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2 **PRESCRIBING INFORMATION**

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

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

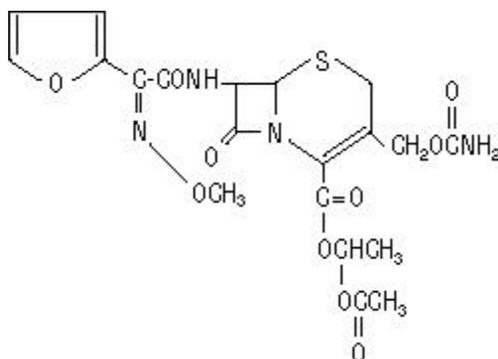
8  
9 To reduce the development of drug-resistant bacteria and maintain the effectiveness of  
10 CEFTIN and other antibacterial drugs, CEFTIN should be used only to treat or prevent infections  
11 that are proven or strongly suspected to be caused by bacteria.

12 **DESCRIPTION**

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

15 Chemically, cefuroxime axetil, the 1-(acetyloxy) ethyl ester of cefuroxime, is (*RS*)-1-  
16 hydroxyethyl (6*R*,7*R*)-7-[2-(2-furyl)glyoxyl-amido]-3-(hydroxymethyl)-8-oxo-5-thia-1-  
17 azabicyclo[4.2.0]-oct-2-ene-2-carboxylate, 7<sup>2</sup>-(*Z*)-(O-methyl-oxime), 1-acetate 3-carbamate. Its  
18 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.

19 Cefuroxime axetil is in the amorphous form and has the following structural formula:  
20



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

27 CEFTIN for Oral Suspension, when reconstituted with water, provides the equivalent of  
28 125 mg or 250 mg of cefuroxime (as cefuroxime axetil) per 5 mL of suspension. CEFTIN for  
29 Oral Suspension contains the inactive ingredients acesulfame potassium, aspartame, povidone  
30 K30, stearic acid, sucrose, tutti-frutti flavoring, and xanthan gum.  
31

32 **CLINICAL PHARMACOLOGY**

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

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

40  
 41 **Table 1. Postprandial Pharmacokinetics of Cefuroxime Administered as CEFTIN Tablets**  
 42 **to Adults<sup>a</sup>**

| Dose <sup>b</sup><br>(Cefuroxime<br>Equivalent) | Peak Plasma<br>Concentration<br>(mcg/mL) | Time of Peak<br>Plasma<br>Concentration<br>(hr) | Mean<br>Elimination<br>Half-life (hr) | AUC<br>(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               |

43 <sup>a</sup> Mean values of 12 healthy adult volunteers.

44 <sup>b</sup> Drug administered immediately after a meal.

45  
 46 **Table 2. Postprandial Pharmacokinetics of Cefuroxime Administered as CEFTIN for Oral**  
 47 **Suspension to Pediatric Patients<sup>a</sup>**

| Dose <sup>b</sup><br>(Cefuroxime<br>Equivalent) | n  | Peak Plasma<br>Concentration<br>(mcg/mL) | Time of Peak<br>Plasma<br>Concentration<br>(hr) | Mean<br>Elimination<br>Half-life<br>(hr) | AUC<br>(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               |

48 <sup>a</sup> Mean age = 23 months.

49 <sup>b</sup> Drug administered with milk or milk products.

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

57 suspension averaged 71% of the peak plasma concentration of the tablets. Therefore, the safety  
58 and effectiveness of both the tablet and oral suspension formulations had to be established in  
59 separate clinical trials.

60

61 **Table 3. Pharmacokinetics of Cefuroxime Administered as 250 mg/5 mL or 2 x 125 mg/5**  
62 **mL CEFTIN for Oral Suspension to Adults<sup>a</sup> With Food**

| <b>Dose<br/>(Cefuroxime<br/>Equivalent)</b> | <b>Peak Plasma<br/>Concentration<br/>(mcg/mL)</b> | <b>Time of Peak<br/>Plasma<br/>Concentration<br/>(hr)</b> | <b>Mean<br/>Elimination<br/>Half-life (hr)</b> | <b>AUC<br/>(mcg•hr/mL)</b> |
|---|---|---|--|----------------------------|
| 250 mg/5 mL                                 | 2.23  | 3   | 1.40   | 8.92                       |
| 2 x 125 mg/5 mL                             | 2.37  | 3   | 1.44   | 9.75                       |

63 <sup>a</sup> Mean values of 18 healthy adult volunteers.

