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CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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April 9, 2004

OVERNIGHT COURIER 4/9/04

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

CITIZEN PETITION

This petition is submitted in quadruplicate under Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §355(j)(2)(C) and 21 CFR §10.20 and §10.30, and 21 CFR §314.93, to request the Commissioner of Food and Drug Administration to make a determination that an abbreviated new drug application (ANDA) may be submitted for Cefprozil Tablets for Oral Suspension, 125 mg and 250 mg.

A. Action Requested

The petitioner requests that the Commissioner of Food and Drug Administration declare that Cefprozil Tablets for Oral Suspension, 125 mg and 250 mg are suitable for submission as an ANDA. The reference-listed drug product upon which this petition is based is Cefzil® (cefprozil) for Oral Suspension 250 mg / 5 mL. Cefzil® is also approved in a 125 mg / 5 mL suspension, as well as in tablet strengths of 250 mg and 500 mg. Cefzil® is manufactured by Bristol Myers Squibb Company. Since Cefzil® for Oral Suspension 250 mg / 5 mL is the designated RLD upon which this petition is based and a 125 mg / 5 mL suspension product is also approved, this petition requests only a change in dosage form (from powder for oral suspension to tablets for oral suspension) from that of the listed drug.

B. Statement of Grounds

Section 505(j)(2)(C) for the Federal Food, Drug and Cosmetic Act provides for submission of an ANDA for a new drug that differs in dosage form from a listed drug, provided that the FDA has approved a petition seeking permission to file such an application. This petition seeks a change in dosage form from that of the reference-listed drug product (i.e. from a powder for oral suspension to a tablet for oral suspension).

Cefprozil Tablets for Oral Suspension are presented for administration by mixing a single tablet in a specified amount of water.

The new dosage form is expected to offer an alternative to the powder for oral suspension and may provide the following advantages:

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CP1

- Unit dose dispensing
- Convenience of carrying and administration during travel
- Storage of the product will not require special conditions like refrigeration
- Better precision of dosage over the traditional teaspoonful

The proposed drug product will only differ in dosage form. The indications, dosage recommendations, strengths and route of administration, are the same as those included in approved labeling of the listed drug. Therefore, the proposed change in dosage form (from a powder for oral suspension to tablet for oral suspension) will not raise questions of the safety and efficacy of the proposed product. The proposed labeling will be the same as that of the approved labeling of the listed drug except for the dosage form, inactive ingredients, directions for preparation and marketer of the product. Thus, the Agency should conclude that clinical investigations are not necessary to demonstrate the proposed product's safety or effectiveness.

The approved labeling for the reference-listed drug, Bristol Myers Squibb's Cefzil® Oral Suspension, is provided in Attachment 1. Please note that the Bristol insert labeling is combined labeling for their approved suspension and tablet versions of this product. The proposed package insert for Cefprozil Tablets for Oral Suspension is provided in Attachment 2. A copy of the appropriate page from the electronic *Approved Drug Products with Therapeutic Equivalence Evaluations*, 24th Edition (commonly referred to as the Electronic Orange Book) showing the listing of the reference-listed drug product upon which this petition is based is included in Attachment 3.

C. Request for Pediatric Waiver

In December of 2003, Congress passed the Pediatric Research Equity Act of 2003 that amended the Federal Food, Drug and Cosmetic Act to provide the Agency authority to require drug firms to study certain drugs in pediatric patients, if the Agency felt that such study would provide beneficial health data for that patient population. The act also provided a provision for a waiver from such requirement if:

- (iii) the drug or biological product;
- (I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and
- (II) is not likely to be used in a substantial number of pediatric patients.

The petitioner hereby requests that a waiver from the conduct of pediatric studies be granted for the approval of this petition to permit subsequent ANDA filing.

