



ROCEPHIN®

(ceftriaxone sodium)

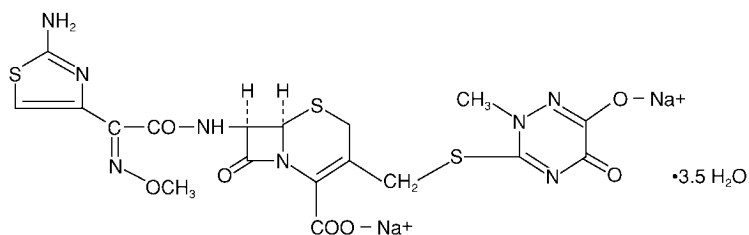
FOR INJECTION

**Rx only**

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

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

The chemical formula of ceftriaxone sodium is C<sub>18</sub>H<sub>16</sub>N<sub>8</sub>Na<sub>2</sub>O<sub>7</sub>S<sub>3</sub>•3.5H<sub>2</sub>O. It has a calculated molecular weight of 661.59 and the following structural formula:



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

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

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

## ROCEPHIN® (ceftriaxone sodium)

27 **Table 1**            **Ceftriaxone Plasma Concentrations After Single Dose**  
28                            **Administration**

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

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

30 ND = Not determined.

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

35 Ceftriaxone concentrations in urine are high, as shown in Table 2.

36 **Table 2**            **Urinary Concentrations of Ceftriaxone After Single Dose**  
37                            **Administration**

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

38 ND = Not determined.

39 Thirty-three percent to 67% of a ceftriaxone dose was excreted in the urine as unchanged  
40 drug and the remainder was secreted in the bile and ultimately found in the feces as  
41 microbiologically inactive compounds. After a 1 gm IV dose, average concentrations of  
42 ceftriaxone, determined from 1 to 3 hours after dosing, were 581 µg/mL in the  
43 gallbladder bile, 788 µg/mL in the common duct bile, 898 µg/mL in the cystic duct bile,  
44 78.2 µg/gm in the gallbladder wall and 62.1 µg/mL in the concurrent plasma.

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

## ROCEPHIN® (ceftriaxone sodium)

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

57 **Table 3**                    **Average Pharmacokinetic Parameters of Ceftriaxone in**  
58 **Pediatric Patients With Meningitis**

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

59 Compared to that in healthy adult subjects, the pharmacokinetics of ceftriaxone were only  
60 minimally altered in elderly subjects and in patients with renal impairment or hepatic  
61 dysfunction (Table 4); therefore, dosage adjustments are not necessary for these patients  
62 with ceftriaxone dosages up to 2 gm per day. Ceftriaxone was not removed to any  
63 significant extent from the plasma by hemodialysis. In 6 of 26 dialysis patients, the  
64 elimination rate of ceftriaxone was markedly reduced, suggesting that plasma  
65 concentrations of ceftriaxone should be monitored in these patients to determine if dosage  
66 adjustments are necessary.

67 **Table 4**                    **Average Pharmacokinetic Parameters of Ceftriaxone in**  
68 **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

69 \*Creatinine clearance.

70 **Pharmacokinetics in the Middle Ear Fluid:** In one study, total ceftriaxone  
71 concentrations (bound and unbound) were measured in middle ear fluid obtained during  
72 the insertion of tympanostomy tubes in 42 pediatric patients with otitis media. Sampling  
73 times were from 1 to 50 hours after a single intramuscular injection of 50 mg/kg of

## ROCEPHIN® (ceftriaxone sodium)

74 ceftriaxone. Mean ( $\pm$  SD) ceftriaxone levels in the middle ear reached a peak of 35 ( $\pm$  12)  
75  $\mu\text{g/mL}$  at 24 hours, and remained at 19 ( $\pm$  7)  $\mu\text{g/mL}$  at 48 hours. Based on middle ear  
76 fluid ceftriaxone concentrations in the 23 to 25 hour and the 46 to 50 hour sampling time  
77 intervals, a half-life of 25 hours was calculated. Ceftriaxone is highly bound to plasma  
78 proteins. The extent of binding to proteins in the middle ear fluid is unknown.

