTION 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 *Clostridium difficile* colitis.

PRECAUTIONS: General: Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of ceftriaxone for injection 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 ceftriaxone for injection 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, ceftriaxone for injection dosage should not exceed 2 g daily without close monitoring of serum concentrations.

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

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

Ceftriaxone 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 ceftriaxone for injection; some of these patients also had symptoms of gallbladder disease. These abnormalities appear on sonography as an echo without acoustical shadowing suggesting sludge or as an echo with acoustical shadowing which may be misinterpreted as gallstones. The chemical nature of the sonographically detected material has been determined to be predominantly a ceftriaxone-calcium salt. The condition appears to be transient and reversible upon discontinuation of ceftriaxone for injection and institution of conservative management. Therefore, ceftriaxone for injection 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 g/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 (prenatal 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 ceftriaxone for injection is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of ceftriaxone for injection 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. Ceftriaxone for injection should not be administered to hyperbilirubinemic neonates, especially prematures.

ADVERSE REACTIONS: Ceftriaxone for injection is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to ceftriaxone for injection 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, lightness 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 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, epistaxis, biliary lithiasis, agranulocytosis, renal precipitations, and nephrolithiasis.

OVERDOSAGE:

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

DOSAGE AND ADMINISTRATION: Ceftriaxone for injection 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, ceftriaxone for injection 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 (e.g., dialysis patients) and in patients with both renal and hepatic dysfunctions.

DIRECTIONS FOR USE: Intramuscular Administration: Reconstitute ceftriaxone for injection 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, ceftriaxone for injection 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 g	3.6 mL	2.1 mL
2 g	7.2 mL	4.2 mL

Intravenous Administration: Ceftriaxone for injection 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 COMPATIBILITY

Vial

After reconstituted equivalent of concentration

COMPATIBLE with other drugs and protected necessary. The length of:

Ceftriaxone is less than 10%

Diluent
Sterile Water
0.9% Sodium Solution
5% Dextrose
Bacteriostatic 0.9% Bar
1% Lidocaine (without ep

Ceftriaxone 1 40 mg/mL, r periods store

Sterile Water
0.9% Sodium
5% Dextrose
10% Dextrose
5% Dextrose
5% Dextrose

*Data available containers or

The following temperature 40 mg/mL, 5% Sodium in 5% Dext container, 5

Ceftriaxone hydrochloric hydrochloric

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After the int discarded.

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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.

DOSEAGE AND ADMINISTRATION: Ceftriaxone for injection 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.

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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 (e.g., dialysis patients) and in patients with both renal and hepatic dysfunctions.

DIRECTIONS FOR USE: Intramuscular Administration: Reconstitute ceftriaxone for injection 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, ceftriaxone for injection 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 g	3.6 mL	2.1 mL
2 g	7.2 mL	4.2 mL

Intravenous Administration: Ceftriaxone for injection 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 section).

Vial Dosage Size	Amount of Diluent to be Added
250 mg	2.4 mL
500 mg	4.8 mL
1 g	9.6 mL
2 g	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: Ceftriaxone for injection sterile powder should be stored at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature] 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.

Ceftriaxone for injection 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

Ceftriaxone for injection 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.

The following intravenous ceftriaxone for injection 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 intravenous 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 (DSW). No compatibility studies have been conducted with the intravenous 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.

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.

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.

Ceftriaxone for injection 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.**

Ceftriaxone solutions should not be physically mixed with 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, the calcium salt of 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: Ceftriaxone for injection 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 68180-611-01) and box of 10 (NDC 68180-611-10).

Vials containing 500 mg equivalent of ceftriaxone. Box of 1 (NDC 68180-622-01) and box of 10 (NDC 68180-622-10).

Vials containing 1 g equivalent of ceftriaxone. Box of 1 (NDC 68180-633-01) and box of 10 (NDC 68180-633-10).

Vials containing 2 g equivalent of ceftriaxone. Box of 10 (NDC 68180-644-10).

CLINICAL STUDIES—Clinical Trials in Pediatric Patients With Acute Bacterial Otitis Media: In two adequate and well controlled U.S. 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 - U.S. 14	74% (220/296)	Amoxicillin/clavulanate 82% (247/302)	(-14.4%, -0.5%)	Ceftriaxone is lower than control at study day 14 and 28
	58% (167/288)	67% (200/297)	(-17.5%, -1.2%)	
Study 2 - U.S. 14	54% (113/210)	TMP-SMZ 60% (124/206)	(-16.4%, 3.6%)	Ceftriaxone is equivalent to control at study day 14 and 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)

- REFERENCES:**
- 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.
 - National Committee for Clinical Laboratory Standards, *Supplemental Tables*. NCCLS document M100-S10 (M7) (ISBN 1-56238-309-9). NCCLS, Wayne, PA 19087-1898, 2000.
 - 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.
 - 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.
 - 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.

Manufactured for: Lupin Pharmaceuticals, Inc. 111 South Calvert Street Baltimore, Maryland 21202 United States
Manufactured by: Lupin Limited Mumbai 400 098 INDIA
(Date: August, 2003) (ID# 203993)

204005

USUAL DOSAGE: For dosage recommendations and other important prescribing information, read accompanying insert.

Storage Prior to Reconstitution:
Store powder at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Storage After Reconstitution:
See package insert.

PROTECT FROM LIGHT
Code No. MP/DRUGS/28/18/88

NDC 68180-611-01

Single Use Vial

Ceftriaxone for Injection USP

250 mg

For Intramuscular or Intravenous Use

Rx Only

Each vial contains sterile ceftriaxone sodium USP equivalent to ceftriaxone 250 mg

Lupin Pharmaceuticals, Inc.

SEP 30 2003

SEP 30 2003

Lupin Pharmaceuticals, Inc.

Each vial contains sterile ceftriaxone 500 mg equivalent to

ceftriaxone sodium USP

Rx Only

For Intramuscular or Intravenous Use

500 mg

Ceftriaxone for Injection USP

Single Use Vial

NDC 68180-622-01

Code No. MP/DRUGS/28/18/88

PROTECT FROM LIGHT

See package insert.

Storage After Reconstitution:

Controlled Room Temperature].

Storage Prior to Reconstitution:

Store powder at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Storage After Reconstitution:

204006

204007

USUAL DOSAGE: For dosage recommendations and other important prescribing information, read accompanying insert.

Storage Prior to Reconstitution:
Store powder at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Storage After Reconstitution:
See package insert.

PROTECT FROM LIGHT

Code No. MP/DRUGS/28/18/88

NDC 68180-633-01

Single Use Vial

Ceftriaxone for Injection USP

1 g

Intramuscular or Intravenous Use

Rx Only

Each vial contains sterile ceftriaxone sodium USP equivalent to ceftriaxone 1 g

Lupin Pharmaceuticals, Inc.

SEP 30 2003

SEP 30 2003

SEP 30 2003

APPROVED

APPROVED

APPROVED



Manufactured for:
Lupin Pharmaceuticals, Inc.
 111 South Calvert Street
 Baltimore, Maryland 21202
 United States
 Manufactured by:
Lupin Limited
 Mumbai 400 098 INDIA

Directions for Use:
For I.M. Administration:
 Reconstitute with 0.9 mL
 1% Lidocaine Hydrochloride
 Injection (USP) or Sterile Water
 for Injection (USP). Each 1 mL
 of solution contains
 approximately 250 mg
 equivalent of ceftriaxone.
**A 350 mg/mL concentration is
 not recommended for the
 250 mg vial since it may not
 be possible to withdraw the
 entire contents.**

For I.V. Administration:
 Reconstitute with 2.4 mL of an
 I.V. diluent specified in the
 accompanying package insert.
 Each 1 mL of solution contains
 approximately 100 mg
 equivalent of ceftriaxone.
 Withdraw entire contents and
 dilute to the desired
 concentration with the
 appropriate I.V. diluent.

Directions for Use:
For I.M. Administration:
 Reconstitute with 1.0 mL
 1% Lidocaine Hydrochloride
 Injection (USP) or Sterile
 Water for Injection (USP).
 Each 1 mL of solution
 contains approximately
 350 mg equivalent of
 ceftriaxone.
For I.V. Administration:
 Reconstitute with 4.8 mL of
 an I.V. diluent specified in the
 accompanying package
 insert. Each 1 mL of solution
 contains approximately
 100 mg equivalent of
 ceftriaxone. Withdraw entire
 contents and dilute to the
 desired concentration with
 the appropriate I.V. diluent.



Manufactured for:
Lupin Pharmaceuticals, Inc.
 111 South Calvert Street
 Baltimore, Maryland 21202
 United States
 Manufactured by:
Lupin Limited
 Mumbai 400 098 INDIA



Manufactured for:
Lupin Pharmaceuticals, Inc.
 111 South Calvert Street
 Baltimore, Maryland 21202
 United States
 Manufactured by:
Lupin Limited
 Mumbai 400 098 INDIA

Directions for Use:
For I.M. Administration:
 Reconstitute with 2.1 mL
 1% Lidocaine Hydrochloride
 Injection (USP) or Sterile
 Water for Injection (USP).
 Each 1 mL of solution
 contains approximately
 350 mg equivalent of
 ceftriaxone.

For I.V. Administration:
 Reconstitute with 9.6 mL of
 an I.V. diluent specified in
 the accompanying package
 insert. Each 1 mL of
 solution contains
 approximately 100 mg
 equivalent of ceftriaxone.
 Withdraw entire contents
 and dilute to the desired
 concentration with the
 appropriate I.V. diluent.

For I.M. Administration: Reconstitute with 1.0 mL 1% Lidocaine Hydrochloride Injection (USP) or Sterile Water for Injection (USP). Each 1 mL of solution contains approximately 350 mg equivalent of ceftriaxone.
For I.V. Administration: See package insert.
USUAL DOSAGE: See package insert.
Storage Prior to Reconstitution: Store powder at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature).
Storage After Reconstitution: See package insert.
PROTECT FROM LIGHT
Manufactured for:
Lepin Pharmaceuticals, Inc.
111 South Calvert Street
Baltimore, Maryland 21202 United States
Manufactured by:
Lepin Limited
Mumbai 400 099 INDIA
Code No. MPVDFUS228/1/03

NDC 68180-622-01

Single Use Vial

Ceftriaxone for Injection USP

500 mg

For I.M. or I.V. Use
Rx Only

Each vial contains sterile ceftriaxone sodium USP equivalent to ceftriaxone 500 mg

Lepin Pharmaceuticals, Inc.



204002

LOT NO: 003

EXP: SEP 03

For I.M. Administration: Reconstitute with 4.2 mL 1% Lidocaine Hydrochloride Injection (USP) or Sterile Water for Injection (USP). Each 1 mL of solution contains approximately 350 mg equivalent of ceftriaxone.
For I.V. Administration: See package insert.
USUAL DOSAGE: See package insert.
Storage Prior to Reconstitution: Store powder at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature).
Storage After Reconstitution: See package insert.
PROTECT FROM LIGHT
Manufactured for:
Lepin Pharmaceuticals, Inc.
111 South Calvert Street
Baltimore, Maryland 21202 United States
Manufactured by:
Lepin Limited
Mumbai 400 099 INDIA
Code No. MPVDFUS228/1/03

NDC 68180-644-01

Single Use Vial

Ceftriaxone for Injection USP

2 g

For I.M. or I.V. Use
Rx Only

Each vial contains sterile ceftriaxone sodium USP equivalent to ceftriaxone 2 g

Lepin Pharmaceuticals, Inc.



