



ROCEPHIN®

(ceftriaxone sodium)

FOR INJECTION

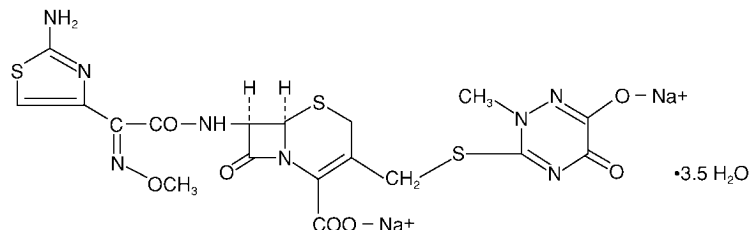
**Rx only**

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)glyoxylamido]-8-oxo-3-[[1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-*as*-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7<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.

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29 **Table 1 Ceftriaxone Plasma Concentrations After Single Dose**  
30 **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

31 \*IV doses were infused at a constant rate over 30 minutes.  
32 ND = Not determined.

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

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

38 **Table 2 Urinary Concentrations of Ceftriaxone After Single Dose**  
39 **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

40 ND = Not determined.

41 Thirty-three percent to 67% of a ceftriaxone dose was excreted in the urine as unchanged  
42 drug and the remainder was secreted in the bile and ultimately found in the feces as  
43 microbiologically inactive compounds. After a 1 gm IV dose, average concentrations of  
44 ceftriaxone, determined from 1 to 3 hours after dosing, were 581 µg/mL in the  
45 gallbladder bile, 788 µg/mL in the common duct bile, 898 µg/mL in the cystic duct bile,  
46 78.2 µg/gm in the gallbladder wall and 62.1 µg/mL in the concurrent plasma.

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

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

59 **Table 3 Average Pharmacokinetic Parameters of Ceftriaxone in**  
60 **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)

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

69 **Table 4 Average Pharmacokinetic Parameters of Ceftriaxone in**  
70 **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

71 \*Creatinine clearance.

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

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

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

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

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

89 Aerobic gram-negative microorganisms:

90 *Acinetobacter calcoaceticus*

91 *Enterobacter aerogenes*

92 *Enterobacter cloacae*

93 *Escherichia coli*

94 *Haemophilus influenzae* (including ampicillin-resistant and beta-lactamase producing  
95 strains)

96 *Haemophilus parainfluenzae*

97 *Klebsiella oxytoca*

98 *Klebsiella pneumoniae*

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

100 *Morganella morganii*

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

102 *Neisseria meningitidis*

103 *Proteus mirabilis*

104 *Proteus vulgaris*

105 *Serratia marcescens*

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

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

110 Aerobic gram-positive microorganisms:

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

112 *Staphylococcus epidermidis*

113 *Streptococcus pneumoniae*

114 *Streptococcus pyogenes*

115 Viridans group streptococci

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

119 Anaerobic microorganisms:

120 *Bacteroides fragilis*

121 *Clostridium* species

122 *Peptostreptococcus* species

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

124 The following in vitro data are available, **but their clinical significance is unknown.**  
125 Ceftriaxone exhibits in vitro minimal inhibitory concentrations (MICs) of  $\leq 8$   $\mu\text{g/mL}$  or  
126 less against most strains of the following microorganisms, however, the safety and  
127 effectiveness of ceftriaxone in treating clinical infections due to these microorganisms  
128 have not been established in adequate and well-controlled clinical trials.

