

1 PRESCRIBING INFORMATION

2 **CEFTIN<sup>®</sup> Tablets**  
3 (cefuroxime axetil tablets)

4  
5 **CEFTIN<sup>®</sup> for Oral Suspension**  
6 (cefuroxime axetil powder for oral suspension)

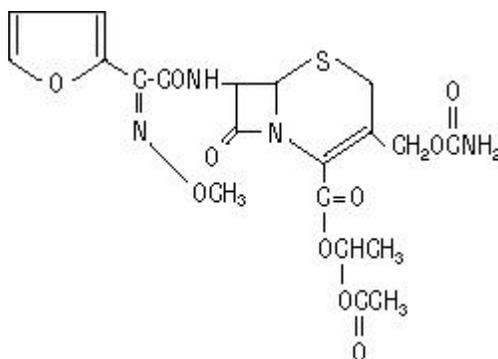
7  
8 To reduce the development of drug-resistant bacteria and maintain the effectiveness of  
9 CEFTIN and other antibacterial drugs, CEFTIN should be used only to treat or prevent infections  
10 that are proven or strongly suspected to be caused by bacteria.

11 **DESCRIPTION**

12 CEFTIN Tablets and CEFTIN for Oral Suspension contain cefuroxime as cefuroxime axetil.  
13 CEFTIN is a semisynthetic, broad-spectrum cephalosporin antibiotic for oral administration.

14 Chemically, cefuroxime axetil, the 1-(acetyloxy) ethyl ester of cefuroxime, is (*RS*)-1-  
15 hydroxyethyl (6*R*,7*R*)-7-[2-(2-furyl)glyoxyl-amido]-3-(hydroxymethyl)-8-oxo-5-thia-1-  
16 azabicyclo[4.2.0]-oct-2-ene-2-carboxylate, 7<sup>2</sup>-(*Z*)-(O-methyl-oxime), 1-acetate 3-carbamate. Its  
17 molecular formula is C<sub>20</sub>H<sub>22</sub>N<sub>4</sub>O<sub>10</sub>S, and it has a molecular weight of 510.48.

18 Cefuroxime axetil is in the amorphous form and has the following structural formula:



20  
21 CEFTIN Tablets are film-coated and contain the equivalent of 250 or 500 mg of cefuroxime  
22 as cefuroxime axetil. CEFTIN Tablets contain the inactive ingredients colloidal silicon dioxide,  
23 croscarmellose sodium, hydrogenated vegetable oil, hypromellose, methylparaben,  
24 microcrystalline cellulose, propylene glycol, propylparaben, sodium benzoate, sodium lauryl  
25 sulfate, and titanium dioxide.

26 CEFTIN for Oral Suspension, when reconstituted with water, provides the equivalent of  
27 125 mg or 250 mg of cefuroxime (as cefuroxime axetil) per 5 mL of suspension. CEFTIN for  
28 Oral Suspension contains the inactive ingredients acesulfame potassium, aspartame, povidone  
29 K30, stearic acid, sucrose, tutti-frutti flavoring, and xanthan gum.

31 **CLINICAL PHARMACOLOGY**

32 **Absorption and Metabolism:** After oral administration, cefuroxime axetil is absorbed from  
 33 the gastrointestinal tract and rapidly hydrolyzed by nonspecific esterases in the intestinal mucosa  
 34 and blood to cefuroxime. Cefuroxime is subsequently distributed throughout the extracellular  
 35 fluids. The axetil moiety is metabolized to acetaldehyde and acetic acid.

36 **Pharmacokinetics:** Approximately 50% of serum cefuroxime is bound to protein. Serum  
 37 pharmacokinetic parameters for CEFTIN Tablets and CEFTIN for Oral Suspension are shown in  
 38 Tables 1 and 2.

39  
 40 **Table 1. Postprandial Pharmacokinetics of Cefuroxime Administered as CEFTIN Tablets**  
 41 **to Adults\***

Dose <sup>†</sup> (Cefuroxime Equivalent)	Peak Plasma Concentration (mcg/mL)	Time of Peak Plasma Concentration (hr)	Mean Elimination Half-Life (hr)	AUC (mcg-hr mL)
125 mg	2.1	2.2	1.2	6.7
250 mg	4.1	2.5	1.2	12.9
500 mg	7.0	3.0	1.2	27.4
1,000 mg	13.6	2.5	1.3	50.0

42 \*Mean values of 12 healthy adult volunteers.

43 <sup>†</sup>Drug administered immediately after a meal.

44  
 45 **Table 2. Postprandial Pharmacokinetics of Cefuroxime Administered as CEFTIN for Oral**  
 46 **Suspension to Pediatric Patients\***

Dose <sup>†</sup> (Cefuroxime Equivalent)	n	Peak Plasma Concentration (mcg/mL)	Time of Peak Plasma Concentration (hr)	Mean Elimination Half-Life (hr)	AUC (mcg-hr mL)
10 mg/kg	8	3.3	3.6	1.4	12.4
15 mg/kg	12	5.1	2.7	1.9	22.5
20 mg/kg	8	7.0	3.1	1.9	32.8

47 \*Mean age = 23 months.

48 <sup>†</sup>Drug administered with milk or milk products.

49  
 50 **Comparative Pharmacokinetic Properties:** A 250 mg/5 mL-dose of CEFTIN Suspension  
 51 is bioequivalent to 2 times 125 mg/5 mL-dose of CEFTIN Suspension when administered with  
 52 food (see Table 3). **CEFTIN for Oral Suspension was not bioequivalent to CEFTIN Tablets**  
 53 **when tested in healthy adults. The tablet and powder for oral suspension formulations are**  
 54 **NOT substitutable on a milligram-per-milligram basis.** The area under the curve for the  
 55 suspension averaged 91% of that for the tablet, and the peak plasma concentration for the  
 56 suspension averaged 71% of the peak plasma concentration of the tablets. Therefore, the safety

57 and effectiveness of both the tablet and oral suspension formulations had to be established in  
58 separate clinical trials.

59

60 **Table 3. Pharmacokinetics of Cefuroxime Administered as 250 mg/5 mL or 2 x 125 mg/5**  
61 **mL CEFTIN for Oral Suspension to Adults\* With Food**

Dose (Cefuroxime Equivalent)	Peak Plasma Concentration (mcg/mL)	Time of Peak Plasma Concentration (hr)	Mean Elimination Half-Life (hr)	C (mcg-hr mL)
250 mg/5 mL	2.23	3	1.40	8.92
2 x 125 mg/5 mL	2.37	3	1.44	9.75

62 \*Mean values of 18 healthy adult volunteers.