64

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

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

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

77 In a study of 28 adults with normal and markedly impaired renal function, the elimination  
78 half-life of cefuroxime was prolonged in relation to severity of renal impairment. In a study of 16  
79 adult hemodialysis patients with end-stage renal disease, the majority of a cefuroxime dose was  
80 removed by hemodialysis. In a study of 20 elderly patients (mean age = 83.9 years) having a  
81 mean creatinine clearance of 34.9 mL/min, the mean serum elimination half-life was 3.5 hours.  
82 Despite the lower elimination of cefuroxime in geriatric patients, dosage adjustment based on  
83 age is not necessary (see PRECAUTIONS: Geriatric Use).

84 **Microbiology: Mechanism of Action:** Cefuroxime axetil is a bactericidal agent that acts by  
85 inhibition of bacterial cell wall synthesis. Cefuroxime axetil has activity in the presence of some  
86 beta-lactamases, both penicillinases and cephalosporinases, of Gram-negative and Gram-positive  
87 bacteria.

88 **Mechanism of Resistance:** Resistance to cefuroxime axetil is primarily through  
89 hydrolysis by beta-lactamase, alteration of penicillin-binding proteins (PBPs), decreased  
90 permeability and the presence of bacterial efflux pumps.

91 Susceptibility to cefuroxime axetil will vary with geography and time; local susceptibility data  
92 should be consulted, if available. Cefuroxime axetil has been shown to be active against most  
93 isolates of the following bacteria, both in vitro and in clinical infections as described in the  
94 Indications and Usage section:

- 95 • Gram-positive bacteria
- 96 *Staphylococcus aureus* (methicillin-susceptible isolates only)
- 97 *Streptococcus pneumoniae*
- 98 *Streptococcus pyogenes*
- 99 • Gram-negative bacteria
- 100 *Escherichia coli*<sup>a</sup>
- 101 *Klebsiella pneumoniae*<sup>a</sup>
- 102 *Haemophilus influenzae*<sup>b</sup>
- 103 *Haemophilus parainfluenzae*
- 104 *Moraxella catarrhalis*
- 105 *Neisseria gonorrhoeae*

106 <sup>a</sup> Most extended spectrum beta-lactamase (ESBL)-producing and carbapenemase-producing  
107 isolates are resistant to cefuroxime axetil.

108 <sup>b</sup> Beta-lactamase-negative, ampicillin resistant (BLNAR) isolates of *H. influenzae* must be  
109 considered resistant to cefuroxime axetil.

- 110 • Spirochetes
- 111 *Borrelia burgdorferi*

112 The following in vitro data are available, **but their clinical significance is unknown**. At  
113 least 90 percent of the following microorganisms exhibit an in vitro minimum inhibitory  
114 concentration (MIC) less than or equal to the susceptible breakpoint for cefuroxime axetil.  
115 However, the efficacy of cefuroxime axetil in treating clinical infections due to these  
116 microorganisms **has not been** established in adequate and well-controlled clinical trials.

- 117 • Gram-positive bacteria
- 118 *Staphylococcus epidermidis* (methicillin-susceptible isolates only)
- 119 *Staphylococcus saprophyticus* (methicillin-susceptible isolates only)
- 120 *Streptococcus agalactiae*
- 121 • Gram-negative bacteria
- 122 *Morganella morganii*
- 123 *Proteus inconstans*
- 124 *Proteus mirabilis*
- 125 *Providencia rettgeri*
- 126 • Anaerobic bacteria
- 127 *Peptococcus niger*

128 **Susceptibility Test Methods:** When available, the clinical microbiology laboratory should  
129 provide the results of in vitro susceptibility test results for antimicrobial drug products used in  
130 resident hospitals to the physician as periodic reports that describe the susceptibility profile of

131 nosocomial and community-acquired pathogens. These reports should aid the physician in  
 132 selecting an antibacterial drug product for treatment.

133 **Dilution Techniques:** Quantitative methods are used to determine antimicrobial minimal  
 134 inhibitory concentrations (MICs). These MICs provide reproducible estimates of the  
 135 susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a  
 136 standardized test method (broth or agar)<sup>1,2</sup>. The MIC values should be interpreted according to  
 137 criteria provided in Table 4<sup>2,3</sup>.

138 **Diffusion Techniques:** Quantitative methods that require measurement of zone diameters  
 139 also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds.  
 140 The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds.  
 141 The zone size should be determined using a standardized test method<sup>4</sup>. This procedure uses  
 142 paper disks impregnated with 30 mcg cefuroxime axetil to test the susceptibility of  
 143 microorganisms to cefuroxime axetil. The disk diffusion interpretive criteria are provided in  
 144 Table 4<sup>3</sup>.