204004

LOT NO: 003

EXP: SEP 03

For I.M. Administration: Reconstitute with 2.1 mL 1% Lidocaine Hydrochloride Injection (USP) or Sterile Water for Injection (USP). Each 1 mL of solution contains approximately 350 mg equivalent of ceftriaxone.
For I.V. Administration: See package insert.
USUAL DOSAGE: See package insert.
Storage Prior to Reconstitution: Store powder at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature).
Storage After Reconstitution: See package insert.
PROTECT FROM LIGHT
Manufactured for:
Lepin Pharmaceuticals, Inc.
111 South Calvert Street
Baltimore, Maryland 21202 United States
Manufactured by:
Lepin Limited
Mumbai 400 099 INDIA
Code No. MPVDFUS228/1/03

NDC 68180-633-01

Single Use Vial

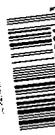
Ceftriaxone for Injection USP

1 g

For I.M. or I.V. Use
Rx Only

Each vial contains sterile ceftriaxone sodium USP equivalent to ceftriaxone 1 g

Lepin Pharmaceuticals, Inc.



204003

LOT NO: P 30

EXP: 2003



For Intramuscular or Intravenous Use
Rx Only

250 mg

Ceftriaxone for Injection USP

Single Use Vials

NDC 68180-611-10

SEP 30 2003

Lupin Pharmaceuticals, Inc.

10 Vials

APPROVED

NDC 68180-611-10

Single Use Vials

Ceftriaxone for Injection USP

250 mg

For Intramuscular or Intravenous Use

Rx Only

Each vial contains sterile ceftriaxone sodium USP equivalent to ceftriaxone 250 mg

10 Vials

Lupin Pharmaceuticals, Inc.



N 68180 61110 13

LOT NO.:

EXP.:

Manufactured for:
Lupin Pharmaceuticals, Inc.
111 South Calvert Street
Baltimore, Maryland 21202 United States

Manufactured by:
Lupin Limited
Mumbai 400 098 INDIA

204064

Directions for Use:

For I.M. Administration: Reconstitute with 0.9 mL 1% Lidocaine Hydrochloride Injection (USP) or Sterile Water for Injection (USP). Each 1 mL of solution contains approximately 250 mg equivalent of ceftriaxone. **A 350 mg/mL concentration is not recommended for the 250 mg vial since it may not be possible to withdraw the entire contents.**

For IV Administration: Reconstitute with 2.4 mL of an I.V. diluent specified in the accompanying package insert. Each 1 mL of solution contains approximately 100 mg equivalent of ceftriaxone. Withdraw entire contents and dilute to the desired concentration with the appropriate I.V. diluent.

USUAL DOSAGE: For dosage recommendations and other important prescribing information, read accompanying insert.

Storage Prior to Reconstitution: Store powder at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Storage After Reconstitution: See package insert. **PROTECT FROM LIGHT**

Code No. MP/DRUGS/28/18/88

NDC 68180-611-10

Single Use Vials

Ceftriaxone for Injection USP

250 mg

For Intramuscular or Intravenous Use

Rx Only

10 Vials

Lupin Pharmaceuticals, Inc.

Lupin Pharmaceuticals, Inc.

10 Vials

For Intramuscular or Intravenous Use
Rx Only

Ceftriaxone for Injection USP

1 g

NDC 68180-633-10
Single Use Vials

APPROVED

NDC 68180-633-10
Single Use Vials

Ceftriaxone for Injection USP

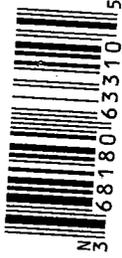
1 g

For Intramuscular or Intravenous Use
Rx Only

Each vial contains sterile ceftriaxone sodium USP
equivalent to ceftriaxone 1 g

10 Vials

Lupin Pharmaceuticals, Inc.



SEP 30 2003

LOT NO.:

EXP.:

Manufactured for:
Lupin Pharmaceuticals, Inc.
111 South Calvert Street
Baltimore, Maryland 21202 United States
Manufactured by:
Lupin Limited
Mumbai 400 098 INDIA

204069

Directions for Use:

For I.M. Administration: Reconstitute with 2.1 mL 1% Lidocaine Hydrochloride Injection (USP) or Sterile Water for Injection (USP). Each 1 mL of solution contains approximately 350 mg equivalent of ceftriaxone.

For I.V. Administration: Reconstitute with 9.6 mL of an I.V. diluent specified in the accompanying package insert. Each 1 mL of solution contains approximately 100 mg equivalent of ceftriaxone. Withdraw entire contents and dilute to the desired concentration with the appropriate I.V. diluent.

USUAL DOSAGE: For dosage recommendations and other important prescribing information, read accompanying insert.

Storage Prior to Reconstitution: Store powder at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Storage After Reconstitution: See package insert.

PROTECT FROM LIGHT

Code No. MP/D/US/28/18/88

NDC 68180-633-10

Single Use Vials

Ceftriaxone for Injection USP

1 g

For Intramuscular or Intravenous Use

Rx Only

10 Vials

Lupin Pharmaceuticals, Inc.



Lupin Pharmaceuticals, Inc.

10 Vials

For Intramuscular or Intravenous Use

Rx Only

2 g

Ceftriaxone for Injection USP

Single Use Vials

NDC 68180-644-10

APPROVED



NDC 68180-644-10

LOT NO.:

EXP:

Manufactured for:
Lupin Pharmaceuticals, Inc.
111 South Calvert Street
Baltimore, Maryland 21202 United States
Manufactured by:
Lupin Limited
Mumbai 400 098 INDIA

EXP 3 0 2003

NDC 68180-644-10

Single Use Vials

Ceftriaxone for Injection USP

2 g

For Intramuscular or Intravenous Use

Rx Only

Each vial contains sterile ceftriaxone sodium USP
equivalent to ceftriaxone 2 g

10 Vials

Lupin Pharmaceuticals, Inc.

204070

Directions for Use:

For I.M. Administration: Reconstitute with 4.2 mL 1% Lidocaine Hydrochloride Injection (USP) or Sterile Water for Injection (USP). Each 1 mL of solution contains approximately 350 mg equivalent of ceftriaxone.

For I.V. Administration: Reconstitute with 19.2 mL of an I.V. diluent specified in the accompanying package insert. Each 1 mL of solution contains approximately 100 mg equivalent of ceftriaxone. Withdraw entire contents and dilute to the desired concentration with the appropriate I.V. diluent.

USUAL DOSAGE: For dosage recommendations and other important prescribing information, read accompanying insert.

Storage Prior to Reconstitution: Store powder at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Storage After Reconstitution: See package insert.

PROTECT FROM LIGHT

Code No. MP/DRUGS/28/18/88

NDC 68180-644-10

Single Use Vials

Ceftriaxone for Injection USP

2 g

For Intramuscular or Intravenous Use

Rx Only

10 Vials

Lupin Pharmaceuticals, Inc.



For Intramuscular or Intravenous Use
Rx Only

Ceftriaxone for Injection USP

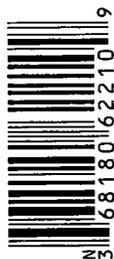
500 mg

Single Use Vials

NDC 68180-622-10

Lupin Pharmaceuticals, Inc.

10 Vials



N 3 68180 62210 9

LOT NO.:

EXP:

Manufactured for:
Lupin Pharmaceuticals, Inc.
111 South Calvert Street
Baltimore, Maryland 21202 United States

Manufactured by:
Lupin Limited
Mumbai 400 098 INDIA

NDC 68180-622-10

Single Use Vials

Ceftriaxone for Injection USP

500 mg

For Intramuscular or Intravenous Use

Rx Only

Each vial contains sterile ceftriaxone sodium USP
equivalent to ceftriaxone 500 mg

10 Vials

Lupin Pharmaceuticals, Inc.

03 SEP 2003

204057

Directions for Use:

For I.M. Administration: Reconstitute with 1.0 mL 1% Lidocaine Hydrochloride Injection (USP) or Sterile Water for Injection (USP). Each 1 mL of solution contains approximately 350 mg equivalent of ceftriaxone.

For I.V. Administration: Reconstitute with 4.8 mL of an I.V. diluent specified in the accompanying package insert. Each 1 mL of solution contains approximately 100 mg equivalent of ceftriaxone. Withdraw entire contents and dilute to the desired concentration with the appropriate I.V. diluent.

USUAL DOSAGE: For dosage recommendations and other important prescribing information, read accompanying insert.

Storage Prior to Reconstitution: Store powder at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Storage After Reconstitution: See package insert.

PROTECT FROM LIGHT

Code No. MP/DRUGS/28/18/88

NDC 68180-622-10

Single Use Vials

Ceftriaxone for Injection USP

500 mg

For Intramuscular or Intravenous Use

Rx Only

Lupin Pharmaceuticals, Inc.

10 Vials

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-125

CSO LABELING REVIEW(S)

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **65-125**

Date of Submission: **May 14, 2003**

Applicant's Name: **Lupin Limited**

Established Name: **Ceftriaxone for Injection USP, 250 mg/vial, 500 mg/vial, 1 g/vial and 2 g/vial**

Labeling Deficiencies:

1. GENERAL COMMENTS

- a. Revise the storage temperature recommendations of the unreconstituted powder throughout your labels and labeling as follows:

Store powder at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

- b. The manufacturer's address, as seen throughout your labels and labeling is not the same as the address of the manufacturer found on page 189 of your original submission (dated March 22, 2002). Please comment and/or revise.

2. CONTAINER 250 mg, 500 mg, 1 g and 2 g single use vials

- a. See GENERAL COMMENTS (1) above.
- b. Revise the container labels to contain the same information as the reference listed drug and/or comment. (Please note that the reference listed drug only lists one diluent amount rather than two for reconstitution.) You may delete one of the addresses to provide more space.
- c. Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert.
- d. Relocate the routes of administration to appear below the strength prominently.
- e. Add the statement "A 350 mg/mL concentration ... contents." to the 250 mg container label as seen on the 250 mg carton labeling.
- f. We acknowledge your intention to distinguish your product strengths by different color schemes.

3. CARTON 1 and 10 x 250 mg, 1 and 10 x 500 mg, 1 and 10 x 1 g, 10 x 2 g

- a. See comments under CONTAINER (2) above.
- b. Please distinguish the product strengths in a similar manner in which you intend to distinguish the strengths on the container labels.
- c. You have used a different format for your "Each Vial Contains" statements on your cartons of 1s and cartons of 10s. We further note that the word "contains" is seen with a lower case "c" on the cartons of 10s and with an upper case "C" on the cartons of 1s.
- d. The innovator does not use an "Each Vial Contains" statement. Please comment.