Pediatric studies, both clinical and pharmacokinetic, have been conducted with the Reference-Listed Drug, Cefzil® (cefprozil), as detailed in the product labeling for the RLD and adequate dosing and administration information for the pediatric population is contained therein. Furthermore, the approved RLD labeling details indication in the treatment of otitis media and acute sinusitis for the age group 6 months to 12 years and indication in the treatment of pharyngitis / tonsillitis or uncomplicated skin and skin structure infections for the age group 2 to 12 years. Children above 13 years of age and older are dosed according to the dosage and

administration for adults. The planned labeling for the petitioner's proposed product, Cefprozil Tablets for Oral Suspension 125 mg and 250 mg, will be the same as that of the RLD providing the same dosing guidelines for all indicated age groups. The petitioner's formulation is not being proposed to offer therapeutic benefits or differences over presently approved drug product and is targeted towards the exact same pediatric population for which pediatric studies have already been conducted by the manufacturer of the Reference-Listed Drug, Cefzil® (cefprozil) Powder for Oral Suspension. Therefore, additional studies should not be necessary for approval of this alternative dosage form provided primarily for convenience of the same patient population that would use the approved suspension product.

For the reasons stated above and consistent with the provisions of the Pediatric Research Equity Act of 2003, the petitioner respectfully requests that this waiver be granted.

D. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR §25.31.

E. Economic Impact

According to 21 CFR §10.30(b), the petitioner will, upon request by the Commissioner, submit economic impact information.

F. Certification

The undersigned certifies that to the best of its knowledge, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Sincerely,


Robert W. Pollock *pk*

Vice President
Lachman Consultant Services, Inc.
1600 Stewart Avenue
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RWP/pk

Attachments: 1. Labeling for the Innovator (Cefzil®)
2. Labeling for the Generic product
3. *Approved Drug Products with Therapeutic Equivalence Evaluations 24th Edition*

cc: Emily Thakur (Office of Generic Drugs)

R03P4100

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590



ATTACHMENT 1

Cefzil® (CEFPROZIL) Tablets Rx only

250 mg and 500 mg

Cefzil® (CEFPROZIL)

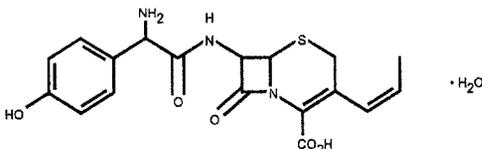
for Oral Suspension

125 mg/5 mL and 250 mg/5 mL

DESCRIPTION

CEFZIL® (cefprozil) is a semi-synthetic broad-spectrum cephalosporin antibiotic.

Cefprozil is a cis and trans isomeric mixture (≥ 90% cis). The chemical name for the monohydrate is (6R, 7R)-7-[(R)-2-amino-2-(p-hydroxyphenyl)acetamido]-8-oxo-3-propenyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate, and the structural formula is:



Cefprozil is a white to yellowish powder with a molecular formula for the monohydrate of $C_{21}H_{29}N_3O_5S \cdot H_2O$ and a molecular weight of 407.45.

CEFZIL tablets and CEFZIL for oral suspension are intended for oral administration. CEFZIL tablets contain cefprozil equivalent to 250 mg or 500 mg of anhydrous cefprozil. In addition, each tablet contains the following inactive ingredients: cellulose, hydroxypropylmethylcellulose, magnesium stearate, methylcellulose, simethicone, sodium starch glycolate, polyethylene glycol, polysorbate 80, sorbic acid, and titanium dioxide. The 250 mg tablets also contain FD&C Yellow No. 6.

CEFZIL for oral suspension contains cefprozil equivalent to 125 mg or 250 mg anhydrous cefprozil per 5 mL constituted suspension. In addition, the oral suspension contains the following inactive ingredients: aspartame, cellulose, citric acid, colloidal silicon dioxide, FD&C Red No. 3, flavors (natural and artificial), glycine, polysorbate 80, simethicone, sodium benzoate, sodium carboxymethylcellulose, sodium chloride, and sucrose.

CLINICAL PHARMACOLOGY

The pharmacokinetic data were derived from the capsule formulation; however, bioequivalence has been demonstrated for the oral solution, capsule, tablet, and suspension formulations under fasting conditions.

Following oral administration of cefprozil to fasting subjects, approximately 95% of the dose was absorbed. The average plasma half-life in normal subjects was 1.3 hours, while the steady state volume of distribution was estimated to be 0.23 L/kg. The total body clearance and renal clearance rates were approximately 3 mL/min/kg and 2.3 mL/min/kg, respectively.