145  
 146 **Table 4. Susceptibility Test Interpretive Criteria for Cefuroxime Axetil**

| Pathogen                                  | Minimum Inhibitory Concentrations<br>(mcg/mL) |                     |                  | Disk Diffusion Zone Diameters<br>(mm) |                     |                  |
|---|---|---------------------|------------------|---------------------------------------|---------------------|------------------|
|   | (S)<br>Susceptible                            | (I)<br>Intermediate | (R)<br>Resistant | (S)<br>Susceptible                    | (I)<br>Intermediate | (R)<br>Resistant |
| <i>Enterobacteriaceae</i> <sup>a</sup>    | ≤4  | 8 - 16              | ≥32              | ≥23                                   | 15 – 22             | ≤14              |
| <i>Haemophilus spp.</i> <sup>a,b</sup>    | ≤4  | 8                   | ≥16              | ≥20                                   | 17 – 19             | ≤16              |
| <i>Moraxella catarrhalis</i> <sup>a</sup> | ≤4  | 8                   | ≥16              | -                                     | -                   | -                |
| <i>Streptococcus pneumoniae</i>           | ≤1  | 2                   | ≥4               | -                                     | -                   | -                |

147 <sup>a</sup> For *Enterobacteriaceae*, *Haemophilus spp.*, and *Moraxella catarrhalis*, susceptibility interpretive  
 148 criteria are based on a dose of 500 mg every 12 hours in patients with normal renal function.

149 <sup>b</sup> *Haemophilus spp.* includes only isolates of *H. influenzae* and *H. parainfluenzae*.

150  
 151 Susceptibility of staphylococci to cefuroxime axetil may be deduced from testing only  
 152 penicillin and either ceftiofur or oxacillin.

153 Susceptibility of *Streptococcus pyogenes* may be deduced from testing penicillin.

154 A report of Susceptible indicates that the antimicrobial is likely to inhibit growth of the  
 155 pathogen if the antimicrobial compound reaches the concentration at the infection site necessary  
 156 to inhibit growth of the pathogen. A report of Intermediate indicates that the result should be  
 157 considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically  
 158 feasible drugs, the test should be repeated. This category implies possible clinical applicability in  
 159 body sites where the drug is physiologically concentrated or in situations where a high dosage of

160 drug can be used. This category also provides a buffer zone that prevents small uncontrolled  
161 technical factors from causing major discrepancies in interpretation. A report of Resistant  
162 indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial  
163 compound reaches the concentrations usually achievable at the infection site; other therapy  
164 should be selected.

165 **Quality Control:** Standardized susceptibility test procedures require the use of laboratory  
166 controls to monitor and ensure the accuracy and precision of supplies and reagents used in the  
167 assay, and the techniques of the individual performing the test<sup>1,2,4</sup>. The QC ranges for MIC and  
168 disk diffusion testing using the 30 mcg disk are provided in Table 5<sup>3</sup>.

169

170 **Table 5. Acceptable Quality Control (QC) Ranges for Cefuroxime Axetil**

| QC Strain                                  | Minimum Inhibitory Concentrations (mcg/mL) | Disk Diffusion Zone Diameters (mm) |
|--|--|------------------------------------|
| <i>Escherichia coli</i> ATCC 25922         | 2 - 8                                      | 20 – 26                            |
| <i>Staphylococcus aureus</i> ATCC 25923    | -  | 27 – 35                            |
| <i>Staphylococcus aureus</i> ATCC 29213    | 0.5 - 2                                    | -                                  |
| <i>Streptococcus pneumoniae</i> ATCC 49619 | 0.25 - 1                                   | -                                  |
| <i>Haemophilus influenzae</i> ATCC 49766   | 0.25 - 1                                   | 28 – 36                            |
| <i>Neisseria gonorrhoeae</i> ATCC 49226    | 0.25 - 1                                   | 33 – 41                            |