4. INSERT

a. GENERAL COMMENT

"mcg/mL" rather than "" throughout the insert labeling

b. DESCRIPTION

i. Second paragraph

A). "molecular formula" rather than "

B). $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3.5 H_2O$

ii. Chemical structure – Revise the waters of hydration as follows:

• 3.5 H₂O [the "3.5" and the "H₂O" should appear on the same line of text – also note the placement of the period between the "3" and the "5".

c. DOSAGE AND ADMINISTRATION

Compatibility and Stability

i. First sentence – Ceftriaxone for Injection sterile powder should be stored at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature] and protected from light.

ii. Paragraph beginning "Ceftriaxone has been shown ..."

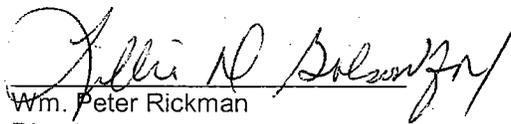
A). Third line – "10 mg/mL" rather than ""

B). Fourth line – "(D5W)" rather than ""

Please revise your container labels and carton and insert labeling, as instructed above, and submit 12 copies of each piece (container labels and carton and insert labeling) in final print, or 4 copies in draft, if you prefer.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - <http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.


Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BASIS OF APPROVAL:**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Container Labels: 250 mg, 500 mg, 1 gram and 2 gram

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Rocephin® for Injection

NDA Number: 50-585

NDA Drug Name: Rocephin® (ceftriaxone sodium) for Injection

NDA Firm: Hoffmann-LaRoche

Date of Approval of NDA Insert and supplement #: 8-25-00 (S-047)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Basis of Approval for the Carton Labeling:

Other Comments

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 25	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. Stability protocols found unacceptable by chemist M. Shih.	?		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	

Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

- Has the firm submitted sufficient data to justify the listed storage temperature recommendations? Yes - per M. Shih --- but R. Adams has asked me to ask the firm to revise the storage temperature recommendations for the sterile powder as follows: Store powder at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. I have asked the firm to revise as he suggested.
- Has the firm verified that the desired concentration can be achieved for each strength with the addition of the specified amount of diluent indicated in the labeling? Yes - per M. Shih -- However because the RLD does not list two different quantities for the amount of diluent that may be added to reconstitute an IM dose on their 500 mg, 1 g and 2 g container labels and carton labeling we have asked the firm to revise their 500 mg, 1 g and 2 g container labels and carton labeling to be the same as the RLD's - and only include one amount of diluent (the same amount as the RLD) to be used in the preparation of the solution. Information can be found in the DOSAGE AND ADMINISTRATION section of the package insert if an end user wishes to have the option of either reconstituting the end product in either a 250 mg/mL or 350 mg/mL concentration.
- Has the sodium content as stated in the DESCRIPTION section been verified? Yes - per M. Shih

FOR THE RECORD: (portions taken from previous review)

- Review based on the labeling of Rocephin®, (NDA 50-585/S-047) revised July 2000 (in draft); approved 8-25-00. This is the first generic for this drug product.

- Patent/ Exclusivities

Patent Data – 50-585

No	Expiration	Use Code	Use	File
None				

Exclusivity Data - 50-585

Code/sup	Expiration	Use Code	Description	Labeling Impact
None			There is no unexpired exclusivity for this product	

- Storage Conditions: (sterile powder)
 NDA - room temperature - 77°F (25°C) - Protect From Light.
 ANDA - room temperature - 77°F (25°C) -- Protect From Light.
 USP - Preserve in containers for sterile solids.
 There is a table in the insert indicating how long the reconstituted solution is stable for under refrigeration (4°C) and at room temperature (25°C) in various IV fluids.
- Product Line:
 The innovator markets their product in boxes of 1s for the 250 mg, 500 mg and 1 gram strengths and in boxes of 10s for all four strengths.
 The applicant proposes to market their product in the same packaging configuration. The vials will be made of USP Type 1 Glass with flip-off caps - 250 mg (white), 500 mg (green), 1 g (light blue), 2 g (red) [v 1.2 p 619].

5. The name and address of the manufacturer is located on page 189, vol. 1.1.

Lupin Limited
201 & 202, New Industrial Area No. 2
Mandideep, Distt. Raisen,
Madhya Pradesh
India - 462 046

6. Inactive Ingredients:
There are no inactive ingredients [see page 157 (Volume 1.1)].

7. This is a **FIRST GENERIC**.

Date of Review: 6-26-03

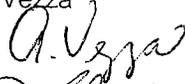
Date of Submission: 5-14-03

Primary Reviewer: Adolph Vezza

Date:

Team Leader: Lillie Golson

Date:



7/3/03



7/3/03

cc: ANDA: 65-125
DUP/DIVISION FILE
HFD-613/AVezza/LGolson (no cc)
aev/6/26/03|V:\FIRMSAM\LUPIN\LTRS&REV\65125na2.L
Review

**APPEARS THIS WAY
ON ORIGINAL**

**APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **65-125**

Date of Submission: ^{22 AU 9/24/03} **August 25, 2003**

Applicant's Name: **Lupin Limited**

Established Name: **Ceftriaxone for Injection USP, 250 mg/vial, 500 mg/vial, 1 g/vial and 2 g/vial**

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? **Yes**

Container Labels: 250 mg, 500 mg, 1 gram and 2 gram

Satisfactory in FPL as of August 25, 2003 submission [vol 3.2].

Carton Labeling: 1 x 250 mg & 10 x 250 mg, 1 x 500 mg and 10 x 500 mg, 1 x 1 g and 10 x 1 g, 10 x 2 g

Satisfactory in FPL as of August 25, 2003 submission [vol 3.2].

Professional Package Insert Labeling: ^{22 AU}

Satisfactory in FPL as of August 25, 2003 submission [vol 3.2 - ID # 203993].

Revisions needed post-approval: none ^{22 AU}

BASIS OF APPROVAL:

Was this approval based upon a petition? **No**

What is the RLD on the 356(h) form: **Rocephin® for Injection**

NDA Number: **50-585**

NDA Drug Name: **Rocephin® (ceftriaxone sodium) for Injection**

NDA Firm: **Hoffmann-LaRoche**

Date of Approval of NDA Insert and supplement #: **8-25-00 (S-047)**

Has this been verified by the MIS system for the NDA? **Yes**

Was this approval based upon an OGD labeling guidance? **No**

Basis of Approval for the Container Labels: **side-by-sides**

Basis of Approval for the Carton Labeling: **side-by-sides**

Other Comments

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 25	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information		X	

on the label).			
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. Stability protocols found unacceptable by chemist M. Shih.	?		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. **Has the firm submitted sufficient data to justify the listed storage temperature recommendations? Yes - per M. Shih --- but R. Adams has asked me to ask the firm to revise the storage temperature recommendations for the sterile powder as follows: Store powder at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. I have asked the firm to revise as he suggested.**
2. **Has the firm verified that the desired concentration can be achieved for each strength with the addition of the specified amount of diluent indicated in the labeling? Yes - per M. Shih -- However because the RLD does not list two different quantities for the amount of diluent that may be added to reconstitute an IM dose on their 500 mg, 1 g and 2 g container labels and carton labeling we have asked the firm to revise their 500 mg, 1 g and 2 g container labels and carton labeling to be the same as the RLD's - and only include one amount of diluent (the same amount as the RLD) to be used in the preparation of the solution. Information can be found in the DOSAGE AND ADMINISTRATION section of the package insert if an end user wishes to have the option of either reconstituting the end product in either a 250 mg/mL or 350 mg/mL concentration.**
3. **Has the sodium content as stated in the DESCRIPTION section been verified? Yes - per M. Shih**

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of Rocephin®, (NDA 50-585/S-047) revised July 2000 (in draft); approved 8-25-00. This is the first generic for this drug product.

2. Patent/ Exclusivities

Patent Data – 50-585

No	Expiration	Use Code	Use	File
None				

Exclusivity Data - 50-585

Code/sup	Expiration	Use Code	Description	Labeling Impact
None			There is no unexpired exclusivity for this product	

3. Storage Conditions: (sterile powder)
 NDA - room temperature - 77°F (25°C) - Protect From Light.
 ANDA - Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect From Light.
 USP - Preserve in containers for sterile solids
 There is a table in the insert indicating how long the reconstituted solution is stable for under refrigeration (4°C) and at room temperature (25°C) in various IV fluids.

4. Product Line:
 The innovator markets their product in boxes of 1s for the 250 mg, 500 mg and 1 gram strengths and in boxes of 10s for all four strengths.
 The applicant proposes to market their product in the same packaging configuration. The vials will be made of USP Type 1 Glass with flip-off caps - 250 mg (white), 500 mg (green), 1 g (light blue), 2 g (red) [v 1.2 p 619].

5. The name and address of the manufacturer is located on page 189, vol. 1.1.

Lupin Limited
 201 & 202, New Industrial Area No. 2
 Mandideep, Distt. Raisen,
 Madhya Pradesh
 India - 462 046

6. Inactive Ingredients:
 There are no inactive ingredients [see page 157 (Volume 1.1)].

7. This is a **FIRST GENERIC**.

Date of Review: 9-22-03

Date of Submission: ^{22 90} 8-25-03

Primary Reviewer: Adolph Veza

Date: 9/24/03

Team Leader: Lillie Golson

Date: 9/24/03

cc: ANDA: 65-125
 DUP/DIVISION FILE
 HFD-613/AVeza/LGolson (no cc)
 aev/9/22/03|V:\FIRMSAM\LUPIN\LTRS&REV65125.APL
 Review

c. DESCRIPTION

- i. The following letters should be italicized in the chemical name:
"6*R*", "7*R*", "as", "O-methyloxime"
- ii. Revise the molecular weight to read "661.60" per USP 26.
- iii. Place a dot before the waters of hydration in the chemical formula.

d. CLINICAL PHARMACOLOGY

- i. Third line - "or 350 mg/mL" rather than "or _____"
- ii. Paragraph after Table 1, second sentence - Delete the period after "IM".
- iii. Table 3 - Be consistent as to whether or not the subtitles are underlined.
- iv. Microbiology
 - A). Delete the period after the sub-subsection title "Aerobic gram-negative microorganisms:"
 - B). Insert a blank line space between "*Serratia marcescens*" and the next sentence "Ceftriaxone is ..."
 - C). Insert a blank line space between "*Peptostreptococcus* species" and "NOTE: Most strains ..."
 - D). Delete the blank line space between the sentence beginning "The following *in vitro* ..." and the following paragraph.
 - E). Leave a blank line space between the sub-subsections "Aerobic gram-negative microorganisms:", "Aerobic gram-positive microorganisms:" and "Anaerobic microorganisms:" as they occur at the end of this subsection.
- v. Diffusion techniques
 - A). Paragraph beginning "Disk diffusion ...", third line - ">" rather than "_____"
 - B). Paragraph beginning "As with other ...", last line - Delete the quotation marks and place a "4" superscripted after "dilution" (i.e., "dilution⁴").
 - C). Last table in this section
 - 1). "*thetaitaomicron*" (spelling)
 - 2). Add the following sentence immediately after the above table:
"ATCC[®] is a registered trademark of the American Type Culture Collection."

e. PRECAUTIONS

- i. General, last line - Delete the extra period.
- ii. Pediatric Use, first sentence - "pediatric patients" rather than "_____"

f. ADVERSE REACTIONS

- i. Local Reactions, second sentence - "The incidence of warmth, tightness or induration was ..."
- ii. Hematologic, first line - "eosinophilia (6%), thrombocytosis (5.1% ..."
- iii. Last paragraph, last line - "... palpitations, epistaxis, biliary lithiasis, agranulocytosis, renal precipitations, and nephrolithiasis."

g. OVERDOSAGE

Add the following section (OVERDOSAGE) with the associated text below immediately after the "ADVERSE REACTIONS" section:

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

h. DOSAGE AND ADMINISTRATION

- i. Compatibility and Stability, second line - "-- 25°C (77°F) -- or below and ..."
- ii. Add the following two paragraphs immediately before the paragraph (single sentence beginning "After the indicated ...":

"Ceftriaxone has been shown to be compatible with intravenous 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 intravenous 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.