129 Aerobic gram-negative microorganisms:

130 *Citrobacter diversus*

131 *Citrobacter freundii*

132 *Providencia* species (including *Providencia rettgeri*)

133 *Salmonella* species (including *Salmonella typhi*)

134 *Shigella* species

135 Aerobic gram-positive microorganisms:

136 *Streptococcus agalactiae*

137 Anaerobic microorganisms:

138 *Prevotella (Bacteroides) bivia*

139 *Porphyromonas (Bacteroides) melaninogenicus*

### 140 **Susceptibility Tests:**

141 **Dilution Techniques:** Quantitative methods are used to determine antimicrobial minimal  
142 inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of  
143 bacteria to antimicrobial compounds. The MICs should be determined using a  
144 standardized procedure.<sup>1</sup> Standardized procedures are based on a dilution method (broth  
145 or agar) or equivalent with standardized inoculum concentrations and standardized  
146 concentrations of ceftriaxone powder. The MIC values should be interpreted according to  
147 the following criteria<sup>2</sup> for aerobic organisms other than *Haemophilus* spp, *Neisseria*  
148 *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

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

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	<u>MIC (µg/mL)</u>	<u>Interpretation</u>
	≤2	(S) Susceptible
151	The absence of resistant strains precludes defining any categories other than	
152	“Susceptible”. Strains yielding results suggestive of a “Nonsusceptible” category should	
153	be submitted to a reference laboratory for further testing.	
154	The following interpretive criteria <sup>2</sup> should be used when testing <i>Neisseria gonorrhoeae</i>	
155	when using GC agar base and 1% defined growth supplement.	

	<u>MIC (µg/mL)</u>	<u>Interpretation</u>
	≤0.25	(S) Susceptible
156	The absence of resistant strains precludes defining any categories other than	
157	“Susceptible”. Strains yielding results suggestive of a “Nonsusceptible” category should	
158	be submitted to a reference laboratory for further testing.	
159	The following interpretive criteria <sup>2</sup> should be used when testing <i>Streptococcus</i> spp	
160	including <i>Streptococcus pneumoniae</i> using cation-adjusted Mueller-Hinton broth with 2	
161	to 5% lysed horse blood.	

	<u>MIC (µg/mL)</u>	<u>Interpretation</u>
	≤0.5	(S) Susceptible
	1	(I) Intermediate
	≥2	(R) Resistant
162	A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the	
163	antimicrobial compound in the blood reaches the concentrations usually achievable. A	
164	report of “Intermediate” indicates that the results should be considered equivocal, and if	
165	the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test	
166	should be repeated. This category implies possible clinical applicability in body sites	
167	where the drug is physiologically concentrated or in situations where high dosage of the	
168	drug can be used. This category also provides a buffer zone which prevents small	
169	uncontrolled technical factors from causing major discrepancies in interpretation. A	
170	report of “Resistant” indicates that the pathogen is not likely to be inhibited if the	
171	antimicrobial compound in the blood reaches the concentrations usually achievable; other	
172	therapy should be selected.	
173	Standardized susceptibility test procedures require the use of laboratory control	
174	microorganisms to control the technical aspects of the laboratory procedures.	
175	Standardized ceftriaxone powder should provide the following MIC values: <sup>2</sup>	

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<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

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

178 **Diffusion Techniques:** Quantitative methods that require measurement of zone  
179 diameters also provide reproducible estimates of the susceptibility of bacteria to  
180 antimicrobial compounds. One such standardized procedure<sup>3</sup> requires the use of  
181 standardized inoculum concentrations. This procedure uses paper discs impregnated with  
182 30 µg of ceftriaxone to test the susceptibility of microorganisms to ceftriaxone.

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

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

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

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

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

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

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

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

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

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

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

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

210 As with standardized dilution techniques, diffusion methods require the use of laboratory  
211 control microorganisms that are used to control the technical aspects of the laboratory  
212 procedures. For the diffusion technique, the 30 µg ceftriaxone disc should provide the  
213 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

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

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

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

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<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

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

### 222 INDICATIONS AND USAGE

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

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

233 Rocephin is indicated for the treatment of the following infections when caused by  
234 susceptible organisms:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## 292 CONTRAINDICATIONS

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

## **ROCEPHIN® (ceftriaxone sodium)**

### **295 Neonates ( ≤ 28 days)**

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

300 **Rocephin must not be co-administered with calcium-containing IV solutions,**  
301 **including continuous calcium-containing infusions such as parenteral nutrition, in**  
302 **neonates because of the risk of precipitation of ceftriaxone-calcium salt.** Cases of  
303 fatal reactions with ceftriaxone-calcium precipitates in lung and kidneys in neonates have  
304 been described. In some cases the infusion lines and the times of administration of  
305 ceftriaxone and calcium-containing solutions differed.