171

## 172 **INDICATIONS AND USAGE**

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

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

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

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

- 188 **2. Acute Bacterial Otitis Media** caused by *Streptococcus pneumoniae*, *Haemophilus*  
189 *influenzae* (including beta-lactamase-producing strains), *Moraxella catarrhalis* (including  
190 beta-lactamase-producing strains), or *Streptococcus pyogenes*.
- 191 **3. Acute Bacterial Maxillary Sinusitis** caused by *Streptococcus pneumoniae* or *Haemophilus*  
192 *influenzae* (non-beta-lactamase-producing strains only) (see CLINICAL STUDIES).
- 193 **NOTE:** In view of the insufficient numbers of isolates of beta-lactamase-producing strains of  
194 *Haemophilus influenzae* and *Moraxella catarrhalis* that were obtained from clinical trials with  
195 CEFTIN Tablets for patients with acute bacterial maxillary sinusitis, it was not possible to  
196 adequately evaluate the effectiveness of CEFTIN Tablets for sinus infections known,  
197 suspected, or considered potentially to be caused by beta-lactamase-producing *Haemophilus*  
198 *influenzae* or *Moraxella catarrhalis*.
- 199 **4. Acute Bacterial Exacerbations of Chronic Bronchitis and Secondary Bacterial**  
200 **Infections of Acute Bronchitis** caused by *Streptococcus pneumoniae*, *Haemophilus*  
201 *influenzae* (beta-lactamase negative strains), or *Haemophilus parainfluenzae* (beta-lactamase  
202 negative strains) (see DOSAGE AND ADMINISTRATION and CLINICAL STUDIES).
- 203 **5. Uncomplicated Skin and Skin-Structure Infections** caused by *Staphylococcus aureus*  
204 (including beta-lactamase-producing strains) or *Streptococcus pyogenes*.
- 205 **6. Uncomplicated Urinary Tract Infections** caused by *Escherichia coli* or *Klebsiella*  
206 *pneumoniae*.
- 207 **7. Uncomplicated Gonorrhea**, urethral and endocervical, caused by penicillinase-producing  
208 and non-penicillinase-producing strains of *Neisseria gonorrhoeae* and uncomplicated  
209 gonorrhea, rectal, in females, caused by non-penicillinase-producing strains of *Neisseria*  
210 *gonorrhoeae*.
- 211 **8. Early Lyme Disease (erythema migrans)** caused by *Borrelia burgdorferi*.
- 212 **CEFTIN for Oral Suspension:** CEFTIN for Oral Suspension is indicated for the treatment of  
213 pediatric patients 3 months to 12 years of age with mild to moderate infections caused by  
214 susceptible strains of the designated microorganisms in the conditions listed below. The safety  
215 and effectiveness of CEFTIN for Oral Suspension in the treatment of infections other than those  
216 specifically listed below have not been established either by adequate and well-controlled trials  
217 or by pharmacokinetic data with which to determine an effective and safe dosing regimen.
- 218 **1. Pharyngitis/Tonsillitis** caused by *Streptococcus pyogenes*.
- 219 **NOTE:** The usual drug of choice in the treatment and prevention of streptococcal infections,  
220 including the prophylaxis of rheumatic fever, is penicillin given by the intramuscular route.  
221 CEFTIN for Oral Suspension is generally effective in the eradication of streptococci from the  
222 nasopharynx; however, substantial data establishing the efficacy of cefuroxime in the  
223 subsequent prevention of rheumatic fever are not available. Please also note that in all clinical  
224 trials, all isolates had to be sensitive to both penicillin and cefuroxime. There are no data from  
225 adequate and well-controlled trials to demonstrate the effectiveness of cefuroxime in the  
226 treatment of penicillin-resistant strains of *Streptococcus pyogenes*.

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

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

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

## 238 **CONTRAINDICATIONS**

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

## 241 **WARNINGS**

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

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

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

264 *C. difficile* produces toxins A and B which contribute to the development of CDAD.  
265 Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these

266 infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be  
267 considered in all patients who present with diarrhea following antibiotic use. Careful medical  
268 history is necessary since CDAD has been reported to occur over 2 months after the  
269 administration of antibacterial agents.

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

## 274 **PRECAUTIONS**

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

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

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

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

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

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

299 **Information for Patients/Caregivers (Pediatric): *Phenylketonurics:*** CEFTIN for Oral  
300 Suspension 125 mg/5 mL contains phenylalanine 11.8 mg per 5 mL (1 teaspoonful) constituted  
301 suspension. CEFTIN for Oral Suspension 250 mg/5 mL contains phenylalanine 25.2 mg per  
302 5 mL (1 teaspoonful) constituted suspension.

303 1. During clinical trials, the tablet was tolerated by pediatric patients old enough to swallow the  
304 cefuroxime axetil tablet whole. The crushed tablet has a strong, persistent, bitter taste and

305 should not be administered to pediatric patients in this manner. Pediatric patients who cannot  
306 swallow the tablet whole should receive the oral suspension.

- 307 2. Discontinuation of therapy due to taste and/or problems of administering this drug occurred  
308 in 1.4% of pediatric patients given the oral suspension. Complaints about taste (which may  
309 impair compliance) occurred in 5% of pediatric patients.
- 310 3. Patients should be counseled that antibacterial drugs, including CEFTIN, should only be used  
311 to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When  
312 CEFTIN is prescribed to treat a bacterial infection, patients should be told that although it is  
313 common to feel better early in the course of therapy, the medication should be taken exactly  
314 as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the  
315 effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will  
316 develop resistance and will not be treatable by CEFTIN or other antibacterial drugs in the  
317 future.

