CEFTIN® Tablets (cefuroxime axetil tablets)

CEFTIN® for Oral Suspension (cefuroxime axetil powder for oral suspension)

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

DESCRIPTION

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



CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY Absorption and Metabolism: After oral administration, cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolyzed by nonspecific esterases in the intestinal mucosa and blood to cefuroxime. Cefuroxime is subsequently distributed throughout the extracellular fluids. The axetil moiety is metabolized to acetaldehyde and acetic acid. Pharmacokinetics: Approximately 50% of serum cefuroxime is bound to protein. Serum pharmacokinetic parameters for CEFTIN Tablets and CEFTIN for Oral Suspen-sion are shown in Tables 1 and 2.

Table 1. Postprandial Pharmacokinetics of Cefuroxime Administered as CEFTIN Tablets to Adults

Dose [†] (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

*Mean values of 12 healthy adult volunteers. [†]Drug administered immediately after a meal.

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

Dose [†] (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 15 mg/kg 20 mg/kg	8 12 8	3.3 5.1 7.0	3.6 2.7 3.1	1.4 1.9 1.9	12.4 22.5 32.8

*Mean age = 23 months. [†]Drug administered with milk or milk products.

Comparative Pharmacokinetic Properties: A 250 mg/5 mL-dose of CEFTIN Suspen-sion is bioequivalent to 2 times 125 mg/5 mL-dose of CEFTIN Suspension when administered with food (see Table 3). CEFTIN for Oral Suspension was not bioequiv-alent to CEFTIN Tablets when tested in healthy adults. The tablet and powder for oral suspension formulations are NOT substitutable on a milligram-per-milligram basis. The area under the curve for the suspension averaged 91% of that for the tablet, and the peak plasma concentration for the suspension averaged 71% of the peak plasma concentration of the tablets. Therefore, the safety and effectiveness of both the tablet and oral suspension formulations had to be established in separate clinical trials. clinical trials.

Table 3. Pharmacokinetics of Cefuroxime Administered as 250 mg/5 mL or 2 x 125 mg/5 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)	AUC (mcg-hr mL)
250 mg/5 mL 2 x 125 mg/5 mL	2.23 2.37	3 3	1.40 1.44	8.92 9.75

*Mean values of 18 healthy adult volunteers

Food Effect on Pharmacokinetics: Absorption of the tablet is greater when taken after food (absolute bioavailability of CEFTIN Tablets increases from 37% to 52%). Despite this difference in absorption, the clinical and bacteriologic responses of patients were independent of food intake at the time of tablet administration in 2 studies where this was assessed. All pharmacokinetic and clinical effectiveness and safety studies in pediatric attent to the subsection formulation were conducted in the ford cath a No.

All pharmacokinetic and clinical effectiveness and safety studies in pediatric patients using the suspension formulation were conducted in the fed state. No data are available on the absorption kinetics of the suspension formulation when administered to fasted pediatric patients. Renal Excretion: Cefuroxime is excreted unchanged in the urine; in adults, approx-imately 50% of the administered dose is recovered in the urine within 12 hours. The pharmacokinetics of cefuroxime in the urine of pediatric patients have not been studied at this time. Until further data are available, the renal pharmacokinetic properties of cefuroxime axetil established in adults should not be extrapolated to pediatric patients. Because cefuroxime is renally excreted, the serum half-life is prolonged in patients with reduced renal function. In a study of 20 elderly patients (mean age = 83.9 years), having a mean creatinine clearance of 34.9 mL/min, the mean serum elimination half-life was 3.5 hours. Despite the lower elimination of cefuroxime in geriatric patients, dosage adjustment based on age is not necessary (see PRECAUTIONS: Geriatric Use). **Microbiology:** The in vivo bactericidal activity of cefuroxime axetil is due to cefu-roxime's binding to essential target proteins and the resultant inhibition of cell-wall synthesis.

wall synthesis. Cefuroxime has bactericidal activity against a wide range of common pathogens, including many beta-lactamase-producing strains. Cefuroxime is stable to many bacterial beta-lactamases, especially plasmid-mediated enzymes that are commonly found in extremelation found in enterobacteriaceae. Cefuroxime has been demonstrated to be active against most strains of the