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

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

85 Aerobic gram-negative microorganisms:

86 *Acinetobacter calcoaceticus*

87 *Enterobacter aerogenes*

88 *Enterobacter cloacae*

89 *Escherichia coli*

90 *Haemophilus influenzae* (including ampicillin-resistant and beta-lactamase producing  
91 strains)

92 *Haemophilus parainfluenzae*

93 *Klebsiella oxytoca*

94 *Klebsiella pneumoniae*

95 *Moraxella catarrhalis* (including beta-lactamase producing strains)

96 *Morganella morganii*

97 *Neisseria gonorrhoeae* (including penicillinase- and nonpenicillinase-producing strains)

98 *Neisseria meningitidis*

99 *Proteus mirabilis*

100 *Proteus vulgaris*

101 *Serratia marcescens*

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

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

106 Aerobic gram-positive microorganisms:

107 *Staphylococcus aureus* (including penicillinase-producing strains)

108 *Staphylococcus epidermidis*

109 *Streptococcus pneumoniae*

110 *Streptococcus pyogenes*

111 Viridans group streptococci

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

## ROCEPHIN® (ceftriaxone sodium)

115 Anaerobic microorganisms:

116 *Bacteroides fragilis*

117 *Clostridium* species

118 *Peptostreptococcus* species

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

120 The following in vitro data are available, **but their clinical significance is unknown.**

121 Ceftriaxone exhibits in vitro minimal inhibitory concentrations (MICs) of  $\leq 8$   $\mu\text{g/mL}$  or  
122 less against most strains of the following microorganisms, however, the safety and  
123 effectiveness of ceftriaxone in treating clinical infections due to these microorganisms  
124 have not been established in adequate and well-controlled clinical trials.

125 Aerobic gram-negative microorganisms:

126 *Citrobacter diversus*

127 *Citrobacter freundii*

128 *Providencia* species (including *Providencia rettgeri*)

129 *Salmonella* species (including *Salmonella typhi*)

130 *Shigella* species

131 Aerobic gram-positive microorganisms:

132 *Streptococcus agalactiae*

133 Anaerobic microorganisms:

134 *Prevotella (Bacteroides) bivia*

135 *Porphyromonas (Bacteroides) melaninogenicus*

### 136 **Susceptibility Tests:**

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

<u>MIC (<math>\mu\text{g/mL}</math>)</u>	<u>Interpretation</u>
$\leq 8$	(S) Susceptible
16-32	(I) Intermediate
$\geq 64$	(R) Resistant

145 The following interpretive criteria<sup>2</sup> should be used when testing *Haemophilus* species  
146 using *Haemophilus* Test Media (HTM).

<u>MIC (<math>\mu\text{g/mL}</math>)</u>	<u>Interpretation</u>
$\leq 2$	(S) Susceptible

## ROCEPHIN® (ceftriaxone sodium)

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

150 The following interpretive criteria<sup>2</sup> should be used when testing *Neisseria gonorrhoeae*  
151 when using GC agar base and 1% defined growth supplement.

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤0.25	(S) Susceptible

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

155 The following interpretive criteria<sup>2</sup> should be used when testing *Streptococcus* spp  
156 including *Streptococcus pneumoniae* using cation-adjusted Mueller-Hinton broth with 2  
157 to 5% lysed horse blood.

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

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

169 Standardized susceptibility test procedures require the use of laboratory control  
170 microorganisms to control the technical aspects of the laboratory procedures.  
171 Standardized ceftriaxone powder should provide the following MIC values:<sup>2</sup>

<u>Microorganism</u>	<u>ATCC® #</u>	<u>MIC (µg/mL)</u>
<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

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

## ROCEPHIN® (ceftriaxone sodium)

174 **Diffusion Techniques:** Quantitative methods that require measurement of zone  
175 diameters also provide reproducible estimates of the susceptibility of bacteria to  
176 antimicrobial compounds. One such standardized procedure<sup>3</sup> requires the use of  
177 standardized inoculum concentrations. This procedure uses paper discs impregnated with  
178 30 µg of ceftriaxone to test the susceptibility of microorganisms to ceftriaxone.

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

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥21	(S) Susceptible
14-20	(I) Intermediate
≤13	(R) Resistant

183 The following interpretive criteria<sup>3</sup> should be used when testing *Haemophilus* species  
184 when using Haemophilus Test Media (HTM).

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥26	(S) Susceptible

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

188 The following interpretive criteria<sup>3</sup> should be used when testing *Neisseria gonorrhoeae*  
189 when using GC agar base and 1% defined growth supplement.

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥35	(S) Susceptible

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

193 The following interpretive criteria<sup>3</sup> should be used when testing *Streptococcus* spp other  
194 than *Streptococcus pneumoniae* when using Mueller-Hinton agar supplemented with 5%  
195 sheep blood incubated in 5% CO<sub>2</sub>.

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥27	(S) Susceptible
25-26	(I) Intermediate
≤24	(R) Resistant

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

199 Disc diffusion interpretive criteria for ceftriaxone discs against *Streptococcus*  
200 *pneumoniae* are not available, however, isolates of pneumococci with oxacillin zone

## ROCEPHIN® (ceftriaxone sodium)

201 diameters of >20 mm are susceptible (MIC ≤0.06 µg/mL) to penicillin and can be  
202 considered susceptible to ceftriaxone. *Streptococcus pneumoniae* isolates should not be  
203 reported as penicillin (ceftriaxone) resistant or intermediate based solely on an oxacillin  
204 zone diameter of ≤19 mm. The ceftriaxone MIC should be determined for those isolates  
205 with oxacillin zone diameters ≤19 mm.