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

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

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

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

334 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Although lifetime studies in  
335 animals have not been performed to evaluate carcinogenic potential, no mutagenic activity was  
336 found for cefuroxime axetil in a battery of bacterial mutation tests. Positive results were obtained  
337 in an in vitro chromosome aberration assay; however, negative results were found in an in vivo  
338 micronucleus test at doses up to 1.5 g/kg. Reproduction studies in rats at doses up to  
339 1,000 mg/kg/day (9 times the recommended maximum human dose based on mg/m<sup>2</sup>) have  
340 revealed no impairment of fertility.

341 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Reproduction studies have been  
342 performed in mice at doses up to 3,200 mg/kg/day (14 times the recommended maximum human  
343 dose based on mg/m<sup>2</sup>) and in rats at doses up to 1,000 mg/kg/day (9 times the recommended  
344 maximum human dose based on mg/m<sup>2</sup>) and have revealed no evidence of impaired fertility or

345 harm to the fetus due to cefuroxime axetil. There are, however, no adequate and well-controlled  
346 studies in pregnant women. Because animal reproduction studies are not always predictive of  
347 human response, this drug should be used during pregnancy only if clearly needed.

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

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

351 **Pediatric Use:** The safety and effectiveness of CEFTIN have been established for pediatric  
352 patients aged 3 months to 12 years for acute bacterial maxillary sinusitis based upon its approval  
353 in adults. Use of CEFTIN in pediatric patients is supported by pharmacokinetic and safety data in  
354 adults and pediatric patients, and by clinical and microbiological data from adequate and  
355 well-controlled studies of the treatment of acute bacterial maxillary sinusitis in adults and of  
356 acute otitis media with effusion in pediatric patients. It is also supported by postmarketing  
357 adverse events surveillance (see CLINICAL PHARMACOLOGY, INDICATIONS AND  
358 USAGE, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and CLINICAL  
359 STUDIES).

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

## 368 **ADVERSE REACTIONS**

369 **CEFTIN TABLETS IN CLINICAL TRIALS: Multiple-Dose Dosing Regimens: 7 to**  
370 **10 Days Dosing:** Using multiple doses of cefuroxime axetil tablets, 912 patients were treated  
371 with cefuroxime axetil (125 to 500 mg twice daily). There were no deaths or permanent  
372 disabilities thought related to drug toxicity. Twenty (2.2%) patients discontinued medication due  
373 to adverse events thought by the investigators to be possibly, probably, or almost certainly  
374 related to drug toxicity. Seventeen (85%) of the 20 patients who discontinued therapy did so  
375 because of gastrointestinal disturbances, including diarrhea, nausea, vomiting, and abdominal  
376 pain. The percentage of cefuroxime axetil tablet-treated patients who discontinued study drug  
377 because of adverse events was very similar at daily doses of 1,000, 500, and 250 mg (2.3%,  
378 2.1%, and 2.2%, respectively). However, the incidence of gastrointestinal adverse events  
379 increased with the higher recommended doses.

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

383

384 **Table 6. Adverse Reactions—CEFTIN Tablets**  
 385 **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<br><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       |                            |      |

386  
 387 **5-Day Experience (see CLINICAL STUDIES):** In clinical trials using CEFTIN in a dose  
 388 of 250 mg twice daily in the treatment of secondary bacterial infections of acute bronchitis,  
 389 399 patients were treated for 5 days and 402 patients were treated for 10 days. No difference in  
 390 the occurrence of adverse events was found between the 2 regimens.

391 **In Clinical Trials for Early Lyme Disease With 20 Days Dosing:** Two multicenter  
 392 trials assessed cefuroxime axetil tablets 500 mg twice a day for 20 days. The most common  
 393 drug-related adverse experiences were diarrhea (10.6% of patients), Jarisch-Herxheimer reaction  
 394 (5.6%), and vaginitis (5.4%). Other adverse experiences occurred with frequencies comparable  
 395 to those reported with 7 to 10 days dosing.