Ceturoxime has been demonstrated to be active against most strains of the following microorganisms both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section (see INDICATIONS AND USAGE section). Aerobic Gram-Positive Microorganisms: Staphylococcus aureus (including beta-lactamase-producing strains) Streptococcus pyogenes Aerobic Gram-Negative Microorganisms: Fscherichia coli

<u>Microorganism</u> Escherichia coli ATCC 25922 Staphylococcus aureus ATCC 25923

Zone Diameter (mm) 20-26 27-35

- Escherichia coli ATCC 25922 20-26 Staphylococcus aureus ATCC 25923 27-35
 INDICATIONS AND USAGE
 NOTE: CEFTIN TABLETS AND CEFTIN FOR ORAL SUSPENSION ARE NOT BIO-EQUIVALENT AND ARE NOT SUBSTITUTABLE ON A MILLIGRAM-PER-MILLIGRAM BASIS (SEE CLINICAL PHARMACOLOGY).
 CEFTIN Tablets: CEFTIN Tablets are indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorgan-isms in the conditions listed below:
 Pharyngits/Tonsillitis caused by Streptococcus pyogenes.
 NOTE: The usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever, is penicillin given by the intramuscular oute. CEFTIN Tablets are generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cefuroxime in the subsequent prevention of rheumatic fever are not available. Please also note that in all clinical trials, all isolates had to be sensitive to both penicillin and cefuroxime. There are no data from adequate and well-controlled trials to demonstrate the effectiveness of cefuroxime in the treatment of penicillin-resistant strains of Streptococcus progenes.
 Acute Bacterial Ottiis Media caused by Streptococcus pneumoniae, Haemophilus influenzae (including beta-lactamase-producing strains), Noravella catarrhalis (including beta-lactamase-producing strains), Noravella catarrhalis (including beta-lactamase-producing strains), Noravella catarrhalis (including beta-lactamase-producing strains only). (See CLINICAL STUDIES section.)
 NOTE: In view of the insufficient numbers of isolates of beta-lactamase-producing strains of Haemophilus influenzae and Moravella catarrhalis that were obtained from clinical trials with CEFTIN Tablets for patients with acute bacterial maxillary sinusitis, it was not possible to adequately evaluate the effectiveness of CEFTIN Tabl

- Oncomplicated Gonorrhea, urethral and endocervical, caused by penicillinase-producing and non-penicillinase-producing strains of *Neisseria gonorrhoeae* and uncomplicated gonorrhea, rectal, in females, caused by non-penicillinase-producing strains of *Neisseria gonorrhoeae*.
 Early Lyme Disease (erythema migrans) caused by *Borrelia burgdorferi*.

- Early Lyme Disease (erythema migrans) caused by Borrelia burgdorferi.
 CEFTIN for Oral Suspension: CEFTIN for Oral Suspension is indicated for the treatment of pediatric patients 3 months to 12 years of age with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below. The safety and effectiveness of CEFTIN for Oral Suspension in the treatment of infections other than those specifically listed below have not been established litter by adequate and well-controlled trials or by pharmacokinetic data with which to determine an effective and safe dosing regimen.
 Pharynglist/Tonsilitis caused by Streptococcus progenes. NOTE: The usual drug of choice in the treatment and prevention of streptococcial infections, including the prophylaxis of rheumatic fever, is penicillin given by the intramuscular route. CEFTIN for Oral Suspension is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cefuroxime in the subsequent prevention of rheumatic fever are not available. Please also note that in all clinical trials, all isolates had to be sensitive to both penicillin ad ecfuroxime. There are no data from adequate and well-controlled trials to demonstrate the effectiveness of cefuroxime in the treatment of penicillin-resistant strains of *Streptococcus progenes*.
 Acute Bacterial Ottis Media caused by *Streptococcus progenes*.
 Impetigo caused by Staphylococcus averus (including beta-lactamase-producing strains), or *Streptococcus progenes*.
 Impetigo caused by Staphylococcus averus (including beta-lactamase-producing strains), or Streptococcus progenes.
 To reduce the development of drug-resistant bacteria and maintain the effective

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

CONTRAINDICATIONS CEFTIN products are contraindicated in patients with known allergy to the cepha-losporin group of antibiotics.