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."

- iii. Add the following immediately after the paragraph (single sentence beginning "After the indicated ...":

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

i. CLINICAL STUDIES

Second table - The genus and species names for the organisms listed in the table should be in *italic* print.

j. REFERENCES

- i. The section title should be in **bold** print.
- ii. The titles of the articles in the journals should be in *italic* print.

Please revise your container labels and insert labeling, as instructed above, and submit 12 copies of each piece (container labels and carton and insert labeling) in final print, or 4 copies in draft, if you prefer.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - <http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.


Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BASIS OF APPROVAL:**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Container Labels: 250 mg, 500 mg, 1 gram and 2 gram

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Rocephin® for Injection

NDA Number: 50-585

NDA Drug Name: Rocephin® (ceftriaxone sodium) for Injection

NDA Firm: Hoffmann-LaRoche

Date of Approval of NDA Insert and supplement #: 8-25-00 (S-047)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Basis of Approval for the Carton Labeling:

Other Comments

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 25	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. Stability protocols found unacceptable by chemist M. Shih.	?		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	

Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. Has the firm submitted sufficient data to justify the listed storage temperature recommendations? Yes - per M. Shih
2. Has the firm verified that the desired concentration can be achieved for each strength with the addition of the specified amount of diluent indicated in the labeling? Yes - per M. Shih
3. Has the sodium content as stated in the DESCRIPTION section been verified? Yes - per M. Shih

FOR THE RECORD:

1. Review based on the labeling of Rocephin®, (NDA 50-585/S-047) revised July 2000 (in draft); approved 8-25-00. This is the first generic for this drug product.
2. Patent/ Exclusivities

Patent Data – 50-585

No	Expiration	Use Code	Use	File
None				

Exclusivity Data - 50-585

Code/sup	Expiration	Use Code	Description	Labeling Impact
None			There is no unexpired exclusivity for this product	

3. Storage Conditions: (sterile powder)
 NDA - room temperature - 77°F (25°C) - Protect From Light.
 ANDA - room temperature - 77°F (25°C) - - Protect From Light.
 USP - Preserve in containers for sterile solids
 There is a table in the insert indicating how long the reconstituted solution is stable for under refrigeration (4°C) and at room temperature (25°C) in various IV fluids.
4. Product Line:
 The innovator markets their product in boxes of 1s for the 250 mg, 500 mg and 1 gram strengths and in boxes of 10s for all four strengths.
 The applicant proposes to market their product in the same packaging configuration. The vials will be made of USP Type 1 Glass with flip-off caps - 250 mg (white), 500 mg (green), 1 g (light blue), 2 g (red) [v 1.2 p 619].
5. Lupin is the manufacturer (page 189, vol. 1.1).
6. Inactive Ingredients:
 There are no inactive ingredients [see page 157 (Volume 1.1) .
7. This is a **FIRST GENERIC**.

Date of Review: 1-14-03

Date of Submission: 3-28-02

Primary Reviewer: Adolph Veza

Date: 2/5/03

Team Leader: Lillie Golson

Date: 2/5/03

A. Veza
Lillie Golson

cc: ANDA: 65-125
DUP/DIVISION FILE
HFD-613/AVeza/LGolson (no cc)
aev/1/14/03|V:\FIRMSAM\LUPIN\LTRS&REV\65125na1.I
Review

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-125

CHEMISTRY REVIEW(S)



ANDA 65-125

Ceftriaxone for Injection USP

Lupin Limited

Maria C. Shih

Division of Chemistry II, Office of Generic Drugs

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APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. ANDA: 65-125

2. REVIEW #: 1

3. REVIEW DATE: 8/20/02

4. REVIEWER: Maria C. Shih

5. PREVIOUS DOCUMENTS:

Previous Documents

Original Submission
New Correspondence
Acceptable for filing
New Correspondence

Document Date

28- MAR-2002
24-JUNE-2002
3-JULY-2002
24-JULY-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original Submission
New Correspondence
New Correspondence

Document Date

28- MAR-2002
24-JUNE-2002
24-JULY-2002

CHEMISTRY REVIEW

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Lupin Limited
Address: The World Trade Center
401 E. Pratt Street, Suite 2225
Baltimore, MD 21202
Representative: Vinita Gupta
Telephone: 410-576-2000

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Ceftriaxone for Injection USP

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug Rocephin® by Hoffman LaRoche Inc. under NDA #50-585,
Sterile powder for 500 mg, 1 g, 2 g, and 10 g.

Firm claims (pages 15-9, also in New Correspondence 6/24/02) that there are no
unexpired patents or exclusivity for this product.

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Sterile powder for injection

12. STRENGTH/POTENCY: 250 mg, 500 mg, 1 g, and 2 g

13. ROUTE OF ADMINISTRATION: IV/IM

14. Rx/OTC DISPENSED: X Rx OTC

CHEMISTRY REVIEW

Chemistry Review Data Sheet

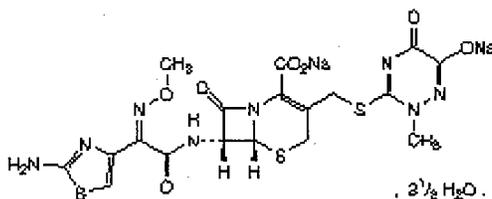
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

 X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ceftriaxone Sodium [104376-79-6]



$C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3\frac{1}{2}H_2O$ 661.60

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[(2-amino-4-thiazolyl) (methoxyimino) acetyl]amino]-8-oxo-3-[[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)thio]methyl]-, disodium salt, [6R-[6a,7b(Z)]]-, hydrate, (2:7). (6R,7R)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-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 [104376-79-6].

Anhydrous 598.56

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1	II	Lupin	Sterile Ceftriaxone Sodium	1	Inadequate	8/16/02	-
2	III			6			

CHEMISTRY REVIEW

Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for ANDA 65-125

The Executive Summary

I. Recommendations

- A. **Recommendation and Conclusion on Approvability**
Not Recommended for Approval (MINOR)
- B. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**
N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Reference Listed Drug Rocephin® (Ceftriaxone for Injection) by Hoffman LaRoche Inc. (HLR) under NDA #50-585, Sterile powder for 500 mg, 1 g, 2 g, and 10 g.

Drug substance

Sterile Ceftriaxone Sodium is manufactured under Lupin's DMF #1 using _____ as the key starting material. Deficiency letter is being issued to the DMF holder (per CR #1 dated 8/16/02).

Drug product

This application is the **first generic** for this dosage form.

Currently there are two other approved ANDAs from HLR's Rocephin®: #63-239 (250 mg/vial and 1g/vial, approved 8/13/93) and #62-654 (ADD-Advantage Vials, 1 g/vial and 2 g/vial, approved 4/30/87)). There has been no distribution for the former since approval.

This is a single entity product, the sterile API is _____ or other manufacturing steps are involved. The dry powder is relatively stable, but tends to degrade when reconstituted in solution. Firms usually use _____ to maintain the labeling claim for potency and to meet the specifications. See under Composition for the comparative formulations with RLD and other approved ANDAs.

The copies of specifications from NDA 50-585, and ANDA 62-654 are attached in this review.



Executive Summary Section

B. Description of How the Drug Product is Intended to be Used

N/A

C. Basis for Approvability or Not-Approval Recommendation

The application is not approvable for minor CMC issues. The deficiencies are related to overage and controls of drug substance and drug product, also some stability issues for reconstituted solutions.

III. Administrative

cc: ANDA 65-125
ANANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-643/MShih/8/20/02/ *M. Shih 8/20/02*

HFD-643/RAdams/8/23/02 *R.C. Adams 8/30/02*

V:\firmsam\LUPIN\ltrs&rev\65125rv1.NAD.doc

F/T by: TOH 8/30/02

TYPE OF LETTER: NOT APPROVABLE - MINOR

**APPEARS THIS WAY
ON ORIGINAL**

Redacted 14

Page(s) of trade

secret and /or

confidential

commercial

information

ANDA 65-125

Ceftriaxone for Injection USP

Lupin Limited

**Maria C. Shih
Division of Chemistry II, Office of Generic Drugs**

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APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. ANDA: 65-125
2. REVIEW #: 2
3. REVIEW DATE: 11/25/02
4. REVIEWER: Maria C. Shih
5. PREVIOUS DOCUMENTS:

Previous Documents

Original Submission
New Correspondence
Acceptable for filing
New Correspondence
CMC deficiency #1

Document Date

28- MAR-2002
24-JUNE-2002
3-JULY-2002
24-JULY-2002
9-Sept-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

CMC Minor Amendment

Document Date

14-OCT-2002

APPEARS THIS WAY
ON ORIGINAL

CHEMISTRY REVIEW

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Lupin Limited
The World Trade Center
Address: 401 E. Pratt Street, Suite 2225
Baltimore, MD 21202
Representative: Vinita Gupta
Telephone: 410-576-2000

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Ceftriaxone for Injection USP

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug Rocephin® by Hoffman LaRoche Inc. under NDA #50-585, Sterile powder for 500 mg, 1 g, 2 g, and 10 g.

Firm claims (pages 15-9, also in New Correspondence 6/24/02) that there are no unexpired patents or exclusivity for this product.

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Sterile powder for injection

12. STRENGTH/POTENCY: 250 mg, 500 mg, 1 g, and 2 g

13. ROUTE OF ADMINISTRATION: IV/IM

14. Rx/OTC DISPENSED: Rx OTC

CHEMISTRY REVIEW

Chemistry Review Data Sheet

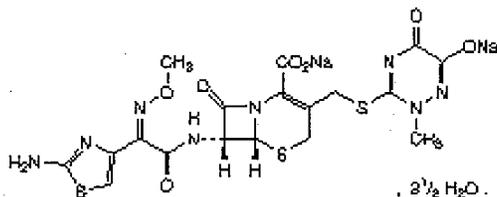
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ceftriaxone Sodium [104376-79-6]



$C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3\frac{1}{2}H_2O$ 661.60

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[2-amino-4-thiazolyl(methoxyimino) acetyl]amino]-8-oxo-3-[[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)thio]methyl]-, disodium salt, [6 R-[6a,7b (Z)]]-, hydrate, (2:7). (6R,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 [104376-79-6].