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

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

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

404  
 405 **Table 7. Adverse Reactions—CEFTIN Tablets**  
 406 **1-g Single-Dose Regimen for Uncomplicated Gonorrhea—Clinical Trials**

|                            |                          |
|----------------------------|--------------------------|
| Incidence ≥1%              | Nausea/vomiting 6.8%     |
|                            | Diarrhea 4.2%            |
| Incidence<br><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    |

407

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

409 In clinical trials using multiple doses of cefuroxime axetil powder for oral suspension,  
 410 pediatric patients (96.7% of whom were younger than 12 years of age) were treated with the  
 411 recommended dosages of cefuroxime axetil (20 to 30 mg/kg/day divided twice a day up to a  
 412 maximum dose of 500 or 1,000 mg/day, respectively). There were no deaths or permanent  
 413 disabilities in any of the patients in these studies. Eleven US patients (1.2%) discontinued  
 414 medication due to adverse events thought by the investigators to be possibly, probably, or almost

415 certainly related to drug toxicity. The discontinuations were primarily for gastrointestinal  
 416 disturbances, usually diarrhea or vomiting. During clinical trials, discontinuation of therapy due  
 417 to the taste and/or problems with administering this drug occurred in 13 (1.4%) pediatric patients  
 418 enrolled at centers in the United States.

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

422

423 **Table 8. Adverse Reactions—CEFTIN for Oral Suspension**

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

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

425

426 **POSTMARKETING EXPERIENCE WITH CEFTIN PRODUCTS**

427 In addition to adverse events reported during clinical trials, the following events have been  
 428 identified during clinical practice in patients treated with CEFTIN Tablets or with CEFTIN for

429 Oral Suspension and were reported spontaneously. Data are generally insufficient to allow an  
430 estimate of incidence or to establish causation.

431 **General:** The following hypersensitivity reactions have been reported: Anaphylaxis,  
432 angioedema, pruritus, rash, serum sickness-like reaction, urticaria.

433 **Gastrointestinal:** Pseudomembranous colitis (see WARNINGS).

434 **Hematologic:** Hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, and  
435 increased prothrombin time.

436 **Hepatic:** Hepatic impairment including hepatitis and cholestasis, jaundice.

437 **Neurologic:** Seizure, encephalopathy.

438 **Skin:** Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

439 **Urologic:** Renal dysfunction.

#### 440 **CEPHALOSPORIN-CLASS ADVERSE REACTIONS**

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

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

#### 450 **OVERDOSAGE**

451 Overdosage of cephalosporins can cause cerebral irritation leading to convulsions or  
452 encephalopathy. Serum levels of cefuroxime can be reduced by hemodialysis and peritoneal  
453 dialysis.

#### 454 **DOSAGE AND ADMINISTRATION**

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

458

459 **Table 9. CEFTIN Tablets**  
 460 (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 twice daily        | 10              |
| Acute bacterial maxillary sinusitis                       | 250 mg twice daily        | 10              |
| Acute bacterial exacerbations of chronic bronchitis       | 250 or 500 mg twice daily | 10 <sup>a</sup> |
| Secondary bacterial infections of acute bronchitis        | 250 or 500 mg twice daily | 5-10            |
| Uncomplicated skin and skin-structure infections          | 250 or 500 mg twice daily | 10              |
| Uncomplicated urinary tract infections                    | 250 mg twice daily        | 7-10            |
| Uncomplicated gonorrhea                                   | 1,000 mg once daily       | single dose     |
| Early Lyme disease  | 500 mg twice daily        | 20              |
| <b>Pediatric Patients (who can swallow tablets whole)</b> |                           |                 |
| Acute otitis media  | 250 mg twice daily        | 10              |
| Acute bacterial maxillary sinusitis                       | 250 mg twice daily        | 10              |

461 <sup>a</sup> The safety and effectiveness of CEFTIN administered for less than 10 days in patients with  
 462 acute exacerbations of chronic bronchitis have not been established.

463  
 464 **CEFTIN for Oral Suspension:** CEFTIN for Oral Suspension may be administered to  
 465 pediatric patients ranging in age from 3 months to 12 years, according to dosages in Table 10:  
 466

467 **Table 10. CEFTIN for Oral Suspension**  
 468 (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 twice daily | 500 mg             | 10              |
| Acute otitis media                               | 30 mg/kg/day divided twice daily | 1,000 mg           | 10              |
| Acute bacterial maxillary sinusitis              | 30 mg/kg/day divided twice daily | 1,000 mg           | 10              |
| Impetigo   | 30 mg/kg/day divided twice daily | 1,000 mg           | 10              |

469

470 **Patients with Renal Impairment:** Because cefuroxime is eliminated primarily by the kidney,  
471 a dosage interval adjustment is required for patients whose creatinine clearance is <30 mL/min,  
472 as listed in Table 11.