WARNINGS

NARNINGS CEFTIN TABLETS AND CEFTIN FOR ORAL SUSPENSION ARE NOT BIOEQUIVALENT AND ARE THEREFORE NOT SUBSTITUTABLE ON A MILLIGRAM-PER-MILLIGRAM BASIS (SEE CLINICAL PHARMACOLOGY). BEFORE THERAPY WITH CEFTIN PRODUCTS IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT STORE CEPHALOSOPO-RINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCTS TO BE GIVEN TO PENICILLINS, OR OTHER DRUGS. VIETHIS PRODUCTS TO BE GIVEN TO PENICILLINS SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF A CLINICALLY SIGNIFICANT ALLERGIC REACTION TO CEFTIN PRODUCTS OCCURS, DISCONTINUE THE DRUG AND INSTITUTE APPROPRIATE THERAPY. SERIOUS ACUTE HYPERSENSITIVITY REAC-TIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTI-HISTAMINES, CORTICOSTREDIOS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED. PSEUGAMEMDRAIDUS COILIS HAS BEEN REPORTED WITH BEATHERING. Therefore, it is important to consider this diagnosis in patients who present with diarrhe subsequent to the administration or antibacterial agents. Tratament with antibacterial agents alters normal flora of the colon and may permit tovergrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. After the diagnosis of pseudomembranous coliti

Autor should be given to Intalagement with nuise and electrolytes, protein supplementation, and treatment with an antibacterial drug effective against *Clostridium difficile*. **PRECAUTIONS General:** As with other broad-spectrum antibiotics, prolonged administration of cefuroxime axelil may result in overgrowth of nonsusceptible microorganisms. If superinfection occurs during therapy, appropriate measures should be taken. Cephalosporins, including cefuroxime axelil, should be given with caution to patients receiving concurrent treatment with potent diuretics because these diuretics are suspected of adversely affecting renal function. Cefuroxime axelil, as with other broad-spectrum antibiotics, should be prescribed with caution in individuals with a history of colitis. The safety and effectiveness of cefuroxime axelil, as with outer broad-spectrum antibiotics, should be prescribed with caution in individuals with a history of colitis. The safety and effectiveness of cefuroxime axelil have not been established in patients with gastrointestinal malabsorption were excluded from participating in clinical trials of cefuroxime axelil. Cephalosporins may be associated with a fall in prothrombin time should be monitored in patients with gastrointestinal malabsorption were excluded from participating in clinical trials of cefuroxime axelil. Prescribing CEFTIN in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. **Information for Patients/Caregivers (Pediatric): Phenylketonurics:** CEFTIN for Oral Suspension 125 mg/5 mL contains phenylalanine 11.8 mg per 5 mL (1 teasponful) constituted suspension. 1. During clinical trials, the tablet was tolerated by pediatric patients old enough to swallow the cefuroxime axelil tablet whole. The crushed table thas a strong, persistent, bitter taste and should note badministered to pediatric patients in this manner. Pedida

ontinuation of therapy due to taste and/or problems

Escherichia coli Haemophius influenzae (including beta-lactamase–producing strains) Haemophilus parainfluenzae Klebsiella pneumoniae Moraxella catarrhalis (including beta-lactamase–producing strains) Neisseria gonorrhoeae (including beta-lactamase–producing strains)

Spirochetes: Borrelia burgdorferi

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

Initiation of the contract of the child significance of these initiality is unknown. Cefuroxime exhibits in vitro minimum inhibitory concentrations (MICs) of 4.0 mcg/mL or less (systemic susceptible breakpoint) against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of cefuroxime in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. *Aerobic Gram-Positive Microorganisms:* Staphylococcus saprophyticus Straptococcus saprophyticus Straptococcus saprophyticus Straptococcus faecalis), are resistant to cefuroxime. Methicillin-resistant staphylococci are resistant to cefuroxime. *Aerobic Gram-Negative Microorganisms:* Morganella morgani Proteus inconstans Proteus microstans

Proteus mirabilis Providencia rettg

rovidencia rettger

NOTE: /seudomonas spp., Campylobacter spp., Acinetobacter calcoaceticus, and most strains of Serratia spp. and Proteus vulgaris are resistant to most first- and second-generation cephalosporins. Some strains of Morganella morganii, Enterobacter cloacae, and Citrobacter spp. have been shown by in vitro tests to be resistant to cefuroxime and other cephalosporins.