Anhydrous 598.56

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
_____	II	Lupin	Sterile Ceftriaxone Sodium	1	CMC (Adeq) Micro (Inadeq)	11/21/02 11/12/02	Per CR #2 Per CR #1
_____	III	_____	_____	6			

CHEMISTRY REVIEW

Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Deficient	11/12/02	Nrapendra Nath
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Waiver granted	9/13/02	Mamata Gokhale
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 65-125

The Executive Summary

I. Recommendations

- A. **Recommendation and Conclusion on Approvability**
Not Recommended for Approval (MINOR)
- B. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**
N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Reference Listed Drug Rocephin® (Ceftriaxone for Injection) by Hoffman LaRoche Inc. (HLR) under NDA #50-585, Sterile powder for 500 mg, 1 g, 2 g, and 10 g.

Drug substance

Sterile Ceftriaxone Sodium is manufactured under Lupin's DMF # _____, using _____ as the key starting material. Deficiency letter is being issued to the DMF holder (per CR #1 dated 8/16/02).

Drug product

This application is the **first generic** for this dosage form.

Currently there are two other approved ANDAs from HLR's Rocephin®: #63-239 (250 mg/vial and 1g/vial, approved 8/13/93) and #62-654 (ADD-Advantage Vials, 1 g/vial and 2 g/vial, approved 4/30/87)). There has been no distribution for the former since approval.

This is a single entity product, the sterile API is _____ or other manufacturing steps are involved. The dry powder is relatively stable, but tends to degrade when reconstituted in solution. Firms usually use _____ to maintain the labeling claim for potency and to meet the specifications. See under Composition for the comparative formulations with RLD and other approved ANDAs.

The copies of specifications from NDA 50-585, and ANDA 62-654 are attached in CR #1.

CHEMISTRY REVIEW

Executive Summary Section

B. Description of How the Drug Product is Intended to be Used

N/A

C. Basis for Approvability or Not-Approval Recommendation

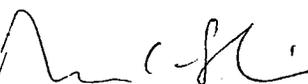
The application is not approvable for DMF issues (Micro).

III. Administrative

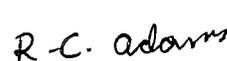
cc: ANDA 65-125
ANANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-643/MShih/11/25/02/

 12/2/02

HFD-643/RAdams/12/1/02

 12/4/02

V:\firmsam\LUPIN\ltrs&rev\65125rv2.NAD.doc

F/T by: mda/12/2/02

TYPE OF LETTER: NOT APPROVABLE - MINOR

**APPEARS THIS WAY
ON ORIGINAL**

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ANDA 65-125

Ceftriaxone for Injection USP

Lupin Limited

Maria C. Shih

Division of Chemistry II, Office of Generic Drugs



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II. Summary of Chemistry Assessments.....7

 A. Description of the Drug Product(s) and Drug Substance(s)7

 B. Description of How the Drug Product is Intended to be Used.....8

 C. Basis for Approvability or Not-Approval Recommendation8

III. Administrative.....8

Chemistry Assessment 9

APPEARS THIS WAY
ON ORIGINAL



Chemistry Review Data Sheet

1. ANDA: 65-125
2. REVIEW #: 3
3. REVIEW DATE: 5/5/03
4. REVIEWER: Maria C. Shih
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	28- MAR-2002
New Correspondence	24-JUNE-2002
Acceptable for filing	3-JULY-2002
New Correspondence	24-JULY-2002
CMC deficiency #1	9-SEPT-2002
CMC deficiency #2	10-DEC-2002

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
CMC Minor Amendment	14-OCT-2002
CMC Minor Amendment	21- JAN-2003



CHEMISTRY REVIEW



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Lupin Limited
The World Trade Center
Address: 401 E. Pratt Street, Suite 2225
Baltimore, MD 21202
Representative: Vinita Gupta
Telephone: 410-576-2000

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Ceftriaxone for Injection USP

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug Rocephin® by Hoffman LaRoche Inc. under NDA #50-585, Sterile powder for 500 mg, 1 g, 2 g, and 10 g.

Firm claims (pages 15-9, also in New Correspondence 6/24/02) that there are no unexpired patents or exclusivity for this product.

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Sterile powder for injection

12. STRENGTH/POTENCY: 250 mg, 500 mg, 1 g, and 2 g

13. ROUTE OF ADMINISTRATION: IV/IM

14. Rx/OTC DISPENSED: Rx OTC



CHEMISTRY REVIEW



Chemistry Review Data Sheet

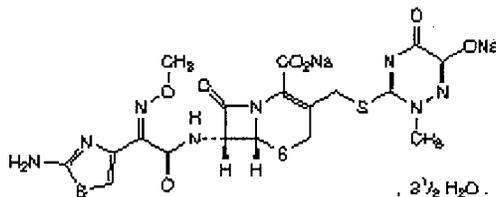
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

 X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ceftriaxone Sodium [104376-79-6]



$C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3\frac{1}{2}H_2O$ 661.60

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[(2-amino-4-thiazolyl)(methoxyimino) acetyl]amino]-8-oxo-3-[[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)thio]methyl]-, disodium salt, [6R-[6a,7b(Z)]]-, hydrate, (2:7). (6R,7R)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7²-(Z)-(O-methoxyimino), disodium salt, sesquaterhydrate [104376-79-6].

Anhydrous 598.56

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
 	II	Lupin	Sterile Ceftriaxone Sodium	1	CMC (Adeq) Micro (Adeq)	11/21/02 4/16/03	Per CR #2 Per CR #2
 	III	 	 	1	Adequate	12/27/02	Per CR #7



CHEMISTRY REVIEW



Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	4/28/03	Nrapendra Nath
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Waiver granted	9/13/02	Mamata Gokhale
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

**APPEARS THIS WAY
ON ORIGINAL**



The Chemistry Review for ANDA 65-125

The Executive Summary

I. Recommendations

- A. **Recommendation and Conclusion on Approvability**
Recommended for Approval

- B. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**
N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Reference Listed Drug Rocephin® (Ceftriaxone for Injection) by Hoffman LaRoche Inc. (HLR) under NDA #50-585, Sterile powder for 500 mg, 1 g, 2 g, and 10 g.

Drug substance

Sterile Ceftriaxone Sodium is manufactured under Lupin's DMF # _____, using _____ as the key starting material. Deficiency letter is being issued to the DMF holder (per CR #1 dated 8/16/02). DMF # _____ is now acceptable for both CMC (11/21/02) and sterility issues (4/16/03).

Drug product

This application is the **first generic** for this dosage form.

Currently there are two other approved ANDAs from HLR's Rocephin®: #63-239 (250 mg/vial and 1g/vial, approved 8/13/93) and #62-654 (ADD-Advantage Vials, 1 g/vial and 2 g/vial, approved 4/30/87)). There has been no distribution for the former since approval.

This is a single entity product, the sterile API is _____ or other manufacturing steps are involved. The dry powder is relatively stable, but tends to degrade when reconstituted in solution. Firms usually use _____ to maintain the labeling claim for potency and to meet the specifications. See under Composition for the comparative formulations with RLD and other approved ANDAs.

The copies of specifications from NDA 50-585, and ANDA 62-654 are attached in CR #1.



Executive Summary Section

B. Description of How the Drug Product is Intended to be Used

N/A

C. Basis for Approvability or Not-Approval Recommendation

The only concern we listed in CR #2 is for sterility issues (Micro), which was addressed in Amendment 1/21/03. The application is now approvable (pending labeling).

III. Administrative

cc: ANDA 65-125
ANANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-643/MShih/5/5/03/

HFD-643/RAdams/

V:\firmsam\LUPIN\ltrs&rev\65125rv3.APD.doc

F/T by:

Copy for M Shih 8/18/03
R.C. Adams 5/20/03
updated 8/18/03

TYPE OF LETTER: APPROVABLE

**APPEARS THIS WAY
ON ORIGINAL**

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ANDA 65-125

Ceftriaxone for Injection USP

Lupin Limited

Maria C. Shih

Division of Chemistry II, Office of Generic Drugs



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APPEARS THIS WAY
ON ORIGINAL



Chemistry Review Data Sheet

1. ANDA: 65-125
2. REVIEW #: 4
3. REVIEW DATE: 9/25/03
4. REVIEWER: Maria C. Shih
5. PREVIOUS DOCUMENTS:

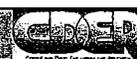
<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	28- MAR-2002
New Correspondence	24-JUNE-2002
Acceptable for filing	3-JULY-2002
New Correspondence	24-JULY-2002
CMC deficiency #1	9-SEPT-2002
CMC deficiency #2	10-DEC-2002
CMC Minor Amendment	14-OCT-2002
CMC Minor Amendment	21- JAN-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
CMC Minor Amendment (Labeling)	25- AUG-2003



CHEMISTRY REVIEW



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Lupin Limited
The World Trade Center
Address: 401 E. Pratt Street, Suite 2225
Baltimore, MD 21202
Representative: Vinita Gupta
Telephone: 410-576-2000

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Ceftriaxone for Injection USP

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug Rocephin® by Hoffman LaRoche Inc. under NDA #50-585, Sterile powder for 500 mg, 1 g, 2 g, and 10 g.

Firm claims (pages 15-9, also in New Correspondence 6/24/02) that there are no unexpired patents or exclusivity for this product.

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Sterile powder for injection

12. STRENGTH/POTENCY: 250 mg, 500 mg, 1 g, and 2 g

13. ROUTE OF ADMINISTRATION: IV/IM

14. Rx/OTC DISPENSED: Rx OTC



CHEMISTRY REVIEW



Chemistry Review Data Sheet

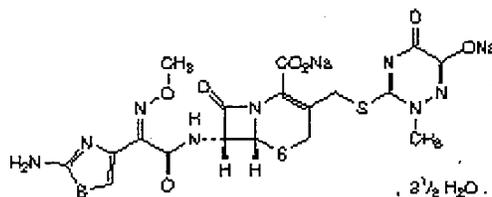
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

 X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ceftriaxone Sodium [104376-79-6]



$C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3\frac{1}{2}H_2O$ 661.60

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[(2-amino-4-thiazolyl)(methoxyimino) acetyl]amino]-8-oxo-3-[[[(1,2,5,6-tetrahydro-2-methyl-5-, 6-dioxo-1,2,4-triazin-3-yl)thio]methyl]-, disodium salt, [6R-[6a,7b(Z)]]-, hydrate, (2:7). (6R,7R)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-as-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7²-(Z)-(O-methoxyimino), disodium salt, sesquaterhydrate [104376-79-6].

Anhydrous 598.56

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	II	Lupin	Sterile Ceftriaxone Sodium	1	CMC (Adeq) Micro (Adeq)	11/21/02 4/16/03	Per CR #2 Per CR #2
—	III	—	—	1	Adequate	12/27/02	Per CR #7



CHEMISTRY REVIEW



Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	4/28/03	Nrapendra Nath
EES	Acceptable	7/25/03	
Methods Validation	N/A		
Labeling	Acceptable	9/24/03	Adolph Vezza
Bioequivalence	Waiver granted	9/13/02	Mamata Gokhale
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

Note:

In CR #3 we found CMC issues acceptable, only labeling issue remained deficient. In Amendment 8/25/03 Lupin responds to our N/A letter 8/18/03. Labeling is now acceptable (9/24/03).