63

64 **Food Effect on Pharmacokinetics:** Absorption of the tablet is greater when taken after food  
65 (absolute bioavailability of CEFTIN Tablets increases from 37% to 52%). Despite this difference  
66 in absorption, the clinical and bacteriologic responses of patients were independent of food  
67 intake at the time of tablet administration in 2 studies where this was assessed.

68 All pharmacokinetic and clinical effectiveness and safety studies in pediatric patients using  
69 the suspension formulation were conducted in the fed state. No data are available on the  
70 absorption kinetics of the suspension formulation when administered to fasted pediatric patients.

71 **Renal Excretion:** Cefuroxime is excreted unchanged in the urine; in adults, approximately  
72 50% of the administered dose is recovered in the urine within 12 hours. The pharmacokinetics of  
73 cefuroxime in the urine of pediatric patients have not been studied at this time. Until further data  
74 are available, the renal pharmacokinetic properties of cefuroxime axetil established in adults  
75 should not be extrapolated to pediatric patients.

76 Because cefuroxime is renally excreted, the serum half-life is prolonged in patients with  
77 reduced renal function. In a study of 20 elderly patients (mean age = 83.9 years) having a mean  
78 creatinine clearance of 34.9 mL/min, the mean serum elimination half-life was 3.5 hours. Despite  
79 the lower elimination of cefuroxime in geriatric patients, dosage adjustment based on age is not  
80 necessary (see PRECAUTIONS: Geriatric Use).

81 **Microbiology:** The in vivo bactericidal activity of cefuroxime axetil is due to cefuroxime's  
82 binding to essential target proteins and the resultant inhibition of cell-wall synthesis.

83 Cefuroxime has bactericidal activity against a wide range of common pathogens, including  
84 many beta-lactamase-producing strains. Cefuroxime is stable to many bacterial beta-lactamases,  
85 especially plasmid-mediated enzymes that are commonly found in enterobacteriaceae.

86 Cefuroxime has been demonstrated to be active against most strains of the following  
87 microorganisms both in vitro and in clinical infections as described in the INDICATIONS AND  
88 USAGE section (see INDICATIONS AND USAGE section).

89 ***Aerobic Gram-Positive Microorganisms:***

90 *Staphylococcus aureus* (including beta-lactamase-producing strains)

91 *Streptococcus pneumoniae*

92 *Streptococcus pyogenes*

93 **Aerobic Gram-Negative Microorganisms:**

94 *Escherichia coli*

95 *Haemophilus influenzae* (including beta-lactamase-producing strains)

96 *Haemophilus parainfluenzae*

97 *Klebsiella pneumoniae*

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

99 *Neisseria gonorrhoeae* (including beta-lactamase-producing strains)

100 **Spirochetes:**

101 *Borrelia burgdorferi*

102 Cefuroxime has been shown to be active in vitro against most strains of the following  
103 microorganisms; however, the clinical significance of these findings is unknown.

104 Cefuroxime exhibits in vitro minimum inhibitory concentrations (MICs) of 4.0 mcg/mL or  
105 less (systemic susceptible breakpoint) against most ( $\geq 90\%$ ) strains of the following  
106 microorganisms; however, the safety and effectiveness of cefuroxime in treating clinical  
107 infections due to these microorganisms have not been established in adequate and  
108 well-controlled trials.

109 **Aerobic Gram-Positive Microorganisms:**

110 *Staphylococcus epidermidis*

111 *Staphylococcus saprophyticus*

112 *Streptococcus agalactiae*

113 NOTE: *Listeria monocytogenes* and certain strains of enterococci, e.g., *Enterococcus faecalis*  
114 (formerly *Streptococcus faecalis*), are resistant to cefuroxime. Methicillin-resistant staphylococci  
115 are resistant to cefuroxime.

116 **Aerobic Gram-Negative Microorganisms:**

117 *Morganella morganii*

118 *Proteus inconstans*

119 *Proteus mirabilis*

120 *Providencia rettgeri*

121 NOTE: *Pseudomonas* spp., *Campylobacter* spp., *Acinetobacter calcoaceticus*, *Legionella* spp.,  
122 and most strains of *Serratia* spp. and *Proteus vulgaris* are resistant to most first- and  
123 second-generation cephalosporins. Some strains of *Morganella morganii*, *Enterobacter cloacae*,  
124 and *Citrobacter* spp. have been shown by in vitro tests to be resistant to cefuroxime and other  
125 cephalosporins.

126 **Anaerobic Microorganisms:**

127 *Peptococcus niger*

128 NOTE: Most strains of *Clostridium difficile* and *Bacteroides fragilis* are resistant to cefuroxime.

129 **Susceptibility Tests: Dilution Techniques:** Quantitative methods that are used to  
130 determine MICs provide reproducible estimates of the susceptibility of bacteria to antimicrobial  
131 compounds. One such standardized procedure uses a standardized dilution method<sup>1</sup> (broth, agar,

132 or microdilution) or equivalent with cefuroxime powder. The MIC values obtained should be  
133 interpreted according to the following criteria:

134

<u>MIC (mcg/mL)</u>	<u>Interpretation</u>
≤4	(S) Susceptible
8-16	(I) Intermediate
≥32	(R) Resistant

135

136 A report of "Susceptible" indicates that the pathogen, if in the blood, is likely to be inhibited  
137 by usually achievable concentrations of the antimicrobial compound in blood. A report of  
138 "Intermediate" indicates that inhibitory concentrations of the antibiotic may be achieved if high  
139 dosage is used or if the infection is confined to tissues or fluids in which high antibiotic  
140 concentrations are attained. This category also provides a buffer zone that prevents small,  
141 uncontrolled technical factors from causing major discrepancies in interpretation. A report of  
142 "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the  
143 blood are unlikely to be inhibitory and that other therapy should be selected.

144 Standardized susceptibility test procedures require the use of laboratory control  
145 microorganisms. Standard cefuroxime powder should give the following MIC values:

146

<u>Microorganism</u>	<u>MIC (mcg/mL)</u>
<i>Escherichia coli</i> ATCC 25922	2-8
<i>Staphylococcus aureus</i> ATCC 29213	0.5-2

147

148 **Diffusion Techniques:** Quantitative methods that require measurement of zone diameters  
149 provide estimates of the susceptibility of bacteria to antimicrobial compounds. One such  
150 standardized procedure<sup>2</sup> that has been recommended (for use with disks) to test the susceptibility  
151 of microorganisms to cefuroxime uses the 30-mcg cefuroxime disk. Interpretation involves  
152 correlation of the diameter obtained in the disk test with the MIC for cefuroxime.