Anaerobic Microorganisms:

Peptococcus niger NOTE: Most strains of *Clostridium difficile* and *Bacteroides fragilis* are resistant to cefuroxime

To ceruroxine. Susceptibility Tests: *Dilution Techniques:* Quantitative methods that are used to determine MICs provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method¹ (broth, agar, or microdilution) or equivalent with cefuroxime powder. The MIC values obtained should be interpreted according to the following criteria: powder. The MIC following criteria:

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

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

utilikely to be inhibitory and that other therapy should be selected. Standardized susceptibility test procedures require the use of laboratory control microorganisms. Standard cefuroxime powder should give the following MIC values:

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

Diffusion Techniques: Quantitative methods that require measurement of zone diameters provide estimates of the susceptibility of bacteria to antimicrobial com-pounds. One such standardized procedure² that has been recommended (for use with disks) to test the susceptibility of microorganisms to cefuroxime uses the 30-mcg ceturoxime disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefuroxime. Reports from the laboratory providing results of the standard single-disk suscep-tibility test with a 30-mcg ceturoxime disk should be interpreted according to the following criteria:

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

Interpretation should be as stated above for results using dilution techniques. As with standard dilution techniques, diffusion methods require the use of laboratory control microcorganisms. The 30-mcg cefuroxime disk provides the following zone diameters in these laboratory test quality control strains:

drug occurred in 1.4% of pediatric patients given the oral suspension. Complaints

drug occurred in 1.4% of pediatric patients given the oral suspension. Complaints about taste (which may impair compliance) occurred in 5% of pediatric patients. 3. Patients should be counseled that antibacterial drugs, including CEFTIN, should only be used to treat bacterial infections. They do not treat viral infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may. (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacterial will develop resistance and will not be treatable by CEFTIN or other antibacterial drugs in the future. **Drug/Laboratory Tesl Interactions**: A false-positive reaction for glucose in the urin curve thin copper reduction tests (Benedict's or Fehling's solution or with CLINITST[®] tables), but not with enzyme-based tests for glycosuria (e.g., CLINISTX[®]). As a false-negative result may occur in the ferricyanide test, it is recom-mended that either the glucose exidase or hexokinase method be used to determine thoodylasma glucose levels in patients receiving cefuroxime axetil. The presence of

blood/plasma glucose levels in patients receiving cefuroxime axetil. The presence of cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

alkaline picrate method. Drug/Drug Interactions: Concomitant administration of probenecid with cefuroxime availit tables increases the area under the serum concentration versus time curve by 50%. The peak serum cefuroxime concentration after a 1.5-g single dose is greater when taken with 1 g of probenecid (mean = 1.4.8 mcg/mL) than without probenecid (mean = 1.2.2 mcg/mL). Drugs that reduce gastric acidity may result in a lower bioavailability of CEFTIN com-pared with that of fasting state and tend to cancel the effect of postprantial absorption. Carcinogenesis, Mutagenesis, Impairment of Fertility: Although lifetime studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic activity was found for cefuroxime avaetil in a battery of bacterial mutation tests. Posi-tive results were obtained in an in vitro chromosome aberration assay; however, negative results were found in an in vivo micronucleus test at doses up to 1.5 g/kg. Reproduction studies in rats at doses up to 1.000 mg/kg/day (9 times the recom-Reproduction studies in rats at doses up to 1,000 mg/kg/day (9 times the recom-mended maximum human dose based on mg/m²) have revealed no impairment of fertilitv

of fertility. **Pregnancy:** *Teratogenic Effects:* Pregnancy Category B. Reproduction studies have been performed in mice at doses up to 3,200 mg/kg/day (14 times the recommended maximum human dose based on mg/m²) and in rats at doses up to 1,000 mg/kg/day (9 times the recommended maximum human dose based on mg/m²) and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime axelil. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Labor and Delivery. Cefuroxime axetil has not been studied for use during labor and delivery.