306 For information regarding all other patients, see **WARNINGS**.

### **307 WARNINGS**

#### **308 Hypersensitivity**

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

#### **318 Interaction with Calcium-Containing Products**

319 **There are no reports to date of intravascular or pulmonary precipitations in**  
320 **patients, other than neonates, treated with ceftriaxone and calcium-containing IV**  
321 **solutions. However, the theoretical possibility exists for an interaction between**  
322 **ceftriaxone and IV calcium-containing solutions in patients other than neonates.**  
323 **Therefore, Rocephin and calcium-containing solutions, including continuous**  
324 **calcium-containing infusions such as parenteral nutrition, should not be mixed or**  
325 **co-administered to any patient irrespective of age, even via different infusion lines at**  
326 **different sites. As a further theoretical consideration and based on 5 half-lives of**  
327 **ceftriaxone, Rocephin and IV calcium-containing solutions should not be**  
328 **administered within 48 hours of each other in any patient (see**  
329 **CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).**

330 **No data are available on potential interaction between ceftriaxone and oral calcium-**  
331 **containing products or interaction between intramuscular ceftriaxone and calcium-**  
332 **containing products (IV or oral).**

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### 333 ***Clostridium difficile***

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

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

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

### 348 **PRECAUTIONS**

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

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

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

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

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

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

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

374 **There have been reports of sonographic abnormalities in the gallbladder of patients**  
375 **treated with Rocephin; some of these patients also had symptoms of gallbladder**  
376 **disease.** These abnormalities appear on sonography as an echo without acoustical  
377 shadowing suggesting sludge or as an echo with acoustical shadowing which may be  
378 misinterpreted as gallstones. The chemical nature of the sonographically detected  
379 material has been determined to be predominantly a ceftriaxone-calcium salt. **The**  
380 **condition appears to be transient and reversible upon discontinuation of Rocephin**  
381 **and institution of conservative management.** Therefore, Rocephin should be  
382 discontinued in patients who develop signs and symptoms suggestive of gallbladder  
383 disease and/or the sonographic findings described above.

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

388 The elimination of Rocephin is not altered by probenecid.

389 As with other cephalosporins, anaphylactic shock cannot be ruled out even if a thorough  
390 patient history is taken.

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

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

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

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

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

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

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

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

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

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

434 *Geriatric Use:* Of the total number of subjects in clinical studies of Rocephin, 32% were  
435 60 and over. No overall differences in safety or effectiveness were observed between  
436 these subjects and younger subjects, and other reported clinical experience has not  
437 identified differences in responses between the elderly and younger patients, but greater  
438 sensitivity of some older individuals cannot be ruled out.

439 The pharmacokinetics of ceftriaxone were only minimally altered in geriatric patients  
440 compared to healthy adult subjects and dosage adjustments are not necessary for geriatric  
441 patients with ceftriaxone dosages up to 2 grams per day (see **CLINICAL**  
442 **PHARMACOLOGY**).

443 No dosage adjustment is necessary for patients with impairment of renal or hepatic  
444 function; however, blood levels should be monitored in patients with severe renal  
445 impairment (e.g., dialysis patients) and in patients with both renal and hepatic  
446 dysfunctions.

## 447 **ADVERSE REACTIONS**

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

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

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

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

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

463 *HEPATIC*—elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported  
464 (<1%) were elevations of alkaline phosphatase and bilirubin.

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

467 *CENTRAL NERVOUS SYSTEM*—headache or dizziness were reported occasionally  
468 (<1%).