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

<u>Microorganism</u>	<u>ATCC® #</u>	<u>Zone Diameter Ranges (mm)</u>
<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

210 **Anaerobic Techniques:** For anaerobic bacteria, the susceptibility to ceftriaxone as MICs  
211 can be determined by standardized test methods.<sup>4</sup> The MIC values obtained should be  
212 interpreted according to the following criteria:

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

213 As with other susceptibility techniques, the use of laboratory control microorganisms is  
214 required to control the technical aspects of the laboratory standardized procedures.  
215 Standardized ceftriaxone powder should provide the following MIC values for the  
216 indicated standardized anaerobic dilution<sup>4</sup> testing method:

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

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

218 **INDICATIONS AND USAGE:** Before instituting treatment with Rocephin, appropriate  
219 specimens should be obtained for isolation of the causative organism and for  
220 determination of its susceptibility to the drug. Therapy may be instituted prior to  
221 obtaining results of susceptibility testing.

222 To reduce the development of drug-resistant bacteria and maintain the effectiveness of  
223 Rocephin and other antibacterial drugs, Rocephin should be used only to treat or prevent  
224 infections that are proven or strongly suspected to be caused by susceptible bacteria.  
225 When culture and susceptibility information are available, they should be considered in



## ROCEPHIN® (ceftriaxone sodium)

226 selecting or modifying antibacterial therapy. In the absence of such data, local  
227 epidemiology and susceptibility patterns may contribute to the empiric selection of  
228 therapy.

229 Rocephin is indicated for the treatment of the following infections when caused by  
230 susceptible organisms:

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

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

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

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

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

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

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

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

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

## ROCEPHIN® (ceftriaxone sodium)

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

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

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

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

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

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

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

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

303 *C. difficile* produces toxins A and B which contribute to the development of CDAD.  
304 Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as  
305 these infections can be refractory to antimicrobial therapy and may require colectomy.  
306 CDAD must be considered in all patients who present with diarrhea following antibiotic

## ROCEPHIN® (ceftriaxone sodium)

307 use. Careful medical history is necessary since CDAD has been reported to occur over  
308 two months after the administration of antibacterial agents.

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

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

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

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

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

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

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

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

338 **There have been reports of sonographic abnormalities in the gallbladder of patients**  
339 **treated with Rocephin; some of these patients also had symptoms of gallbladder**  
340 **disease.** These abnormalities appear on sonography as an echo without acoustical  
341 shadowing suggesting sludge or as an echo with acoustical shadowing which may be  
342 misinterpreted as gallstones. The chemical nature of the sonographically detected  
343 material has been determined to be predominantly a ceftriaxone-calcium salt. **The**  
344 **condition appears to be transient and reversible upon discontinuation of Rocephin**  
345 **and institution of conservative management.** Therefore, Rocephin should be  
346 discontinued in patients who develop signs and symptoms suggestive of gallbladder  
347 disease and/or the sonographic findings described above.

## ROCEPHIN® (ceftriaxone sodium)

348 **Information for Patients:** Patients should be counseled that antibacterial drugs including  
349 Rocephin should only be used to treat bacterial infections. They do not treat viral  
350 infections (eg, common cold). When Rocephin is prescribed to treat a bacterial infection,  
351 patients should be told that although it is common to feel better early in the course of  
352 therapy, the medication should be taken exactly as directed. Skipping doses or not  
353 completing the full course of therapy may (1) decrease the effectiveness of the immediate  
354 treatment and (2) increase the likelihood that bacteria will develop resistance and will not  
355 be treatable by Rocephin or other antibacterial drugs in the future.

356 Diarrhea is a common problem caused by antibiotics which usually ends when the  
357 antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients  
358 can develop watery and bloody stools (with or without stomach cramps and fever) even  
359 as late as two or more months after having taken the last dose of the antibiotic. If this  
360 occurs, patients should contact their physician as soon as possible.

361 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** *Carcinogenesis:* Considering the  
362 maximum duration of treatment and the class of the compound, carcinogenicity studies  
363 with ceftriaxone in animals have not been performed. The maximum duration of animal  
364 toxicity studies was 6 months.

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

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

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

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

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

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

385 **Pediatric Use:** Safety and effectiveness of Rocephin in neonates, infants and pediatric  
386 patients have been established for the dosages described in the DOSAGE AND  
387 ADMINISTRATION section. In vitro studies have shown that ceftriaxone, like some

## ROCEPHIN® (ceftriaxone sodium)

388 other cephalosporins, can displace bilirubin from serum albumin. Rocephin should not be  
389 administered to hyperbilirubinemic neonates, especially prematures.

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

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

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

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

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

405 *HEPATIC*—elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported  
406 (<1%) were elevations of alkaline phosphatase and bilirubin.