Shoho be used winning pregnancy only in leaders. Labor and Delivery: Celruroxime axelli has not been studied for use during labor and delivery. Nursing Mothers: Because cefuroxime is excreted in human milk, consideration should be given to discontinuing nursing temporarily during treatment with cefuroxime axelil. Pediatric Use: The safety and effectiveness of CEFTIN have been established for pedi-atric patients aged 3 months to 12 years for acute bacterial maxillary sinusitis based upon its approval in adults. Use of CEFTIN in pediatric patients, and by clinical and micro-biological data from adequate and well-controlled studies of the treatment of acute bacterial maxillary sinusitis in adults and of acute otitis media with effusion in pedi-taric patients. It is also supported by postmarketing adverse events surveillance (see CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and CLINICAL STUDIES). Geriatric Use: Of the total number of subjects who received cefuroxime axetil in 20 clinical studies of CEFTIN, 375 were 65 and over while 151 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger adult subjects. The geriatric patients reported somewhat fewerg gastro-intestinal events and less frequent vaginal candidiasis compared with patients aged 12 to 64 years old; however, no clinically significant differences were reported between the elderly and younger adult patients. Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients. ADVERSE BEACTIONS

ADVERSE REACTIONS

ADVERSE REACTIONS CFFTIN TABLETS IN CLINICAL TRIALS: Multiple-Dose Dosing Regimens: 7 to 10 Days Dosing: Using multiple doses of cefuroxime axetil tablets, 912 patients were treated with cefuroxime axetil (125 to 500 mg twice daily). There were no deaths or permanent disabilities thought related to drug toxicity. Twenty (2.2%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. Seventeen (85%) of the 20 patients who discontinued therapy did so because of gastrointestinal disturbances, including diarrhea, nausea, vomiting, and abdominal pain. The percentage of cefuroxime axetil tablet-treated patients who discontinued study drug because of adverse events tway every similar at daily doses of 1,000, 500, and 250 mg (2.3%, 2.1%, and 2.2%, respectively). However, the incidence of gastrointestinal adverse events wave events when the higher recommended doses. The following adverse events work tought by the investigators to be possibly, probably, or almost certainly related to cefuroxime axetil tablets in multiple-dose clinical trials (n = 912 cefuroxime axetil-treated patients).

CEFTIN® Tablets (cefuroxime axetil tablets) CEFTIN® for Oral Suspension (cefuroxime axetil powder for oral suspension)

Table 4. Adverse Reactions—CEFTIN Tablets

Multiple-Dose Dosing Regimens-	-Clinical Trials	
Incidence ≥1%	Diarrhea/loose stools Nausea/vomiting Transient elevation in AST Transient elevation in ALT Eosinophilia Transient elevation in LDH	3.7% 3.0% 2.0% 1.6% 1.1% 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	

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

for 10 days. No difference in the occurrence of adverse events was round between the 2 regimens. In Clinical Trials for Early Lyme Disease With 20 Days Dosing: Two multicenter trials assessed cefuroxime axetil tablets 500 mg twice a day for 20 days. The most common drug-related adverse experiences were diarrhea (10.6% of patients), Jarisch-Herxheimer reaction (5.6%), and vaginitis (5.4%). Other adverse experiences occurred with frequencies comparable to those reported with 7 to 10 days dosing. Single-Dose Regimen for Uncomplicated Gonorrhea: In clinical trials using a single dose of cefuroxime axetil (1,000 mg) for the treatment of uncomplicated gonorrhea. There were no deaths or permanent disabilities thought related to drug toxicity in these studies. these studies

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

Table 5. Adverse Reactions—CEFTIN Tablets 1-a Single-Dose Begimen for Uncomplicated Go orrhea—Clinical Trials

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

CEFTIN FOR ORAL SUSPENSION IN CLINICAL TRIALS

CEFTIN FOR ORAL SUSPENSION IN CLINICAL TRIALS In clinical trials using multiple doses of cefuroxime axetil powder for oral suspen-sion, pediatric patients (96.7% of whom were younger than 12 years of age) were treated with the recommended dosages of cefuroxime axetil (20 to 30 mg/kg/day divided twice a day up to a maximum dose of 500 or 1,000 mg/day, respectively). There were no deaths or permanent disabilities in any of the patients in these studies. Eleven US patients (1.2%) discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. The discontinuations were primarily for gastrointestinal disturbances, usually diarrhea or vomiting. During clinical trials, discontinuation of therapy due to the taste and/or problems with administering this drug occurred in 13 (1.4%) pediatric patients encolled at centers in the United States. The following adverse events were thought by the investigators to be possibly, probably, or almost certainly related to cefuroxime axetil-treated US patients).