The Chemistry Review for ANDA 65-125

The Executive Summary

I. Recommendations

- A. **Recommendation and Conclusion on Approvability**
Recommended for Approval
- B. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**
N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Reference Listed Drug Rocephin® (Ceftriaxone for Injection) by Hoffman LaRoche Inc. (HLR) under NDA #50-585, Sterile powder for 500 mg, 1 g, 2 g, and 10 g.

Drug substance

Sterile Ceftriaxone Sodium is manufactured under Lupin's DMF # _____, using _____ as the key starting material. Deficiency letter was issued to the DMF holder (per CR #1 dated 8/16/02). DMF # _____ is now acceptable for both CMC (11/21/02) and sterility issues (4/16/03).

Drug product

This application is the **first generic** for this dosage form.

Currently there are two other approved ANDAs from HLR's Rocephin®: #63-239 (250 mg/vial and 1g/vial, approved 8/13/93) and #62-654 (ADD- Advantage Vials, 1 g/vial and 2 g/vial, approved 4/30/87)). There has been no distribution for the former since approval.

This is a single entity product, the sterile API _____ or other manufacturing steps are involved. The dry powder is relatively stable, but tends to degrade when reconstituted in solution. Firms usually use _____ to maintain the labeling claim for potency and to meet the specifications. See under Composition for the comparative formulations with RLD and other approved ANDAs.

The copies of specifications from NDA 50-585, and ANDA 62-654 are attached in CR #1.



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Description of How the Drug Product is Intended to be Used

N/A

C. Basis for Approvability or Not-Approval Recommendation

In CR #3 we found CMC issues acceptable, only labeling issue remained deficient. In Amendment 8/25/03 Lupin responds to our N/A letter 8/18/03. Labeling is now acceptable (9/24/03).

APPEARS THIS WAY
ON ORIGINAL



Executive Summary Section

III. Administrative

cc: ANDA 65-125
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-643/MShih/9/25/03/

HFD-643/RAdams/

V:\firmsam\LUPIN\ltrs&rev\65125rv4.APD.doc

F/T by:

M. Shih - 9/26/03
D.C. Adams 9/25/03

TYPE OF LETTER: APPROVABLE

**APPEARS THIS WAY
ON ORIGINAL**

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information

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-125

**BIOEQUIVALENCE
REVIEW(S)**

SEP 16 2002

Ceftriaxone For Injection, USP
250 mg, 500 mg, 1 g and 2 g Vials
ANDA # 65-125
Reviewer: Mamata S. Gokhale
v:\firmsam\lupin\ltrs&rev\65125W0302.doc

Lupin Limited
The World Trade Center
401 E. Pratt Street, Suite 2225
Baltimore, MD 21202
Submission Date: March 28, 2002

Review of Waiver Requests

Background

1) The firm has submitted requests for waivers of in vivo bioavailability/bioequivalence study requirements based on 21 CFR 320.22 (b) (1) for its proposed product, Ceftriaxone For Injection, USP, 250 mg/vial, 500 mg/vial, 1 g/vial and 2 g/vial. The Orange Book 2002 indicates that each of these strengths have corresponding RLDs, Rocephin® 250 mg, 500 mg, 1 g and 2 g (NDA 50-585), manufactured by HLR/Roche Laboratories Inc.

2) Rocephin® is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. It contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone activity. Rocephin® is readily soluble in water.

3) The RLD, Rocephin® is supplied as a sterile crystalline powder in glass vials containing 250 mg, 500 mg, 1 g and 2 g equivalent of ceftriaxone. Labeling indicates that Rocephin® powder should be reconstituted with the appropriate diluent depending upon the intravenous (IV) or intramuscular (IM) route of administration. The test product, Ceftriaxone For Injection, 250 mg, 500 mg, 1 g and 2 g is also supplied as a sterile crystalline powder to be administered by IV or IM route upon reconstitution with appropriate diluent.

4) The DBE has not reviewed any submissions for Ceftriaxone For Injection, 250 mg, 500 mg, 1 g and 2 g. This ANDA is a potential first generic.

Formulation Comparison

Active Ingredient	¹ Reference Product	² Test Product
Ceftriaxone Sodium, USP	250 mg/vial	250 mg/vial
	500 mg/vial	500 mg/ vial
	1 g/vial	1 g/vial
	2 g/vial	2 g/vial

¹Confirmed from the FDA's COMIS data base and PDR 2002.

Comments

- 1) All strengths of the test product, Ceftriaxone For Injection, USP, 250 mg/vial, 500 mg/vial, 1 g/vial and 2 g/vial, are eligible for waivers of bioequivalence study requirements.
- 2) The concentration of the active ingredient in each strength the test product is same as that in the reference listed product. The Division of Chemistry II has found the _____ of the active ingredient in the test product acceptable because it was determined that the RLD, Rocephin® also contains similar _____. See the chemistry review dated 8/30/02 on v:/firmsam/lupin/65125RV1.doc.
- 3) There are no inactive ingredients in the test and reference products.

Recommendation

The information submitted by Lupin Limited on Ceftriaxone For Injection, USP, 250 mg/vial, 500 mg/vial, 1 g/vial and 2 g/vial falls under 21 CFR 320.22(b) (1) (i) of the Bioavailability/Bioequivalence regulations. The waivers of *in vivo* bioequivalence study requirements for Ceftriaxone For Injection, USP, 250 mg/vial, 500 mg/vial, 1 g/vial and 2 g/vial are granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product to be bioequivalent to Rocephin® Injection, 250 mg/vial, 500 mg/vial, 1 g/vial and 2 g/vial, manufactured by Roche Laboratories Inc.

Mamata S. Gokhale, Ph.D.
Review Branch III
Division of Bioequivalence

Mamata S. Gokhale 9/13/02

RD INITIALED GJP Singh, Ph.D.
FT INITIALED GJP Singh, Ph.D.

GJP Singh Date 9-14-02

Concur: *Dale P. Conner* Date 9/16/02
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc: ANDA# 65-125 (original, duplicate), Gokhale, HFD-658, Singh, HFD-658, Drug File, Division File

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 65-125

APPLICANT: Lupin Limited

DRUG PRODUCT: Ceftriaxone For Injection, USP
250 mg/vial, 500 mg/vial, 1 g/vial and
2 g/vial

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These Comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA # 65-125
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer: M. Gokhale

V:\FIRMSAM\LUPIN\LTRS&REV\65125W0302.DOC
Printed in final on 9/13/02

Endorsments: (Final with Dates)

HFD-658/ M. Gokhale *MSK 9/13/02*
HFD-658/ GJP. Singh *CGS 9-14-02*
HFD-650/ D. Conner *DA 9/16/02*
HFD-617/ S. Mazzella

Bioequivalency- Acceptable

Submission Date: 28 March, 2002

- | | |
|-----------------|--------------------------------------|
| 1) Waiver (WAI) | Strength: 250 mg vial
Outcome: AC |
| 2) Waiver (WAI) | Strength: 500 mg vial
Outcome: AC |
| 3) Waiver (WAI) | Strength: 1 g vial
Outcome: AC |
| 4) Waiver (WAI) | Strength: 2 g vial
Outcome: AC |

Outcome Decisions: AC- Acceptable

Winbio comments: Waivers are granted

**APPEARS THIS WAY
ON ORIGINAL**

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA #: 65-125

SPONSOR : Lupin Ltd.

DRUG AND DOSAGE FORM : Ceftriaxone For Injection, USP

STRENGTH(S) : 250 mg, 500 mg, 1g and 2 g vials

TYPES OF STUDIES : SD

SDF

MULT

OTHER

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : N/A

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES / <input type="checkbox"/> NO	Inspection status:	Inspection results:
First Generic <input checked="" type="checkbox"/>	Inspection requested: (date)	
New facility <input type="checkbox"/>	Inspection completed: (date)	
For cause <input type="checkbox"/>		
Other <input type="checkbox"/>		

PRIMARY REVIEWER : MAMATA S. GOKHALE, Ph.D. BRANCH : III

INITIAL : MSK

DATE : 9/13/02

TEAM LEADER : GJP SINGH, Ph.D. BRANCH : III

INITIAL : GJP Singh

DATE : 9-14-02

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm.D.

INITIAL : DP

DATE : 9/16/02

Product Quality Microbiology Review

Review for HFD-640

12 November 2002

ANDA: 65-125

Drug Product Name

Proprietary: N/A

Non-proprietary: Ceftriaxone for Injection USP

Drug Product Classification: Antibiotic

Review Number: #1

Subject of this Review

Submission Date: March 28, 2002

Receipt Date: April 10, 2002

(**New Correspondence:** July 24, 2002)

Consult Date: N/A

Date Assigned for Review: November 3, 2002

Submission History (for amendments only)

Date(s) of Previous Submission(s): N/A

Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor

Name: Lupin Limited

Address: The World Trade Center,
401 E. Pratt Street, Suite 2225,
Baltimore, MD 21202

Representative: Vinita Gupta

U.S. Agent: N/A

Telephone: 410-576-2000

Name of Reviewer: Nrapendra Nath

Conclusion: The submission is **not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

- A.
1. TYPE OF SUPPLEMENT: N/A
 2. SUPPLEMENT PROVIDES FOR: N/A
 3. MANUFACTURING SITE:
Lupin Limited
201 & 202, New Industrial Area No. 2
Mandideep, Distt. Raisen,
Madhya Pradesh, India.
 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: 250mg, 500mg, 1g and 2g per vial; IV and I/M
 5. METHOD(S) OF STERILIZATION: _____
 6. PHARMACOLOGICAL CATEGORY: Antibiotic
- B. SUPPORTING/RELATED DOCUMENTS: Type II DMF _____ sterile Ceftriaxone Sodium USP; Lupin Limited, India.
- C. REMARKS: DMF _____ is found deficient for sterility assurance; DMF Holder has been notified.

Reprocessing statement is provided in New Correspondence dated July 24, 2002.

APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

- A. Recommendation on Approvability -**
The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments are provided in the "Product Quality Microbiology Assessment" and "H. List of Microbiology Deficiencies and Comments" sections.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A**

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –** The subject drug product is

- B. Brief Description of Microbiology Deficiencies -**
Multiple deficiencies regarding

- C. Assessment of Risk Due to Microbiology Deficiencies -**
Low.