473

474 **Table 11. Dosing in Patients with Renal Impairment**

| <b>Creatinine Clearance (mL/min)</b> | <b>Recommended Dosage</b>   |
|--------------------------------------|---|
| ≥30                                  | No dosage adjustment  |
| 10 to <30                            | Standard individual dose given every 24 hours                                 |
| <10 (without hemodialysis)           | Standard individual dose given every 48 hours                                 |
| Hemodialysis                         | A single additional standard dose should be given at the end of each dialysis |

475

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

- 478 1. Shake the bottle to loosen the powder.  
479 2. Remove the cap.  
480 3. Add the total amount of water for reconstitution (see Table 12) and replace the cap.  
481 4. Invert the bottle and vigorously rock the bottle from side to side so that water rises through  
482 the powder.  
483 5. Once the sound of the powder against the bottle disappears, turn the bottle upright and  
484 vigorously shake it in a diagonal direction.

485

486 **Table 12. Amount of Water Required for Reconstitution of Labeled Volumes of CEFTIN**  
487 **for Oral Suspension**

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

488

489 **NOTE: SHAKE THE ORAL SUSPENSION WELL BEFORE EACH USE.** Replace cap  
490 securely after each opening. Store the reconstituted suspension between 2° and 8°C (36° and  
491 46°F) (in a refrigerator). DISCARD AFTER 10 DAYS.

#### 492 **HOW SUPPLIED**

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

496 20 Tablets/Bottle                      NDC 0173-0387-00

497 CEFTIN Tablets, 500 mg of cefuroxime (as cefuroxime axetil), are white, capsule-shaped,  
498 film-coated tablets engraved with "GX EG2" on one side and blank on the other side as follows:  
499 20 Tablets/Bottle NDC 0173-0394-00

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

502  
503 **CEFTIN for Oral Suspension:** CEFTIN for Oral Suspension is provided as dry, white to  
504 off-white, tutti-frutti-flavored powder. When reconstituted as directed, CEFTIN for Oral  
505 Suspension provides the equivalent of 125 mg or 250 mg of cefuroxime (as cefuroxime axetil)  
506 per 5 mL of suspension. It is supplied in amber glass bottles as follows:

507 **125 mg/5 mL:**

508 100-mL Suspension NDC 0173-0740-00

509 **250 mg/5 mL:**

510 50-mL Suspension NDC 0173-0741-10

511 100-mL Suspension NDC 0173-0741-00

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

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

## 515 **CLINICAL STUDIES**

516 **Ceftin Tablets: Acute Bacterial Maxillary Sinusitis:** One adequate and well-controlled  
517 study was performed in patients with acute bacterial maxillary sinusitis. In this study each  
518 patient had a maxillary sinus aspirate collected by sinus puncture before treatment was initiated  
519 for presumptive acute bacterial sinusitis. All patients had to have radiographic and clinical  
520 evidence of acute maxillary sinusitis. As shown in the following summary of the study, the  
521 general clinical effectiveness of CEFTIN Tablets was comparable to an oral antimicrobial agent  
522 that contained a specific beta-lactamase inhibitor in treating acute maxillary sinusitis. However,  
523 sufficient microbiology data were obtained to demonstrate the effectiveness of CEFTIN Tablets  
524 in treating acute bacterial maxillary sinusitis due only to *Streptococcus pneumoniae* or non-  
525 beta-lactamase-producing *Haemophilus influenzae*. An insufficient number of beta-lactamase-  
526 producing *Haemophilus influenzae* and *Moraxella catarrhalis* isolates were obtained in this trial  
527 to adequately evaluate the effectiveness of CEFTIN Tablets in the treatment of acute bacterial  
528 maxillary sinusitis due to these 2 organisms.

529 This study enrolled 317 adult patients, 132 patients in the United States and 185 patients in  
530 South America. Patients were randomized in a 1:1 ratio to cefuroxime axetil 250 mg twice daily  
531 or an oral antimicrobial agent that contained a specific beta-lactamase inhibitor. An  
532 intent-to-treat analysis of the submitted clinical data yielded the following results:  
533

534 **Table 13. Clinical Effectiveness of CEFTIN Tablets Compared to Beta-Lactamase**  
 535 **Inhibitor-Containing Control Drug in the Treatment of Acute Bacterial Maxillary Sinusitis**

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

536 <sup>a</sup> 95% Confidence interval around the success difference [-0.08, +0.32].

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

538

539 In this trial and in a supporting maxillary puncture trial, 15 evaluable patients had non-  
 540 beta-lactamase-producing *Haemophilus influenzae* as the identified pathogen. Ten (10) of these  
 541 15 patients (67%) had their pathogen (non-beta-lactamase-producing *Haemophilus influenzae*)  
 542 eradicated. Eighteen (18) evaluable patients had *Streptococcus pneumoniae* as the identified  
 543 pathogen. Fifteen (15) of these 18 patients (83%) had their pathogen (*Streptococcus*  
 544 *pneumoniae*) eradicated.