Table 6. Adverse Reactions—CEFTIN for Oral Suspension Multiple-Dose Dosing Regimens—Clinical Trials

walliple-Dose Dosiliy Regimens-		
Incidence ≥1%	Diarrhea/loose stools Dislike of taste Diaper rash Nausea/vomiting	8.6% 5.0% 3.4% 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	

POSTMARKETING EXPERIENCE WITH CEFTIN PRODUCTS

POSTMARKETING EXPERIENCE WITH CEFTIN PRODUCTS In addition to adverse events reported during clinical trials, the following events have been identified during clinical practice in patients treated with CEFTIN Tablets or with CEFTIN for Oral Suspension and were reported spontaneously. Data are generally insufficient to allow an estimate of incidence or to establish causation. *General:* The following hypersensitivity reactions have been reported: anaphylaxis, angioedema, pruritus, rash, serum sickness-like reaction, urticaria. *Gastrointestinal:* Pseudomembranous colitis (see WARNINGS). *Hematologic:* Hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, and increased prothrombin time. *Hepatic:* Hepatic impairment including hepatitis and cholestasis, jaundice. *Neurologic:* Seizure.

- Neurologic: Seizure

Skin: Fi nema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis. Urologic: Renal dysfunction.

CEPHALOSPORIN-CLASS ADVERSE REACTIONS

Table 9. Amount of Water Required for Reconstitution of Labeled Volumes of CEFTIN for 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

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

HOW SUPPLIED

HOW SUPPLIED CEFTIN Tablets: CEFTIN Tablets, 250 mg of cefuroxime (as cefuroxime axetil), are light blue, capsule-shaped, film-coated tablets engraved with "387" on one side and Glaxo" on the other side as follows:

20 Tablets/Bottle	NDC 0173-0387-00
60 Tablets/Bottle	NDC 0173-0387-42
Unit Dose Packs of 100	NDC 1073-0387-01
CEFTIN Tablets, 500 mg	of cefuroxime (as cefuro)

CET INV IADIES, 500 mg of cefuroxime (as cefuroxime axetil), are dark blue, capsule-shaped, film-coated tablets engraved with "394" on one side and "Glaxo" on the other side as follows: 394-00

20 Tablets/Bottle	NDC 0173-0394-00
60 Tablets/Bottle	NDC 0173-0394-42
Unit Dose Packs of 50	NDC 1073-0394-01

Unit Dose Packs of 50 NDC 1073-0394-01 Store the tablets between 15° and 30°C (59° and 86°F). Replace cap securely after each opening. Protect unit dose packs from excessive moisture. CEFTIN for Oral Suspension: CEFTIN for Oral Suspension is provided as dry, white to off-white, tutti-frutti-flavored powder. When reconstituted as directed, CEFTIN for Oral Suspension provides the equivalent of 125 mg or 250 mg of cefuroxime (as cefuroxime axefli) per 5 mL of suspension. It is supplied in amber glass bottles as follows: 125 mg/5 mL: 10cm Suspension NDC 0173-0740-00

100-mL Suspension	NDC 0173-0740-00
250 mg/5 mL:	
50-mL Suspension	NDC 0173-0741-10
100-mL Suspension	NDC 0173-0741-00

100-mL Suspension NDC 01/3-0/41-00 Before reconstitution, store dry powder between 2° and 30°C (36° and 86°F). After reconstitution, store suspension between 2° and 8°C (36° and 46°F), in a refrigerator. DISCARD AFTER 10 DAYS.