153 Reports from the laboratory providing results of the standard single-disk susceptibility test  
154 with a 30-mcg cefuroxime disk should be interpreted according to the following criteria:

155

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥23	(S) Susceptible
15-22	(I) Intermediate
≤14	(R) Resistant

156

157 Interpretation should be as stated above for results using dilution techniques.

158 As with standard dilution techniques, diffusion methods require the use of laboratory control  
159 microorganisms. The 30-mcg cefuroxime disk provides the following zone diameters in these  
160 laboratory test quality control strains:

161

<u>Microorganism</u>	<u>Zone Diameter (mm)</u>
<i>Escherichia coli</i> ATCC 25922	20-26
<i>Staphylococcus aureus</i> ATCC 25923	27-35

162 **INDICATIONS AND USAGE**

163 **NOTE: CEFTIN TABLETS AND CEFTIN FOR ORAL SUSPENSION ARE NOT**  
164 **BIOEQUIVALENT AND ARE NOT SUBSTITUTABLE ON A**  
165 **MILLIGRAM-PER-MILLIGRAM BASIS (SEE CLINICAL PHARMACOLOGY).**

166 **CEFTIN Tablets:** CEFTIN Tablets are indicated for the treatment of patients with mild to  
167 moderate infections caused by susceptible strains of the designated microorganisms in the  
168 conditions listed below:

169 **1. Pharyngitis/Tonsillitis** caused by *Streptococcus pyogenes*.

170 **NOTE:** The usual drug of choice in the treatment and prevention of streptococcal infections,  
171 including the prophylaxis of rheumatic fever, is penicillin given by the intramuscular route.  
172 CEFTIN Tablets are generally effective in the eradication of streptococci from the  
173 nasopharynx; however, substantial data establishing the efficacy of cefuroxime in the  
174 subsequent prevention of rheumatic fever are not available. Please also note that in all clinical  
175 trials, all isolates had to be sensitive to both penicillin and cefuroxime. There are no data from  
176 adequate and well-controlled trials to demonstrate the effectiveness of cefuroxime in the  
177 treatment of penicillin-resistant strains of *Streptococcus pyogenes*.

178 **2. Acute Bacterial Otitis Media** caused by *Streptococcus pneumoniae*, *Haemophilus*  
179 *influenzae* (including beta-lactamase-producing strains), *Moraxella catarrhalis* (including  
180 beta-lactamase-producing strains), or *Streptococcus pyogenes*.

181 **3. Acute Bacterial Maxillary Sinusitis** caused by *Streptococcus pneumoniae* or *Haemophilus*  
182 *influenzae* (non-beta-lactamase-producing strains only). (See CLINICAL STUDIES section.)

183 **NOTE:** In view of the insufficient numbers of isolates of beta-lactamase-producing strains of  
184 *Haemophilus influenzae* and *Moraxella catarrhalis* that were obtained from clinical trials with  
185 CEFTIN Tablets for patients with acute bacterial maxillary sinusitis, it was not possible to  
186 adequately evaluate the effectiveness of CEFTIN Tablets for sinus infections known,  
187 suspected, or considered potentially to be caused by beta-lactamase-producing *Haemophilus*  
188 *influenzae* or *Moraxella catarrhalis*.

189 **4. Acute Bacterial Exacerbations of Chronic Bronchitis and Secondary Bacterial**  
190 **Infections of Acute Bronchitis** caused by *Streptococcus pneumoniae*, *Haemophilus*  
191 *influenzae* (beta-lactamase negative strains), or *Haemophilus parainfluenzae* (beta-lactamase  
192 negative strains). (See DOSAGE AND ADMINISTRATION section and CLINICAL  
193 STUDIES section.)

194 **5. Uncomplicated Skin and Skin-Structure Infections** caused by *Staphylococcus aureus*  
195 (including beta-lactamase-producing strains) or *Streptococcus pyogenes*.

- 196 **6. Uncomplicated Urinary Tract Infections** caused by *Escherichia coli* or *Klebsiella*  
197 *pneumoniae*.  
198 **7. Uncomplicated Gonorrhea**, urethral and endocervical, caused by penicillinase-producing  
199 and non-penicillinase-producing strains of *Neisseria gonorrhoeae* and uncomplicated  
200 gonorrhea, rectal, in females, caused by non-penicillinase-producing strains of *Neisseria*  
201 *gonorrhoeae*.  
202 **8. Early Lyme Disease (erythema migrans)** caused by *Borrelia burgdorferi*.

203  
204 **CEFTIN for Oral Suspension:** CEFTIN for Oral Suspension is indicated for the treatment of  
205 pediatric patients 3 months to 12 years of age with mild to moderate infections caused by  
206 susceptible strains of the designated microorganisms in the conditions listed below. The safety  
207 and effectiveness of CEFTIN for Oral Suspension in the treatment of infections other than those  
208 specifically listed below have not been established either by adequate and well-controlled trials  
209 or by pharmacokinetic data with which to determine an effective and safe dosing regimen.

- 210 **1. Pharyngitis/Tonsillitis** caused by *Streptococcus pyogenes*.

211 **NOTE:** The usual drug of choice in the treatment and prevention of streptococcal infections,  
212 including the prophylaxis of rheumatic fever, is penicillin given by the intramuscular route.  
213 CEFTIN for Oral Suspension is generally effective in the eradication of streptococci from the  
214 nasopharynx; however, substantial data establishing the efficacy of cefuroxime in the  
215 subsequent prevention of rheumatic fever are not available. Please also note that in all clinical  
216 trials, all isolates had to be sensitive to both penicillin and cefuroxime. There are no data from  
217 adequate and well-controlled trials to demonstrate the effectiveness of cefuroxime in the  
218 treatment of penicillin-resistant strains of *Streptococcus pyogenes*.

- 219 **2. Acute Bacterial Otitis Media** caused by *Streptococcus pneumoniae*, *Haemophilus*  
220 *influenzae* (including beta-lactamase-producing strains), *Moraxella catarrhalis* (including  
221 beta-lactamase-producing strains), or *Streptococcus pyogenes*.