III. Administrative

- A. Reviewer's Signature** Nrapendra Nath 4/25/02
- B. Endorsement Block**
Microbiologist / Nrapendra Nath
Microbiology Team Leader/Neal J. Sweeney 4/25/02
- C. CC Block**
cc:
Original ANDA
HFD- 600/Division File
Field Copy

filename: V:\Microrev\65-125.doc

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Page(s) of trade

secret and /or

confidential

commercial

information

Product Quality Microbiology Review

Review for HFD-640

16 April 2003

ANDA: 65-125

Drug Product Name

Proprietary: N/A

Non-proprietary: Ceftriaxone for Injection USP

Drug Product Classification: Antibiotic

Review Number: #2

Subject of this Review

Submission Date: January 21, 2003

Receipt Date: February 24, 2003

Consult Date: N/A

Date Assigned for Review: March 10, 2003

Submission History (for amendments only)

Date(s) of Previous Submission(s): March 28, 2002 (recd. 4/10/2002)

Date(s) of Previous Micro Review(s): November 12, 2002

Applicant/Sponsor

Name: Lupin Limited

**Address: The World Trade Center,
401 E. Pratt Street, Suite 2225,
Baltimore, MD 21202**

Representative: Vinita Gupta

U.S. Agent: N/A

Telephone: 410-576-2000

Name of Reviewer: Nrapendra Nath

Conclusion: The submission is recommended for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

- A.
1. TYPE OF SUPPLEMENT: N/A
 2. SUPPLEMENT PROVIDES FOR: N/A
 3. MANUFACTURING SITE:
Lupin Limited
201 & 202, New Industrial Area No. 2
Mandideep, Distt. Raisen,
Madhya Pradesh, India.
 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: 250mg, 500mg, 1g and 2g per vial; IV and I/M
 5. METHOD(S) OF STERILIZATION: _____
 6. PHARMACOLOGICAL CATEGORY: Antibiotic
- B. SUPPORTING/RELATED DOCUMENTS: Type II DMF _____ Sterile Ceftriaxone Sodium USP; Lupin Limited, India.
- C. REMARKS: The subject reviewer found DMF # _____ adequate for sterility assurance on 3/21/03.

APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

- A. Recommendation on Approvability -**
The submission is **recommended** for approval on the basis of sterility assurance. Specific comments are provided in the "Product Quality Microbiology Assessment" section.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A**

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –** The subject drug product is
- B. Brief Description of Microbiology Deficiencies -**
None.
- C. Assessment of Risk Due to Microbiology Deficiencies -**
N/A.

III. Administrative

- A. Reviewer's Signature** Nrapendra Nath 4/16/03
- B. Endorsement Block**
Microbiologist / Nrapendra Nath
Microbiology Team Leader/Neal J. Sweeney
- C. CC Block**
cc:
Original ANDA
HFD- 600/Division File
Field Copy

Neal J. Sweeney
4/28/03

filename: V:\Microrev\65-125a1.doc

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information

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-125

**ADMINISTRATIVE
DOCUMENTS**

RECORD OF TELEPHONE CONVERSATION

ANDA #: 65-125

DATE: 07/01/02

DRUG: Ceftriaxone, USP

FIRM: Lupin

FDA PARTICIPANTS: Beth Fritsch

PHONE NUMBER: Vinita Gupta 410-576-2000

TOPIC: Discuss additional pieces of information that are needed

The items that are needed are applicable to both ANDAs, 65-125 and 65-124

- Revised scale up for the 2 g strength
- Side by side labeling - Need explanations in addition to annotations
- Need revised reprocessing statement
- Patent certification and exclusivity statement should be separated

Vinita understands and will provide information ASAP. She will be out of the office on 07/02/02.

**APPEARS THIS WAY
ON ORIGINAL**

RECORD OF TELEPHONE CONVERSATION

ANDA #: 65-125

DATE: 06/14/02

DRUG: Ceftriaxone, USP

FIRM: Lupin

FDA PARTICIPANTS: Beth Fritsch

PHONE NUMBER: Vinita Gupta 410-576-2000

TOPIC: Discuss additional pieces of information that are needed

Left message for Vinita Gupta for the following items. If she has questions, she should follow up with Sandra Middleton.

The items that are needed:

- Revised patent certification stating section 505 instead of 507 of the Act
- Provide exclusivity statement (can't request waiver for patent certification and exclusivity statement)
- Container/carton labeling for the reference listed drug
- Side-by-side annotated and explained labeling (insert and container)
- Revised reprocessing statement stating that the firm will not reprocess without notifying FDA
- Confirm the scale up amount (Blank batch records are blank)

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : June 11, 2002

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

 11-JUN-2002

SUBJECT: Examination of the request for waiver submitted with an ANDA for Ceftriaxone For Injection USP, 250 mg/vial, 500 mg/vial, 1 g/vial, and 2 mg/vial to determine if the application is substantially complete for filing.

Lupin Ltd has submitted ANDA 65-125 for Ceftriaxone for Injection USP, 250 mg/vial, 500 mg/vial, 1 g/vial and 2 g/vial. The ANDA contains a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the request for waiver is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for waiver submitted by Lupin Ltd on March 28, 2002 for its Ceftriaxone product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design
 - (a) Appropriate number of subjects
 - (b) Description of methodology
2. Study results
 - (a) Individual and mean data is provided
 - (b) Individual demographic data
 - (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

Study meets statutory requirements

Study does **NOT** meet statutory requirements

Reason:

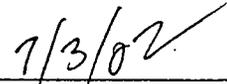
Waiver meets statutory requirements

Waiver does **NOT** meet statutory requirements

Reason:



Director, Division of Bioequivalence



Date

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-125

CORRESPONDENCE



LUPIN

August 25, 2003

Director, Division of Chemistry II,
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II,
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Kind Attn: **Dr. Florence Fang**

ORIG AMENDMENT

N/AM

Re: **ANDA # 65-125, CEFTRIAXONE FOR INJECTION USP, 250 mg, 500 mg, 1 g and 2 g**

MINOR AMENDMENT

(RESPONSE TO CHEMISTRY DEFICIENCY)

Dear Dr. Fang,

Reference is made to your facsimile dt. August 18, 2003 requiring minor amendment to our Abbreviated New Drug Application #65-125; Ceftriaxone for Injection USP, 250 mg, 500 mg, 1 g and 2 g in which agency has requested the following:

Chemistry Deficiency:

We await receipt of the response to the labeling deficiencies sent to you on July 3, 2003.

- We have replied to the labeling deficiencies vide our "Labeling Amendment" submitted August 22, 2003 to Mr. Wm. Peter Rickman - Director, Division of Labeling & Program Support. A copy of the corresponding covering letter is enclosed for your reference.

Lupin limited submit this minor amendment in duplicate and also certify that complete copy of this minor amendment (Field Copy) is being provided to Division of Field Investigations, Food and Drug Administration, Rockville.

RECEIVED

SEP 02 2003

OGD/CDER

Page 1 of 2

Lupin Limited

HARBORPLACE TOWER, 111 SOUTH CALVERT STREET, 21ST FLOOR, BALTIMORE, MD 21202.
TEL.: (410) 576-2000 FAX: (410) 576-2221 EMAIL: vinita@lupinusa.com



LUPIN

We trust that you will find the information contained in this minor amendment addresses the deficiency raised.

If you have any questions regarding this submission, please contact the undersigned at (410) 576-2000.

Sincerely,

For Lupin Limited

VINITA GUPTA
President – Americas & Europe

Encl: As above.



LUPIN

August 22, 2003

Director, Division of Labeling and Program Support,
Office of Generic Drugs, CDER, FDA
Metro Park North II,
7500 Standish Place,
Rockville, MD 20855

Kind Attn: **Mr. Wm. Peter Rickman**

Re: **ANDA # 65-125, CEFTRIAXONE FOR INJECTION USP, 250 mg, 500 mg, 1 g and 2 g**

LABELING AMENDMENT

(RESPONSE TO LABELING DEFICIENCIES)

ORIG AMENDMENT

N/A

Dear Mr. Rickman,

FPL

Reference is made to your facsimile dt. July 3, 2003 regarding labeling deficiencies requiring labeling amendment to our Abbreviated New Drug Application #65-125; Ceftriaxone for Injection USP, 250 mg, 500 mg, 1 g and 2 g; submitted March 28, 2002. Lupin Limited hereby submits this labeling amendment in duplicate.

We also certify that complete copy of this labeling amendment (Field Copy) is being provided to Division of Field Investigations, Food and Drug Administration, Rockville. Enclosed amendment comprises response to the Labeling Deficiencies, including your comments in bold type, followed by our firm's response and any attachment(s) for the response. Twelve copies of each labeling piece (container label, carton labeling & insert labeling) in final print are also being submitted in separate envelopes along with this response.

Also enclosed with this letter is a photocopy of the deficiency facsimiles from the agency for your ready reference.

RECEIVED

AUG 29 2003

Page 1 of 2

OGD/CDER

Lupin Limited



LUPIN

We trust that you will find the information contained in this labeling amendment addresses the deficiencies raised.

If you have any questions regarding this submission, please contact the undersigned at (410) 576-2000.

Sincerely,

For Lupin Limited

VINITA GUPTA
President – Americas & Europe

Encl: As above.

Cc:

Mr. Mark Anderson – Project Manager: Cover letter only by facsimile

Mr. Adolph Vezza – Labeling Review Branch: Cover letter and two copies of each piece of final printed labeling



LUPIN

May 14, 2003

Director, Division of Labeling and Program Support,
Office of Generic Drugs, CDER, FDA
Metro Park North II,
7500 Standish Place,
Rockville, MD 20855

Kind Attn: **Mr. Wm. Peter Rickman**

Re: **ANDA # 65-125, CEFTRIAXONE FOR INJECTION USP, 250 mg, 500mg, 1 g, 2 g**

LABELING AMENDMENT

(RESPONSE TO LABELING DEFICIENCIES)

~~ORIG AMENDMENT~~

N/A

Dear Mr. Wm. Peter Rickman,

Reference is made to your facsimile dt. February 5, 2003 regarding labeling deficiencies requiring labeling amendment to our Abbreviated new Drug Application for Ceftriaxone for Injection USP, 250 mg, 500 mg, 1 g, 2 g; ANDA # 65-125 submitted March 28, 2002. Lupin Limited hereby submits this labeling amendment in duplicate.

We also certify that complete copy of this labeling amendment (Field Copy) is being provided to Division of Field Investigations, Food and Drug Administration, Rockville. Enclosed amendment comprises response to the Labeling Deficiencies, including your comments in bold type, followed by our firm's response and any attachment(s) for the response. Four copies of "draft container, carton & insert labeling" are enclosed after the response to labeling deficiencies.

Also enclosed with this letter is a photocopy of the deficiency facsimiles from the agency for your ready reference.

RECEIVED

MAY 22 2003

OGD / CDER

Page 1 of 2

Lupin Limited

THE WORLD TRADE CENTER, 401 E. PRATT STREET, SUITE 2225, BALTIMORE, MD 21202.
TEL.: (410) 576-2000 FAX: (410) 576-2221 EMAIL: vinita@lupinusa.com



LUPIN

We trust that you will find the information contained in this labeling amendment addresses the deficiencies raised and look forward to your continued review of our Abbreviated New Drug Application.

If you have any questions regarding this submission, please contact the undersigned at (410) 576-2000.

Sincerely,

For Lupin Limited

VINITA GUPTA
President – Americas & Europe

Encl: As above.

Cc: (Cover Letter Only by Facsimile)
Mr. Mark Anderson – Project Manager
Mr. Adolph Veza – Labeling Review Branch



LUPIN

To Micro
M Anderson

January 21, 2003

Director, Division of Chemistry II,
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II,
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/A M

Kind Attn: **Dr. Florence S. Fang**

Re: **ANDA # 65-125, CEFTRIAXONE FOR INJECTION USP, 250mg, 500mg, 1g, 2g**

MINOR AMENDMENT

(RESPONSE TO MICROBIOLOGY AND CHEMISTRY DEFICIENCIES)

Dear Dr. Fang,

Reference is made to your facsimile of December 10, 2002 requiring minor amendment (Microbiology & Chemistry Assessment Section) to our Abbreviated new Drug Application for Ceftriaxone for Injection USP, 250mg, 500mg, 1g, 2g; ANDA # 65-125 submitted March 28, 2002. Lupin Limited hereby submits this minor amendment in duplicate.