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

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

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

477 Cases of fatal reactions with ceftriaxone-calcium precipitates in lung and kidneys in  
478 neonates have been described. In some cases the infusion lines and the times of  
479 administration of ceftriaxone and calcium-containing solutions differed (see  
480 **CONTRAINDICATIONS**).

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

485 *GASTROINTESTINAL* – stomatitis and glossitis.

486 *GENITOURINARY* – oliguria.

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487 *DERMATOLOGIC* – exanthema, allergic dermatitis, urticaria, edema. As with many  
488 medications, isolated cases of severe cutaneous adverse reactions (erythema multiforme,  
489 Stevens-Johnson syndrome or Lyell’s syndrome/toxic epidermal necrolysis) have been  
490 reported.

### 491 **Cephalosporin Class Adverse Reactions**

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

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

498 *Altered Laboratory Tests:* Positive direct Coombs’ test, false-positive test for urinary  
499 glucose, and elevated LDH.

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

### 504 **OVERDOSAGE**

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

### 508 **DOSAGE AND ADMINISTRATION**

509 Rocephin may be administered intravenously or intramuscularly.

510 **Do not use diluents containing calcium, such as Ringer’s solution or Hartmann’s**  
511 **solution, to reconstitute Rocephin. Particulate formation can result. Rocephin and**  
512 **calcium-containing solutions, including continuous calcium-containing infusions**  
513 **such as parenteral nutrition, should not be mixed or co-administered to any patient**  
514 **irrespective of age, even via different infusion lines at different sites (see**  
515 **CONTRAINDICATIONS and WARNINGS).**

516 *NEONATES:* Hyperbilirubinemic neonates, especially prematures, should not be treated  
517 with Rocephin (see **CONTRAINDICATIONS**).

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

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

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

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

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

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

536 For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of  
537 250 mg is recommended.

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

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

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

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

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

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

553 After reconstitution, each 1 mL of solution contains approximately 250 mg or 350 mg  
554 equivalent of ceftriaxone according to the amount of diluent indicated below. If required,  
555 more dilute solutions could be utilized. **A 350 mg/mL concentration is not**  
556 **recommended for the 250 mg vial since it may not be possible to withdraw the entire**  
557 **contents.**

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

## ROCEPHIN® (ceftriaxone sodium)

<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

561

562 *Intravenous Administration:* Rocephin should be administered intravenously by infusion  
563 over a period of 30 minutes. Concentrations between 10 mg/mL and 40 mg/mL are  
564 recommended; however, lower concentrations may be used if desired. Reconstitute vials  
565 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

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

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

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

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

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

587 Rocephin sterile powder should be stored at room temperature—77°F (25°C)—or below  
588 and protected from light. After reconstitution, protection from normal light is not  
589 necessary. The color of solutions ranges from light yellow to amber, depending on the  
590 length of storage, concentration and diluent used.

## ROCEPHIN® (ceftriaxone sodium)

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

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

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

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

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

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

598 The following *intravenous* Rocephin solutions are stable at room temperature (25°C) for  
599 24 hours, at concentrations between 10 mg/mL and 40 mg/mL: Sodium Lactate (PVC  
600 container), 10% Invert Sugar (glass container), 5% Sodium Bicarbonate (glass container),  
601 Freamine III (glass container), Normosol-M in 5% Dextrose (glass and PVC containers),  
602 Ionosol-B in 5% Dextrose (glass container), 5% Mannitol (glass container), 10%  
603 Mannitol (glass container).

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

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

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

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

### **613 ANIMAL PHARMACOLOGY**

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

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

### **622 HOW SUPPLIED**

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

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

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

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

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

632 Bulk pharmacy containers, containing 10 gm equivalent of ceftriaxone. Box of 1 (NDC  
633 0004-1971-01). NOT FOR DIRECT ADMINISTRATION.

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

### **636 CLINICAL STUDIES**

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

## ROCEPHIN® (ceftriaxone sodium)

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

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

644 Week 2 and 4 Bacteriologic Eradication Rates in the Per Protocol Analysis in the Roche  
645 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)

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**Pharmaceuticals**

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