- 222 **3. Impetigo** caused by *Staphylococcus aureus* (including beta-lactamase-producing strains) or  
223 *Streptococcus pyogenes*.

224  
225 To reduce the development of drug-resistant bacteria and maintain the effectiveness of  
226 CEFTIN and other antibacterial drugs, CEFTIN should be used only to treat or prevent  
227 infections that are proven or strongly suspected to be caused by susceptible bacteria. When  
228 culture and susceptibility information are available, they should be considered in selecting or  
229 modifying antibacterial therapy. In the absence of such data, local epidemiology and  
230 susceptibility patterns may contribute to the empiric selection of therapy.

## 231 **CONTRAINDICATIONS**

232 CEFTIN products are contraindicated in patients with known allergy to the cephalosporin  
233 group of antibiotics.

234 **WARNINGS**

235 **CEFTIN TABLETS AND CEFTIN FOR ORAL SUSPENSION ARE NOT**  
236 **BIOEQUIVALENT AND ARE THEREFORE NOT SUBSTITUTABLE ON A**  
237 **MILLIGRAM-PER-MILLIGRAM BASIS (SEE CLINICAL PHARMACOLOGY).**

238 **BEFORE THERAPY WITH CEFTIN PRODUCTS IS INSTITUTED, CAREFUL**  
239 **INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS**  
240 **HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFTIN PRODUCTS,**  
241 **OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS**  
242 **PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION**  
243 **SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG**  
244 **BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY**  
245 **OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN**  
246 **ALLERGY. IF A CLINICALLY SIGNIFICANT ALLERGIC REACTION TO CEFTIN**  
247 **PRODUCTS OCCURS, DISCONTINUE THE DRUG AND INSTITUTE APPROPRIATE**  
248 **THERAPY. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE**  
249 **TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES,**  
250 **INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS**  
251 **ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY**  
252 **MANAGEMENT, AS CLINICALLY INDICATED.**

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

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

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

267 **PRECAUTIONS**

268 **General:** As with other broad-spectrum antibiotics, prolonged administration of cefuroxime  
269 axetil may result in overgrowth of nonsusceptible microorganisms. If superinfection occurs  
270 during therapy, appropriate measures should be taken.

271 Cephalosporins, including cefuroxime axetil, should be given with caution to patients  
272 receiving concurrent treatment with potent diuretics because these diuretics are suspected of  
273 adversely affecting renal function.

274 Cefuroxime axetil, as with other broad-spectrum antibiotics, should be prescribed with  
275 caution in individuals with a history of colitis. The safety and effectiveness of cefuroxime axetil  
276 have not been established in patients with gastrointestinal malabsorption. Patients with  
277 gastrointestinal malabsorption were excluded from participating in clinical trials of cefuroxime  
278 axetil.

279 Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include  
280 patients with renal or hepatic impairment or poor nutritional state, as well as patients receiving a  
281 protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant  
282 therapy. Prothrombin time should be monitored in patients at risk and exogenous Vitamin K  
283 administered as indicated.

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

287 Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic  
288 is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery  
289 and bloody stools (with or without stomach cramps and fever) even as late as 2 or more months  
290 after having taken the last dose of the antibiotic. If this occurs, patients should contact their  
291 physician as soon as possible.

292 **Information for Patients/Caregivers (Pediatric): *Phenylketonurics*:** CEFTIN for Oral  
293 Suspension 125 mg/5 mL contains phenylalanine 11.8 mg per 5 mL (1 teaspoonful) constituted  
294 suspension. CEFTIN for Oral Suspension 250 mg/5 mL contains phenylalanine 25.2 mg per  
295 5 mL (1 teaspoonful) constituted suspension.

- 296 1. During clinical trials, the tablet was tolerated by pediatric patients old enough to swallow the  
297 cefuroxime axetil tablet whole. The crushed tablet has a strong, persistent, bitter taste and  
298 should not be administered to pediatric patients in this manner. Pediatric patients who cannot  
299 swallow the tablet whole should receive the oral suspension.
- 300 2. Discontinuation of therapy due to taste and/or problems of administering this drug occurred  
301 in 1.4% of pediatric patients given the oral suspension. Complaints about taste (which may  
302 impair compliance) occurred in 5% of pediatric patients.
- 303 3. Patients should be counseled that antibacterial drugs, including CEFTIN, should only be used  
304 to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When  
305 CEFTIN is prescribed to treat a bacterial infection, patients should be told that although it is  
306 common to feel better early in the course of therapy, the medication should be taken exactly  
307 as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the  
308 effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will  
309 develop resistance and will not be treatable by CEFTIN or other antibacterial drugs in the  
310 future.

311 **Drug/Laboratory Test Interactions:** A false-positive reaction for glucose in the urine may  
312 occur with copper reduction tests (Benedict's or Fehling's solution or with CLINITEST<sup>®</sup> tablets),  
313 but not with enzyme-based tests for glycosuria (e.g., CLINISTIX<sup>®</sup>). As a false-negative result  
314 may occur in the ferricyanide test, it is recommended that either the glucose oxidase or  
315 hexokinase method be used to determine blood/plasma glucose levels in patients receiving  
316 cefuroxime axetil. The presence of cefuroxime does not interfere with the assay of serum and  
317 urine creatinine by the alkaline picrate method.

318 **Drug/Drug Interactions:** Concomitant administration of probenecid with cefuroxime axetil  
319 tablets increases the area under the serum concentration versus time curve by 50%. The peak  
320 serum cefuroxime concentration after a 1.5-g single dose is greater when taken with 1 g of  
321 probenecid (mean = 14.8 mcg/mL) than without probenecid (mean = 12.2 mcg/mL).

322 Drugs that reduce gastric acidity may result in a lower bioavailability of CEFTIN compared  
323 with that of fasting state and tend to cancel the effect of postprandial absorption.

324 In common with other antibiotics, cefuroxime axetil may affect the gut flora, leading to lower  
325 estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone  
326 contraceptives.

327 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Although lifetime studies in  
328 animals have not been performed to evaluate carcinogenic potential, no mutagenic activity was  
329 found for cefuroxime axetil in a battery of bacterial mutation tests. Positive results were obtained  
330 in an in vitro chromosome aberration assay; however, negative results were found in an in vivo  
331 micronucleus test at doses up to 1.5 g/kg. Reproduction studies in rats at doses up to  
332 1,000 mg/kg/day (9 times the recommended maximum human dose based on mg/m<sup>2</sup>) have  
333 revealed no impairment of fertility.