We also certify that complete copy of this minor amendment (Field Copy) is being provided to Baltimore FDA District Office. Enclosed amendment comprises separate responses to the Microbiology & Chemistry Deficiencies, including your comments in bold type, followed by our firm's response and any attachment(s) for the response.

Also enclosed with this letter is a photocopy of the deficiency facsimile from the agency for your ready reference.

Page 1 of 2

Lupin Limited

THE WORLD TRADE CENTER, 401 E. PRATT STREET, SUITE 2225, BALTIMORE, MD 21202.
TEL.: (410) 576-2000 FAX: (410) 576-2221 EMAIL: vinita@lupinusa.com

RECEIVED

FEB 24 2003

OGD / CDER

MW
2/27/03



As Lupin Limited is also the DMF (#) holder for API in our subject ANDA; we confirm that concurrent to this amendment, all the issues communicated to the DMF holder by the agency has been addressed separately. A copy of communication from DMF holder in this regard is also enclosed.

We trust that you will find the information contained in this minor amendment addresses the deficiencies raised and look forward to your continued review of our Abbreviated New Drug Application.

If you have any questions regarding this submission, please contact the undersigned at (410) 576-2000.

Sincerely,

For Lupin Limited

VINITA GUPTA
President – Americas & Europe

Encl: As above.



LUPIN

October 14, 2002

Director, Division of Chemistry II,
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II,
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/A/m

Kind Attn: **Dr. Florence S. Fang**

Re: **ANDA # 65-125, CEFTRIAXONE FOR INJECTION USP, 250mg, 500mg, 1g, 2g**

MINOR AMENDMENT

(Chemistry Assessment Section)

Dear Dr. Fang,

Reference is made to your facsimile of September 09, 2002 requiring minor amendment (chemistry assessment section) to our Abbreviated new Drug Application for Ceftriaxone for Injection USP, 250mg, 500mg, 1g, 2g; ANDA # 65-125 submitted March 28, 2002. Lupin Limited hereby submits this minor amendment in duplicate.

We also certify that a complete copy of this minor amendment (Field Copy) is being provided to Baltimore FDA District Office. Enclosed amendment comprises response to the chemistry deficiencies, including your comments in bold type, followed by our firm's response and any attachment(s) for the response. Also enclosed with this letter is a photocopy of the deficiency facsimile from the agency for your ready reference.

As Lupin Limited is also the DMF (#), holder for API in our subject ANDA; we confirm that concurrent to this amendment, all the issues communicated to the DMF holder by the agency has been addressed separately. A copy of communication from DMF holder in this regard is also enclosed.

We also acknowledge, that the sterility assurance portion of the application is pending review and any deficiencies will be forwarded to us in a separate communication.

Lupin Limited

THE WORLD TRADE CENTER, 401 E. PRATT STREET, SUITE 2225, BALTIMORE, MD 21202.
TEL.: (410) 576-2000 FAX: (410) 576-2221 EMAIL: vinita@lupinusa.com

Page 1 of 2
RECEIVED

OCT 23 2002

OGD / CDER

Handwritten signature and date:
10/23/02



LUPIN

We trust that you will find the information contained in this minor amendment addresses the deficiencies raised and look forward to your continued review of our Abbreviated New Drug Application.

If you have any questions regarding this submission, please contact the undersigned at (410) 576-2000.

Sincerely,

For Lupin Limited

VINITA GUPTA
President – Americas & Europe

Encl: As above.



LUPIN

July 24, 2002

Beth Fabian Fritsch
Office of Generic Drugs
CDERE, FDA
Metro Park North II,
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

Re: ANDA #~~65~~⁵-125, CEFTRIAZONE FOR INJECTION USP, 250mg, 500mg, 1g, 2g

TELEPHONE AMENDMENT

Dear Beth,

We submit herewith a telephone amendment to the above-referred abbreviated new drug application in response to the telephone conversation the undersigned had with Beth Fabian-Fritsch of Office of Generic Drugs. Please find below our response to the points raised by Office of Generic Drugs. This amendment is being submitted in duplicate as a hard copy.

We certify that a true and complete copy of the telephone amendment is being provided to Baltimore FDA District Office.

1. Scale Up Size -

We agree with the observation made by Office of Generic Drugs. In the earlier communication, we had provided the largest batch size amongst all strengths for the commercial production of Ceftriaxone for Injection USP, however, as required by the Office of Generic Drugs, we are now providing strength wise scale up batch size for intended commercial production as below:

Strength	Scale up Batch Size for Intended Commercial Production
Ceftriaxone for Injection USP 250mg	1000 vials
Ceftriaxone for Injection USP 500mg	1000 vials
Ceftriaxone for Injection USP 1g	1000 vials
Ceftriaxone for Injection USP 2 g	1000 vials

RECEIVED

JUL 26 2002

OGD / CDER

Lupin Limited

THE WORLD TRADE CENTER, 401 E. PRATT STREET, SUITE 2225, BALTIMORE, MD 21202.
TEL.: (410) 576-2000 FAX: (410) 576-2221 EMAIL: vinita@lupinusa.com

2. Side by Side Labeling [Summary of the Differences and Similarities for Container Label & Package Insert]

A summary explaining the differences and similarities b/w Container Label & Package Insert of Reference Listed Drug and Proposed Labeling for our ANDA is enclosed as **Enclosure 1**.

3. Reprocessing Statement

The required "Reprocessing Statement" is enclosed as **Enclosure 2**.

4. Patent & Exclusivity Statements

Required separate certifications on "Patent Situation" and "Orange Book Exclusivity" are enclosed as **Enclosure 3 & Enclosure 4** respectively.

We trust that you will find the information contained in this telephone amendment addresses the issues raised and look forward to your continued review of our Abbreviated New Drug Application.

If you have any questions regarding this submission, please contact the undersigned at (410) 576-2000.

Sincerely,

For Lupin Limited



VINITA GUPTA
President – Americas & Europe

Encl: As above.



LUPIN

NEW CORRESP
NC

NAT
03-JUL-2002
65-125
June 24, 2002
[Handwritten signature]

Dear Vinita,

This is with reference to the preliminary queries raised by FDA regarding ANDA for Ceftriaxone for Injection USP 250mg, 500 mg, 1 g & 2 g. Please find enclosed the following with respect to the points raised by FDA:

1. Method of sterilization -

FDA has asked about method of sterilization. We confirm that Lupin Limited utilizes _____ for manufacture of Ceftriaxone for Injection USP.

2. Patent certification -

We are providing the required Patent Certification (3 original - 1 each for inclusion in the Archival, Review & Field Copy), p. 15

3. Original Certificates -

We are enclosing three (3) original certificates (dated current) each of the following for inclusion in the Archival, Review & Field Copies:

- a. cGMP Certification p. 201
- b. Environmental Consideration-Claim of Categorical Exclusion p. 801
- c. Generic Drug Enforcement Act-Debarment & No Conviction Certificate p. 803
- d. Field Copy Certification p. 812

4. Scale Up Size -

We confirm that the scale up batch size for the intended commercial production is _____ vials.

5. Annotated Labeling [Side by Side Comparison – Container Label & Package Insert]

We are enclosing herewith three (3) copies of the required side-by-side comparison with the differences highlighted for Container Label & Package Insert for inclusion in the Archival, Review & Field Copies.

Side-by-side comparison with the differences highlighted for Container Label - p. 28 - 29

Side-by-side comparison with the differences highlighted for Package Insert - p. 30 - 65

RECEIVED

JUL 03 2002

Continued....

OGD / CDER

Lupin Limited

Corporate Office: 159, C.S.T. Road, Kalina, Santacruz (East), Mumbai 400 098, India. Tel.: (91-22) 693 1001-10, 652 6391.
Fax: (91-22) 652 8321 (Dir), 654 0484. Website: www.lupinworld.com

Page 1 of 2



LUPIN

6. Innovator Label / Package Insert

We are enclosing herewith the copy of the labeling received from the Freedom of Information Branch (Office of Information Technology) for **ROCEPHIN (Ceftriaxone) 250mg, 500mg, 1g & 2g Injection**.

Also enclosed herewith is a copy of the approved Labeling (Dated 25th August 2000) available on the Revised Labeling Branch – CDER Website

Our labeling section is prepared based on above documents.

The revised sections and certifications are paginated, as appropriate.

With best regards,

Rajeev



March 28, 2002

LUPIN

Office of Generic Drugs,
CDER, FDA
Metro Park North II,
7500 Standish Place, Room 150
Rockville, MD 20855

505-11-210K
03 Jul-2002
J. D. Davis

Dear Sir / Madam,

Re: **ANDA OF CEFTRIAXONE FOR INJECTION USP 250 mg, 500 mg, 1 g, 2 g**

We wish to submit this Original Abbreviated New Drug Application (ANDA) of Ceftriaxone for Injection USP 250 mg, 500 mg, 1 g, 2 g

The Archival copy & Field copy of the above application is being submitted in total 3 (Three) volumes each. Two volumes contain data pertaining to the Chemistry, Manufacturing and Controls whereas the other one volume contains the Sterilization Assurance Information and Data.

The chemistry section of the Review copy is being submitted in three volumes and BA/BE section of the Review copy is submitted in one volume.

This application does not contain data pertaining to Bioavailability / Bioequivalence required in Section VI of the application based on the self-evident bioavailability of the subject product. A waiver in this regard has been requested under Section VI of this application.

Also please note, as the specified folders were not available from GPO, all the sections of the Field copy and Chemistry section of the Review Copy are being submitted in "**commercially available folders**".

Kindly be informed that some of the data in the ANDA, is in the name of Lupin Laboratories Limited -name of which has been changed in recent past to Lupin Limited.

A certificate from our company secretary in this regard is enclosed.

RECEIVED

Contd.

APR 10 2002

OGD / CDER

Lupin Limited

THE WORLD TRADE CENTER, 401 E. PRATT STREET, SUITE 2225, BALTIMORE, MD 21202.
TEL.: (410) 576-2000 FAX: (410) 576-2221 EMAIL: vinita@lupinusa.com



LUPIN

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Also, we commit to resolve any issues identified in the methods validation process after approval.

We would be grateful if you could acknowledge receipt of this ANDA to the undersigned at the following address.

**LUPIN LIMITED
The World Trade Center
401 E. Pratt Street, Suite 2225
Baltimore, Maryland 21202 - 3003
United States**

TEL : 410 576 2000
FAX : 410 576 2221

Thanking you.

Sincerely,

For Lupin Limited

**VINITA GUPTA
President – Business Development,
Americas & Europe**

Enclosures: As above

Lupin Limited

THE WORLD TRADE CENTER, 401 E. PRATT STREET, SUITE 2225, BALTIMORE, MD 21202.
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