a refrigerator. DISCARD AFTER 10 DAYS. CLINICAL STUDIES CEFTIN Tablets: Acute Bacterial Maxillary Sinusitis: One adequate and well-controlled study was performed in patients with acute bacterial maxillary sinusitis. In this study each patient had a maxillary sinus aspirate collected by sinus puncture before treatment was initiated for presumptive acute bacterial sinusitis. All patients had to have radiographic and clinical evidence of acute maxillary sinusitis. As shown in the following summary of the study, the general clinical effectiveness of CEFTIN Tablets was comparable to an oral antimicrobial agent that contained a specific beta-lactamase inhibitor in treating acute maxillary sinusitis. However, sufficient micro-biology data were obtained to demonstrate the effectiveness of CEFTIN Tablets in treating acute bacterial maxillary sinusitis due only to Streptococcus pneumoniae or non-beta-lactamase-producing Haemophilus influenzae and Moraxella catarrhalis isolates were obtained to acute bacterial maxillary sinusitis due the effectiveness of CEFTIN Tablets in the treatment of acute bacterial maxillary sinusitis due to these 2 organisms. This study enrolled 317 adult patients, 132 patients in the United States and 185 patients in South America. Patients were randomized in a 1:1 ratio to cefuroxime axetil 250 mg twice daily or an oral antimicrobial agent that contained a specific beta-lactamase inhibitor. An intent-to-treat analysis of the submitted clinical data yielded the following results:

the following results:

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

	US Patients*		South American Patients [†]		
	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%	

'95% Confidence interval around the success difference [-0.08, +0.32] '95% Confidence interval around the success difference [-0.10, +0.16]

*95% Confidence interval around the success difference [-0.08, +0.32]. 195% Confidence interval around the success difference [-0.10, +0.16]. In this trial and in a supporting maxillary puncture trial, 15 evaluable patients had non-beta-lactamase-producing *Haemophilus influenzae* as the identified pathogen. Ten (10) of these 15 patients (67%) had their pathogen (non-beta-lactamase-producing *Haemophilus influenzae* eradicated. Eighteen (18) evaluable patients had *Streptococcus pneumoniae* as the identified pathogen. Fifteen (15) of these 18 patients (83%) had their pathogen (*Streptococcus pneumoniae*) eradicated. *Sately*: The incidence of drug-related gastrointestinal adverse events was statis-tically significantly higher in the control arm (an oral antimicrobial agent that contained a specific beta-lactamase inhibitor) versus the celruroxime axetil arm (12% versus 1%, respectively; *P*=.001). *Early Lyme Disease:* Two adequate and well-controlled studies were performed in patients with early Lyme disease. In these studies all patients had to present with physician-documented erythema migrans, with or without systemic manifestations of infection. Patients were randomized in a 1:1 ratio to a 20-day course of treatment with cefuroxime axetil 300 mg twice daily or doxycycline 100 mg 3 times daily. Patients were assessed at 1 month postfreatment for success in treating early Lyme disease (Part I) and at 1 year postfreatment for success in preventing the progression to the sequelae of late Lyme disease (Part II). A total of 355 adult patients (181 treated with cefuroxime axetil and 174 treated with doxycycline) were nerolled in the 2 studies. In order to objectively validate the clinical diagnosis of early Lyme disease in these patients, 2 approaches were used: 1) blinded expert reading of photographs, when available, of the pretreatment erythema migrans skin lesion; and 2) serologic confirmation (using enzyme-linked immunosorbent assay [ELISA] and immunoblot assay ["Westerm" biol]) of the presence of antib

Table 11. Clinical Effectiveness of CEFTIN Tablets Compared to Doxycycline in the 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%

*95% confidence interval around the satisfactory difference for Part I (-0.08, +0.05), 195% confidence interval around the satisfactory difference for Part II (-0.13, +0.07). *h*s include patients assessed as unsatisfactory clinical outcomes (failure + recur-rence) in Part I (CEFIN - 11 [5 failure, 6 recurrence]; doxycycline - 8 [6 failure, 2 recurrence]).

Statisfactory clinical outcome includes cure + improvement (Part I) and success + improvement (Part II).