334 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Reproduction studies have been  
335 performed in mice at doses up to 3,200 mg/kg/day (14 times the recommended maximum human  
336 dose based on mg/m<sup>2</sup>) and in rats at doses up to 1,000 mg/kg/day (9 times the recommended  
337 maximum human dose based on mg/m<sup>2</sup>) and have revealed no evidence of impaired fertility or  
338 harm to the fetus due to cefuroxime axetil. There are, however, no adequate and well-controlled  
339 studies in pregnant women. Because animal reproduction studies are not always predictive of  
340 human response, this drug should be used during pregnancy only if clearly needed.

341 **Labor and Delivery:** Cefuroxime axetil has not been studied for use during labor and delivery.

342 **Nursing Mothers:** Because cefuroxime is excreted in human milk, consideration should be  
343 given to discontinuing nursing temporarily during treatment with cefuroxime axetil.

344 **Pediatric Use:** The safety and effectiveness of CEFTIN have been established for pediatric  
345 patients aged 3 months to 12 years for acute bacterial maxillary sinusitis based upon its approval  
346 in adults. Use of CEFTIN in pediatric patients is supported by pharmacokinetic and safety data in  
347 adults and pediatric patients, and by clinical and microbiological data from adequate and  
348 well-controlled studies of the treatment of acute bacterial maxillary sinusitis in adults and of  
349 acute otitis media with effusion in pediatric patients. It is also supported by postmarketing  
350 adverse events surveillance (see CLINICAL PHARMACOLOGY, INDICATIONS AND

351 USAGE, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and CLINICAL  
352 STUDIES).

353 **Geriatric Use:** Of the total number of subjects who received cefuroxime axetil in 20 clinical  
354 studies of CEFTIN, 375 were 65 and over while 151 were 75 and over. No overall differences in  
355 safety or effectiveness were observed between these subjects and younger adult subjects. The  
356 geriatric patients reported somewhat fewer gastrointestinal events and less frequent vaginal  
357 candidiasis compared with patients aged 12 to 64 years old; however, no clinically significant  
358 differences were reported between the elderly and younger adult patients. Other reported clinical  
359 experience has not identified differences in responses between the elderly and younger adult  
360 patients.

### 361 **ADVERSE REACTIONS**

#### 362 **CEFTIN TABLETS IN CLINICAL TRIALS: Multiple-Dose Dosing Regimens: 7 to**

363 **10 Days Dosing:** Using multiple doses of cefuroxime axetil tablets, 912 patients were treated  
364 with cefuroxime axetil (125 to 500 mg twice daily). There were no deaths or permanent  
365 disabilities thought related to drug toxicity. Twenty (2.2%) patients discontinued medication due  
366 to adverse events thought by the investigators to be possibly, probably, or almost certainly  
367 related to drug toxicity. Seventeen (85%) of the 20 patients who discontinued therapy did so  
368 because of gastrointestinal disturbances, including diarrhea, nausea, vomiting, and abdominal  
369 pain. The percentage of cefuroxime axetil tablet-treated patients who discontinued study drug  
370 because of adverse events was very similar at daily doses of 1,000, 500, and 250 mg (2.3%,  
371 2.1%, and 2.2%, respectively). However, the incidence of gastrointestinal adverse events  
372 increased with the higher recommended doses.

373 The following adverse events were thought by the investigators to be possibly, probably, or  
374 almost certainly related to cefuroxime axetil tablets in multiple-dose clinical trials (n = 912  
375 cefuroxime axetil-treated patients).

376

377 **Table 4. Adverse Reactions—CEFTIN Tablets**  
 378 **Multiple-Dose Dosing Regimens—Clinical Trials**

Incidence $\geq$ 1%	Diarrhea/loose stools	3.7%
	Nausea/vomiting	3.0%
	Transient elevation in AST	2.0%
	Transient elevation in ALT	1.6%
	Eosinophilia	1.1%
	Transient elevation in LDH	1.0%
Incidence <1% but >0.1%	Abdominal pain	
	Abdominal cramps	
	Flatulence	
	Indigestion	
	Headache	
	Vaginitis	
	Vulvar itch	
	Rash	
	Hives	
	Itch	
	Dysuria	
	Chills	
	Chest pain	
	Shortness of breath	
	Mouth ulcers	
	Swollen tongue	
Sleepiness		
Thirst		
Anorexia		
Positive Coombs test		

379  
 380 **5-Day Experience (see CLINICAL STUDIES section):** In clinical trials using CEFTIN  
 381 in a dose of 250 mg twice daily in the treatment of secondary bacterial infections of acute  
 382 bronchitis, 399 patients were treated for 5 days and 402 patients were treated for 10 days. No  
 383 difference in the occurrence of adverse events was found between the 2 regimens.

384 **In Clinical Trials for Early Lyme Disease With 20 Days Dosing:** Two multicenter  
 385 trials assessed cefuroxime axetil tablets 500 mg twice a day for 20 days. The most common  
 386 drug-related adverse experiences were diarrhea (10.6% of patients), Jarisch-Herxheimer reaction  
 387 (5.6%), and vaginitis (5.4%). Other adverse experiences occurred with frequencies comparable  
 388 to those reported with 7 to 10 days dosing.

389 **Single-Dose Regimen for Uncomplicated Gonorrhea:** In clinical trials using a single  
 390 dose of cefuroxime axetil tablets, 1,061 patients were treated with the recommended dosage of

391 cefuroxime axetil (1,000 mg) for the treatment of uncomplicated gonorrhea. There were no  
 392 deaths or permanent disabilities thought related to drug toxicity in these studies.

393 The following adverse events were thought by the investigators to be possibly, probably, or  
 394 almost certainly related to cefuroxime axetil in 1,000-mg single-dose clinical trials of  
 395 cefuroxime axetil tablets in the treatment of uncomplicated gonorrhea conducted in the United  
 396 States.