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

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

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

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

568  
569  
570

**Table 14. Clinical Effectiveness of CEFTIN Tablets Compared to Doxycycline in the Treatment of Early Lyme Disease**

|  | Part I<br>(1 Month Posttreatment) <sup>a</sup> |                          | Part II<br>(1 Year Posttreatment) <sup>b</sup> |                                       |
|--|--|--------------------------|--|---------------------------------------|
|  | CEFTIN<br>(n = 125)                            | Doxycycline<br>(n = 108) | CEFTIN<br>(n = 105 <sup>c</sup> )              | Doxycycline<br>(n = 83 <sup>c</sup> ) |
| Satisfactory clinical outcome <sup>d</sup> | 91%  | 93%                      | 84%  | 87%                                   |
| Clinical cure/success                      | 72%  | 73%                      | 73%  | 73%                                   |
| Clinical improvement                       | 19%  | 19%                      | 10%  | 13%                                   |

571 <sup>a</sup> 95% confidence interval around the satisfactory difference for Part I (-0.08, +0.05).  
572 <sup>b</sup> 95% confidence interval around the satisfactory difference for Part II (-0.13, +0.07).  
573 <sup>c</sup> n's include patients assessed as unsatisfactory clinical outcomes (failure + recurrence) in  
574 Part I (CEFTIN - 11 [5 failure, 6 recurrence]; doxycycline - 8 [6 failure, 2 recurrence]).  
575 <sup>d</sup> Satisfactory clinical outcome includes cure + improvement (Part I) and success +  
576 improvement (Part II).  
577

578 CEFTIN and doxycycline were effective in prevention of the development of sequelae of late  
579 Lyme disease.

580 **Safety:** Drug-related adverse events affecting the skin were reported significantly more  
581 frequently by patients treated with doxycycline than by patients treated with cefuroxime axetil  
582 (12% versus 3%, respectively;  $P = .002$ ), primarily reflecting the statistically significantly higher  
583 incidence of drug-related photosensitivity reactions in the doxycycline arm versus the  
584 cefuroxime axetil arm (9% versus 0%, respectively;  $P < .001$ ). While the incidence of drug-related  
585 gastrointestinal adverse events was similar in the 2 treatment groups (cefuroxime axetil - 13%;  
586 doxycycline - 11%), the incidence of drug-related diarrhea was statistically significantly higher  
587 in the cefuroxime axetil arm versus the doxycycline arm (11% versus 3%, respectively;  
588  $P = .005$ ).

589 **Secondary Bacterial Infections of Acute Bronchitis:** Four randomized, controlled  
590 clinical studies were performed comparing 5 days versus 10 days of CEFTIN for the treatment of  
591 patients with secondary bacterial infections of acute bronchitis. These studies enrolled a total of  
592 1,253 patients (CAE-516 n = 360; CAE-517 n = 177; CAEA4001 n = 362; CAEA4002 n = 354).  
593 The protocols for CAE-516 and CAE-517 were identical and compared CEFTIN 250 mg twice  
594 daily for 5 days, CEFTIN 250 mg twice daily for 10 days, and AUGMENTIN<sup>®</sup> 500 mg 3 times  
595 daily for 10 days. These 2 studies were conducted simultaneously. CAEA4001 and CAEA4002  
596 compared CEFTIN 250 mg twice daily for 5 days, CEFTIN 250 mg twice daily for 10 days, and  
597 CECLOR<sup>®</sup> 250 mg 3 times daily for 10 days. They were otherwise identical to CAE-516 and  
598 CAE-517 and were conducted over the following 2 years. Patients were required to have  
599 polymorphonuclear cells present on the Gram stain of their screening sputum specimen, but  
600 isolation of a bacterial pathogen from the sputum culture was not required for inclusion. The

601 following table demonstrates the results of the clinical outcome analysis of the pooled studies  
 602 CAE-516/CAE-517 and CAEA4001/CAEA4002, respectively:

603

604 **Table 15. Clinical Effectiveness of CEFTIN Tablets 250 mg Twice Daily in Secondary**  
 605 **Bacterial Infections of Acute Bronchitis: Comparison of 5 Versus 10 Days' Treatment**  
 606 **Duration**

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

607 <sup>a</sup> 95% Confidence interval around the success difference [-0.164, +0.029].

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

609

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

612 **Safety:** In these clinical trials, 399 patients were treated with CEFTIN for 5 days and  
 613 402 patients with CEFTIN for 10 days. No difference in the occurrence of adverse events was  
 614 observed between the 2 regimens.

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