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

409 *CENTRAL NERVOUS SYSTEM*—headache or dizziness were reported occasionally  
410 (<1%).

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

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

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

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

422 **DOSAGE AND ADMINISTRATION:** Rocephin may be administered intravenously or  
423 intramuscularly.

## ROCEPHIN® (ceftriaxone sodium)

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

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

429 For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of  
430 250 mg is recommended.

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

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

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

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

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

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

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

451 No dosage adjustment is necessary for patients with impairment of renal or hepatic  
452 function; however, blood levels should be monitored in patients with severe renal  
453 impairment (eg, dialysis patients) and in patients with both renal and hepatic  
454 dysfunctions.

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

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

459 After reconstitution, each 1 mL of solution contains approximately 250 mg or 350 mg  
460 equivalent of ceftriaxone according to the amount of diluent indicated below. If required,  
461 more dilute solutions could be utilized. **A 350 mg/mL concentration is not**

## ROCEPHIN® (ceftriaxone sodium)

462 **recommended for the 250 mg vial since it may not be possible to withdraw the entire**  
463 **contents.**

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

<u>Vial Dosage Size</u>	<u>Amount of Diluent to be Added</u>	
	<u>250 mg/mL</u>	<u>350 mg/mL</u>
250 mg	0.9 mL	—
500 mg	1.8 mL	1.0 mL
1 gm	3.6 mL	2.1 mL
2 gm	7.2 mL	4.2 mL

467

468 *Intravenous Administration:* Rocephin should be administered intravenously by infusion  
469 over a period of 30 minutes. Concentrations between 10 mg/mL and 40 mg/mL are  
470 recommended; however, lower concentrations may be used if desired. Reconstitute vials  
471 with an appropriate IV diluent (see COMPATIBILITY AND STABILITY).

<u>Vial Dosage Size</u>	<u>Amount of Diluent to be Added</u>
250 mg	2.4 mL
500 mg	4.8 mL
1 gm	9.6 mL
2 gm	19.2 mL

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

475 *COMPATIBILITY AND STABILITY:* Rocephin sterile powder should be stored at room  
476 temperature—77°F (25°C)—or below and protected from light. After reconstitution,  
477 protection from normal light is not necessary. The color of solutions ranges from light  
478 yellow to amber, depending on the length of storage, concentration and diluent used.

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

## ROCEPHIN® (ceftriaxone sodium)

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

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

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

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

485 The following *intravenous* Rocephin solutions are stable at room temperature (25°C) for  
 486 24 hours, at concentrations between 10 mg/mL and 40 mg/mL: Sodium Lactate (PVC  
 487 container), 10% Invert Sugar (glass container), 5% Sodium Bicarbonate (glass container),  
 488 Freamine III (glass container), Normosol-M in 5% Dextrose (glass and PVC containers),  
 489 Ionosol-B in 5% Dextrose (glass container), 5% Mannitol (glass container), 10%  
 490 Mannitol (glass container).

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

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



## ROCEPHIN® (ceftriaxone sodium)

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

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

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

509 Rocephin reconstituted with 5% Dextrose or 0.9% Sodium Chloride solution at  
510 concentrations between 10 mg/mL and 40 mg/mL, and then stored in frozen state (-20°C)  
511 in PVC or polyolefin containers, remains stable for 26 weeks. Reconstituted ADD-  
512 Vantage units, however, should not be stored in a frozen state (-20°C).

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

515 Rocephin solutions should *not* be physically mixed with or piggybacked into solutions  
516 containing other antimicrobial drugs or into diluent solutions other than those listed  
517 above, due to possible incompatibility.

518 **ANIMAL PHARMACOLOGY:** Concretions consisting of the precipitated calcium salt  
519 of ceftriaxone have been found in the gallbladder bile of dogs and baboons treated with  
520 ceftriaxone.

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

527 **HOW SUPPLIED:** Rocephin is supplied as a sterile crystalline powder in glass vials.  
528 The following packages are available:

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

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

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

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

536 Bulk pharmacy containers, containing 10 gm equivalent of ceftriaxone. Box of 1 (NDC  
537 0004-1971-01). NOT FOR DIRECT ADMINISTRATION.

## ROCEPHIN® (ceftriaxone sodium)

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

540 ADD-Vantage Vials containing 1 gm equivalent of ceftriaxone. Box of 10 (NDC 0004-  
541 1964-05).

542 ADD-Vantage Vials containing 2 gm equivalent of ceftriaxone. Box of 10 (NDC 0004-  
543 1965-05).

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

546 \*Registered trademark of Abbott Laboratories, Inc.

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

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

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

555 Week 2 and 4 Bacteriologic Eradication Rates in the Per Protocol Analysis in the Roche  
556 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)

## ROCEPHIN® (ceftriaxone sodium)

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