397

398 **Table 5. Adverse Reactions—CEFTIN Tablets**

399 **1-g Single-Dose Regimen for Uncomplicated Gonorrhea—Clinical Trials**

Incidence ≥1%	Nausea/vomiting 6.8%
	Diarrhea 4.2%
Incidence <1% but >0.1%	Abdominal pain
	Dyspepsia
	Erythema
	Rash
	Pruritus
	Vaginal candidiasis
	Vaginal itch
	Vaginal discharge
	Headache
	Dizziness
	Somnolence
	Muscle cramps
	Muscle stiffness
	Muscle spasm of neck
	Tightness/pain in chest
	Bleeding/pain in urethra
	Kidney pain
	Tachycardia
	Lockjaw-type reaction

400 **CEFTIN FOR ORAL SUSPENSION IN CLINICAL TRIALS**

401 In clinical trials using multiple doses of cefuroxime axetil powder for oral suspension,  
 402 pediatric patients (96.7% of whom were younger than 12 years of age) were treated with the  
 403 recommended dosages of cefuroxime axetil (20 to 30 mg/kg/day divided twice a day up to a  
 404 maximum dose of 500 or 1,000 mg/day, respectively). There were no deaths or permanent  
 405 disabilities in any of the patients in these studies. Eleven US patients (1.2%) discontinued  
 406 medication due to adverse events thought by the investigators to be possibly, probably, or almost  
 407 certainly related to drug toxicity. The discontinuations were primarily for gastrointestinal  
 408 disturbances, usually diarrhea or vomiting. During clinical trials, discontinuation of therapy due

409 to the taste and/or problems with administering this drug occurred in 13 (1.4%) pediatric patients  
 410 enrolled at centers in the United States.

411 The following adverse events were thought by the investigators to be possibly, probably, or  
 412 almost certainly related to cefuroxime axetil for oral suspension in multiple-dose clinical trials  
 413 (n = 931 cefuroxime axetil-treated US patients).

414

415 **Table 6. Adverse Reactions—CEFTIN for Oral Suspension**

416 **Multiple-Dose Dosing Regimens—Clinical Trials**

Incidence ≥1%	Diarrhea/loose stools 8.6% Dislike of taste 5.0% Diaper rash 3.4% Nausea/vomiting 2.6%
Incidence <1% but >0.1%	Abdominal pain Flatulence Gastrointestinal infection Candidiasis Vaginal irritation Rash Hyperactivity Irritable behavior Eosinophilia Positive direct Coombs test Elevated liver enzymes Viral illness Upper respiratory infection Sinusitis Cough Urinary tract infection Joint swelling Arthralgia Fever Ptyalism

417 **POSTMARKETING EXPERIENCE WITH CEFTIN PRODUCTS**

418 In addition to adverse events reported during clinical trials, the following events have been  
 419 identified during clinical practice in patients treated with CEFTIN Tablets or with CEFTIN for  
 420 Oral Suspension and were reported spontaneously. Data are generally insufficient to allow an  
 421 estimate of incidence or to establish causation.

422 **General:** The following hypersensitivity reactions have been reported: anaphylaxis,  
 423 angioedema, pruritus, rash, serum sickness-like reaction, urticaria.

424 **Gastrointestinal:** Pseudomembranous colitis (see WARNINGS).  
425 **Hematologic:** Hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, and  
426 increased prothrombin time.  
427 **Hepatic:** Hepatic impairment including hepatitis and cholestasis, jaundice.  
428 **Neurologic:** Seizure.  
429 **Skin:** Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.  
430 **Urologic:** Renal dysfunction.

#### 431 **CEPHALOSPORIN-CLASS ADVERSE REACTIONS**

432 In addition to the adverse reactions listed above that have been observed in patients treated  
433 with cefuroxime axetil, the following adverse reactions and altered laboratory tests have been  
434 reported for cephalosporin-class antibiotics: toxic nephropathy, aplastic anemia, hemorrhage,  
435 increased BUN, increased creatinine, false-positive test for urinary glucose, increased alkaline  
436 phosphatase, neutropenia, elevated bilirubin, and agranulocytosis.

437 Several cephalosporins have been implicated in triggering seizures, particularly in patients  
438 with renal impairment when the dosage was not reduced (see DOSAGE AND  
439 ADMINISTRATION and OVERDOSAGE). If seizures associated with drug therapy occur, the  
440 drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

#### 441 **OVERDOSAGE**

442 Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. Serum  
443 levels of cefuroxime can be reduced by hemodialysis and peritoneal dialysis.

#### 444 **DOSAGE AND ADMINISTRATION**

445 **NOTE: CEFTIN TABLETS AND CEFTIN FOR ORAL SUSPENSION ARE NOT**  
446 **BIOEQUIVALENT AND ARE NOT SUBSTITUTABLE ON A**  
447 **MILLIGRAM-PER-MILLIGRAM BASIS (SEE CLINICAL PHARMACOLOGY).**  
448

449 **Table 7. CEFTIN Tablets**  
 450 **(May be administered without regard to meals.)**

Population/Infection	Dosage	Duration (days)
<b>Adolescents and Adults (13 years and older)</b>		
Pharyngitis/tonsillitis	250 mg b.i.d.	10
Acute bacterial maxillary sinusitis	250 mg b.i.d.	10
Acute bacterial exacerbations of chronic bronchitis	250 or 500 mg b.i.d.	10*
Secondary bacterial infections of acute bronchitis	250 or 500 mg b.i.d.	5-10
Uncomplicated skin and skin-structure infections	250 or 500 mg b.i.d.	10
Uncomplicated urinary tract infections	250 mg b.i.d.	7-10
Uncomplicated gonorrhea	1,000 mg once	single dose
Early Lyme disease	500 mg b.i.d.	20
<b>Pediatric Patients (who can swallow tablets whole)</b>		
Acute otitis media	250 mg b.i.d.	10
Acute bacterial maxillary sinusitis	250 mg b.i.d.	10

451 \* The safety and effectiveness of CEFTIN administered for less than 10 days in patients with  
 452 acute exacerbations of chronic bronchitis have not been established.

453  
 454 **CEFTIN for Oral Suspension:** CEFTIN for Oral Suspension may be administered to  
 455 pediatric patients ranging in age from 3 months to 12 years, according to dosages in Table 8:  
 456

457 **Table 8. CEFTIN for Oral Suspension**  
 458 **(Must be administered with food. Shake well each time before using.)**

Population/Infection	Dosage	Daily Maximum Dose	Duration (days)
<b>Pediatric Patients (3 months to 12 years)</b>			
Pharyngitis/tonsillitis	20 mg/kg/day divided b.i.d.	500 mg	10
Acute otitis media	30 mg/kg/day divided b.i.d.	1,000 mg	10
Acute bacterial maxillary sinusitis	30 mg/kg/day divided b.i.d.	1,000 mg	10
Impetigo	30 mg/kg/day divided b.i.d.	1,000 mg	10

459  
 460 **Patients With Renal Failure:** The safety and efficacy of cefuroxime axetil in patients with  
 461 renal failure have not been established. Since cefuroxime is renally eliminated, its half-life will  
 462 be prolonged in patients with renal failure.