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

Safety: Drug-related adverse events affecting the skin were reported significantly more frequently by patients treated with doxycycline than by patients treated with cefuroxime axetil (12% versus 3%, respectively; P = .002), primarily reflecting the statistically significantly higher incidence of drug-related photosensitivity reactions cefuroxime axetii (12% versus 3%, respectively; *P* = .002), primarily reflecting the statistically significantly higher incidence of drug-related photosensitivity reactions in the doxycycline arm versus the cefuroxime axetil arm (9% versus 0%, respectively; *P* < .001). While the incidence of drug-related gastrointestinal adverse events was similar in the 2 treatment groups (cefuroxime axetil - 13%; doxycc)(ine - 11%), the incidence of drug-related gastrointestinal adverse events was similar in the 2 treatment groups (cefuroxime axetil - 13%; doxycc)(ine - 11%), the incidence of drug-related diarrhea was statistically significantly higher in the cefurox-ime axetil arm versus the doxyccycline arm (11% versus 3%, respectively; *P* = .005). Secondary Bacterial Infections of Acute Bronchitis: Four randomized, controlled clinical studies were performed comparing 5 days versus 10 days of CEFIN for the treatment of patients with secondary bacterial infections of acute bronchitis. These studies enrolled a total of 1.253 patients (CAE-516 n = .360; CAE-517 n = .177; CAEA4001 n = .362; CAEA4002 n = .364). The protocols for CAE-516 and CAE-517 were identical and compared CEFIN 250 mg twice daily for 5 days, CEFIN 250 mg twice daily for 10 days, and AUGMENTIN® 500 mg 3 times daily for 10 days. These 2 studies were conducted simultaneously. CAEA4001 and CAEA4002 compared CEFIN 250 mg twice daily for 5 days, CEFIN 250 mg twice daily for 10 days. These 2 studies were conducted simultaneously. CAEA4001 and CAEA4002 compared CEFIN 250 mg twice daily for 5 days, CEFIN 250 mg twice daily for 10 days. The secondary bacterial pathogen from the sputum culture was not required to thays. Delymorphonuclear cells present on the Gram stain of the is creening sputum specimen, but isolation of a bacterial pathogen from the sputum culture was not required for inclusion. The following table demonstrates the results of the clinical outcome analysis of the pooled studies CAE-517 and CAEA4001/CAEA4002, respectively: Table 12. Clinical Effectiv

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

DORACE AND ANNION THAT AND CEFTIN FOR ORAL SUSPENSION ARE NOT BIO-Equivalent and are not substitutable on a milligram-per-milligram Basis (see clinical pharmacology).

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

Population/Infection	Dosage	Duration (days)	
Adolescents and Adults (13 years and older)			
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	
Pediatric Patients (who can swallow tablets whole)			
Acute otitis media	250 mg b.i.d.	10	
Acute bacterial maxillary sinusitis	250 mg b.i.d.	10	

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

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

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

Population/Infection	Dosage	Daily Maximum Dose	Duration (days)
Pediatric Patients (3 months to 12 years)			
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

Patients With Renal Failure: The safety and efficacy of cefuroxime axetil in patients with renal failure have not been established. Since cefuroxime is renally eliminated,

With renar lattice have not been established. Since Cellulowine's renary emininated, its half-life will be prolonged in patients with renal failure.
Directions for Mixing CEFTIN for Oral Suspension: Prepare a suspension at the time of dispensing as follows:

Shake the bottle to loosen the powder.
Remove the cap.

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

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

	CAE-516 and CAE-517*		CAEA4001 and CAEA4002 [†]	
	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%

*95% Confidence interval around the success difference [-0.164, +0.029] *95% Confidence interval around the success difference [-0.061, +0.103]

The response rates for patients who were both clinically and bacteriologically evaluable were consistent with those reported for the clinically evaluable patients. **Safety:** In these clinical trials, 399 patients were treated with CEFTIN for 5 days and 402 patients with CEFTIN for 10 days. No difference in the occurrence of adverse events was observed between the 2 regimens.

REFERENCES

- HEPEHENCES
 I. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. 3rd ed. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25. Villanova, Pa: NCCLS; 1993.
 I. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests. 4th ed. Approved Standard NCCLS Document M2-A4, Vol. 10, No. 7. Villanova, Pa: NCCLS; 1990.



GlaxoSmithKline Research Triangle Park, NC 27709

CEFTIN is a registered trademark of GlaxoSmithKline. CLINITEST and CLINISTIX are registered trademarks of Ames Division, Miles Laboratories, Inc.

© 2003, GlaxoSmithKline All rights reserved.

September 2003

RL-2040