463 **Directions for Mixing CEFTIN for Oral Suspension:** Prepare a suspension at the time of  
 464 dispensing as follows:

- 465 1. Shake the bottle to loosen the powder.
- 466 2. Remove the cap.

- 467 3. Add the total amount of water for reconstitution (see Table 9) and replace the cap.  
 468 4. Invert the bottle and vigorously rock the bottle from side to side so that water rises through  
 469 the powder.  
 470 5. Once the sound of the powder against the bottle disappears, turn the bottle upright and  
 471 vigorously shake it in a diagonal direction.  
 472

473 **Table 9. Amount of Water Required for Reconstitution of Labeled Volumes of CEFTIN for**  
 474 **Oral Suspension**

CEFTIN for Oral Suspension	Labeled Volume After Reconstitution	Amount of Water Required for Reconstitution
125 mg/5 mL	100 mL	37 mL
250 mg/5 mL	50 mL	19 mL
	100 mL	35 mL

475  
 476 **NOTE: SHAKE THE ORAL SUSPENSION WELL BEFORE EACH USE.** Replace cap  
 477 securely after each opening. Store the reconstituted suspension between 2° and 8°C (36° and  
 478 46°F) (in a refrigerator). **DISCARD AFTER 10 DAYS.**

479 **HOW SUPPLIED**

480 **CEFTIN Tablets:** CEFTIN Tablets, 250 mg of cefuroxime (as cefuroxime axetil), are white,  
 481 capsule-shaped, film-coated tablets engraved with "GX ES7" on one side and blank on the other  
 482 side as follows:

483 20 Tablets/Bottle NDC 0173-0387-00

484 CEFTIN Tablets, 500 mg of cefuroxime (as cefuroxime axetil), are white, capsule-shaped,  
 485 film-coated tablets engraved with "GX EG2" on one side and blank on the other side as follows:

486 20 Tablets/Bottle NDC 0173-0394-00

487 60 Tablets/Bottle NDC 0173-0394-42

488 **Store the tablets between 15° and 30°C (59° and 86°F). Replace cap securely after each**  
 489 **opening.**

490 **CEFTIN for Oral Suspension:** CEFTIN for Oral Suspension is provided as dry, white to  
 491 off-white, tutti-frutti-flavored powder. When reconstituted as directed, CEFTIN for Oral  
 492 Suspension provides the equivalent of 125 mg or 250 mg of cefuroxime (as cefuroxime axetil)  
 493 per 5 mL of suspension. It is supplied in amber glass bottles as follows:

494 **125 mg/5 mL:**

495 100-mL Suspension NDC 0173-0740-00

496 **250 mg/5 mL:**

497 50-mL Suspension NDC 0173-0741-10

498 100-mL Suspension NDC 0173-0741-00

499 **Before reconstitution, store dry powder between 2° and 30°C (36° and 86°F).**

500 After reconstitution, immediately store suspension between 2° and 8°C (36° and 46°F),  
501 in a refrigerator. DISCARD AFTER 10 DAYS.

## 502 CLINICAL STUDIES

503 **Ceftin Tablets: Acute Bacterial Maxillary Sinusitis:** One adequate and well-controlled  
504 study was performed in patients with acute bacterial maxillary sinusitis. In this study each  
505 patient had a maxillary sinus aspirate collected by sinus puncture before treatment was initiated  
506 for presumptive acute bacterial sinusitis. All patients had to have radiographic and clinical  
507 evidence of acute maxillary sinusitis. As shown in the following summary of the study, the  
508 general clinical effectiveness of CEFTIN Tablets was comparable to an oral antimicrobial agent  
509 that contained a specific beta-lactamase inhibitor in treating acute maxillary sinusitis. However,  
510 sufficient microbiology data were obtained to demonstrate the effectiveness of CEFTIN Tablets  
511 in treating acute bacterial maxillary sinusitis due only to *Streptococcus pneumoniae* or  
512 non-beta-lactamase-producing *Haemophilus influenzae*. An insufficient number of  
513 beta-lactamase-producing *Haemophilus influenzae* and *Moraxella catarrhalis* isolates were  
514 obtained in this trial to adequately evaluate the effectiveness of CEFTIN Tablets in the treatment  
515 of acute bacterial maxillary sinusitis due to these 2 organisms.

516 This study enrolled 317 adult patients, 132 patients in the United States and 185 patients in  
517 South America. Patients were randomized in a 1:1 ratio to cefuroxime axetil 250 mg twice daily  
518 or an oral antimicrobial agent that contained a specific beta-lactamase inhibitor. An  
519 intent-to-treat analysis of the submitted clinical data yielded the following results:

520

521 **Table 10. Clinical Effectiveness of CEFTIN Tablets Compared to Beta-Lactamase**  
522 **Inhibitor-Containing Control Drug in the Treatment of Acute Bacterial Maxillary Sinusitis**

	US Patients*		South American Patients <sup>†</sup>	
	CEFTIN (n = 49)	Control (n = 43)	CEFTIN (n = 87)	Control (n = 89)
Clinical success (cure + improvement)	65%	53%	77%	74%
Clinical cure	53%	44%	72%	64%
Clinical improvement	12%	9%	5%	10%

523 \* 95% Confidence interval around the success difference [-0.08, +0.32].

524 <sup>†</sup> 95% Confidence interval around the success difference [-0.10, +0.16].

525

526 In this trial and in a supporting maxillary puncture trial, 15 evaluable patients had  
527 non-beta-lactamase-producing *Haemophilus influenzae* as the identified pathogen. Ten (10) of  
528 these 15 patients (67%) had their pathogen (non-beta-lactamase-producing *Haemophilus*  
529 *influenzae*) eradicated. Eighteen (18) evaluable patients had *Streptococcus pneumoniae* as the  
530 identified pathogen. Fifteen (15) of these 18 patients (83%) had their pathogen (*Streptococcus*  
531 *pneumoniae*) eradicated.

532 **Safety:** The incidence of drug-related gastrointestinal adverse events was statistically  
 533 significantly higher in the control arm (an oral antimicrobial agent that contained a specific  
 534 beta-lactamase inhibitor) versus the cefuroxime axetil arm (12% versus 1%, respectively;  
 535  $P < .001$ ), particularly drug-related diarrhea (8% versus 1%, respectively;  $P = .001$ ).

536 **Early Lyme Disease:** Two adequate and well-controlled studies were performed in patients  
 537 with early Lyme disease. In these studies all patients had to present with physician-documented  
 538 erythema migrans, with or without systemic manifestations of infection. Patients were  
 539 randomized in a 1:1 ratio to a 20-day course of treatment with cefuroxime axetil 500 mg twice  
 540 daily or doxycycline 100 mg 3 times daily. Patients were assessed at 1 month posttreatment for  
 541 success in treating early Lyme disease (Part I) and at 1 year posttreatment for success in  
 542 preventing the progression to the sequelae of late Lyme disease (Part II).

543 A total of 355 adult patients (181 treated with cefuroxime axetil and 174 treated with  
 544 doxycycline) were enrolled in the 2 studies. In order to objectively validate the clinical diagnosis  
 545 of early Lyme disease in these patients, 2 approaches were used: 1) blinded expert reading of  
 546 photographs, when available, of the pretreatment erythema migrans skin lesion; and 2) serologic  
 547 confirmation (using enzyme-linked immunosorbent assay [ELISA] and immunoblot assay  
 548 ["Western" blot]) of the presence of antibodies specific to *Borrelia burgdorferi*, the etiologic  
 549 agent of Lyme disease. By these procedures, it was possible to confirm the physician diagnosis  
 550 of early Lyme disease in 281 (79%) of the 355 study patients. The efficacy data summarized  
 551 below are specific to this "validated" patient subset, while the safety data summarized below  
 552 reflect the entire patient population for the 2 studies.

553 Analysis of the submitted clinical data for evaluable patients in the "validated" patient subset  
 554 yielded the following results:

555

556 **Table 11. Clinical Effectiveness of CEFTIN Tablets Compared to Doxycycline in the**  
 557 **Treatment of Early Lyme Disease**

	Part I (1 Month Posttreatment)*		Part II (1 Year Posttreatment)†	
	CEFTIN (n = 125)	Doxycycline (n = 108)	CEFTIN (n = 105‡)	Doxycycline (n = 83‡)
Satisfactory clinical outcome§	91%	93%	84%	87%
Clinical cure/success	72%	73%	73%	73%
Clinical improvement	19%	19%	10%	13%

558 \* 95% confidence interval around the satisfactory difference for Part I (-0.08, +0.05).

559 † 95% confidence interval around the satisfactory difference for Part II (-0.13, +0.07).

560 ‡ n's include patients assessed as unsatisfactory clinical outcomes (failure + recurrence) in  
 561 Part I (CEFTIN - 11 [5 failure, 6 recurrence]; doxycycline - 8 [6 failure, 2 recurrence]).

562 § Satisfactory clinical outcome includes cure + improvement (Part I) and success +  
 563 improvement (Part II).

564

565 CEFTIN and doxycycline were effective in prevention of the development of sequelae of late  
 566 Lyme disease.

567 **Safety:** Drug-related adverse events affecting the skin were reported significantly more  
 568 frequently by patients treated with doxycycline than by patients treated with cefuroxime axetil  
 569 (12% versus 3%, respectively;  $P = .002$ ), primarily reflecting the statistically significantly higher  
 570 incidence of drug-related photosensitivity reactions in the doxycycline arm versus the  
 571 cefuroxime axetil arm (9% versus 0%, respectively;  $P < .001$ ). While the incidence of drug-related  
 572 gastrointestinal adverse events was similar in the 2 treatment groups (cefuroxime axetil - 13%;  
 573 doxycycline - 11%), the incidence of drug-related diarrhea was statistically significantly higher  
 574 in the cefuroxime axetil arm versus the doxycycline arm (11% versus 3%, respectively;  
 575  $P = .005$ ).

576 **Secondary Bacterial Infections of Acute Bronchitis:** Four randomized, controlled  
 577 clinical studies were performed comparing 5 days versus 10 days of CEFTIN for the treatment of  
 578 patients with secondary bacterial infections of acute bronchitis. These studies enrolled a total of  
 579 1,253 patients (CAE-516  $n = 360$ ; CAE-517  $n = 177$ ; CAEA4001  $n = 362$ ; CAEA4002  $n = 354$ ).  
 580 The protocols for CAE-516 and CAE-517 were identical and compared CEFTIN 250 mg twice  
 581 daily for 5 days, CEFTIN 250 mg twice daily for 10 days, and AUGMENTIN<sup>®</sup> 500 mg 3 times  
 582 daily for 10 days. These 2 studies were conducted simultaneously. CAEA4001 and CAEA4002  
 583 compared CEFTIN 250 mg twice daily for 5 days, CEFTIN 250 mg twice daily for 10 days, and  
 584 CECLOR<sup>®</sup> 250 mg 3 times daily for 10 days. They were otherwise identical to CAE-516 and  
 585 CAE-517 and were conducted over the following 2 years. Patients were required to have  
 586 polymorphonuclear cells present on the Gram stain of their screening sputum specimen, but  
 587 isolation of a bacterial pathogen from the sputum culture was not required for inclusion. The  
 588 following table demonstrates the results of the clinical outcome analysis of the pooled studies  
 589 CAE-516/CAE-517 and CAEA4001/CAEA4002, respectively:

591 **Table 12. Clinical Effectiveness of CEFTIN Tablets 250 mg Twice Daily in Secondary**  
 592 **Bacterial Infections of Acute Bronchitis: Comparison of 5 Versus 10 Days' Treatment**  
 593 **Duration**

	CAE-516 and CAE-517*		CAEA4001 and CAEA4002 <sup>†</sup>	
	5 Day (n = 127)	10 Day (n = 139)	5 Day (n = 173)	10 Day (n = 192)
Clinical success (cure + improvement)	80%	87%	84%	82%
Clinical cure	61%	70%	73%	72%
Clinical improvement	19%	17%	11%	10%

594 \* 95% Confidence interval around the success difference [-0.164, +0.029].

595 <sup>†</sup> 95% Confidence interval around the success difference [-0.061, +0.103].

596

597 The response rates for patients who were both clinically and bacteriologically evaluable were  
 598 consistent with those reported for the clinically evaluable patients.

599           **Safety:** In these clinical trials, 399 patients were treated with CEFTIN for 5 days and  
600 402 patients with CEFTIN for 10 days. No difference in the occurrence of adverse events was  
601 observed between the 2 regimens.

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