Average peak plasma concentrations after administration of 250 mg, 500 mg, or 1 g doses of cefprozil to fasting subjects were approximately 6.1, 10.5, and 18.3 µg/mL, respectively, and were obtained within 1.5 hours after dosing. Urinary recovery accounted for approximately 60% of the administered dose. (See Table.)

Dosage (mg)	Mean Plasma Cefprozil Concentrations (µg/mL)*			8-hour Urinary Excretion (%)
	Peak appx. 1.5 h	4 h	8 h	
250 mg	6.1	1.7	0.2	60%
500 mg	10.5	3.2	0.4	62%
1000 mg	18.3	8.4	1.0	54%

*Data represent mean values of 12 healthy volunteers.

During the first 4-hour period after drug administration, the average urine concentrations following 250 mg, 500 mg, and 1 g doses were approximately 700 µg/mL, 1000 µg/mL, and 2900 µg/mL, respectively.

Administration of CEFZIL tablet or suspension formulation with food did not affect the extent of absorption (AUC) or the peak plasma concentration (C_{max}) of cefprozil. However, there was an increase of 0.25 to 0.75 hours in the time to maximum plasma concentration of cefprozil (T_{max}).

The bioavailability of the capsule formulation of cefprozil was not affected when administered 5 minutes following an antacid.

Plasma protein binding is approximately 36% and is independent of concentration in the range of 2 µg/mL to 20 µg/mL.

There was no evidence of accumulation of cefprozil in the plasma in individuals with normal renal function following multiple oral doses of up to 1000 mg every 8 hours for 10 days.

In patients with reduced renal function, the plasma half-life may be prolonged up to 5.2 hours depending on the degree of the renal dysfunction. In patients with complete absence of renal function, the plasma half-life of cefprozil has been shown to be as long as 5.9 hours. The half-life is shortened during hemodialysis. Excretion pathways in patients with markedly impaired renal function have not been determined. (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**.)

In patients with impaired hepatic function, the half-life increases to approximately 2 hours. The magnitude of the changes does not warrant a dosage adjustment for patients with impaired hepatic function.

Healthy geriatric volunteers (≥ 65 years old) who received a single 1-g dose of cefprozil had 35%-60% higher AUC and 40% lower renal clearance values compared with healthy adult volunteers 20-40 years of age. The average AUC in young and elderly female subjects was approximately 15-20% higher than in young and elderly male subjects. The magnitude of these age- and gender-related changes in the pharmacokinetics of cefprozil is not sufficient to necessitate dosage adjustments.

Adequate data on CSF levels of cefprozil are not available.

Comparable pharmacokinetic parameters of cefprozil are observed between pediatric patients (6 months-12 years) and adults following oral administration of selected matched doses. The maximum concentrations are achieved at 1-2 hours after dosing. The plasma elimination half-life is approximately 1.5 hours. In general, the observed plasma concentrations of cefprozil in pediatric patients at the 7.5, 15, and 30 mg/kg doses are similar to those observed within the same time frame in normal adult subjects at the 250, 500 and 1000 mg doses, respectively. The comparative plasma concentrations of cefprozil in pediatric patients and adult subjects at the equivalent dose level are presented in the table below.

Population	Dose	Mean (SD) Plasma Cefprozil Concentrations (µg/mL)				$T_{1/2}$ (h)
		1 h	2 h	4 h	6 h	
children (n = 18)	7.5 mg/kg	4.70	3.99	0.91	0.23*	0.94
		(1.57)	(1.24)	(0.30)	(0.13)	(0.32)
adults (n = 12)	250 mg	4.82	4.92	1.70*	0.53	1.28
		(2.13)	(1.13)	(0.53)	(0.17)	(0.34)
children (n = 19)	15 mg/kg	10.86	8.47	2.75	0.61*	1.24
		(2.55)	(2.03)	(1.07)	(0.27)	(0.43)
adults (n = 12)	500 mg	8.39	9.42	3.18*	1.00*	1.29
		(1.95)	(0.98)	(0.76)	(0.24)	(0.14)
children (n = 10)	30 mg/kg	6.69	17.61	8.66	--	2.06
		(4.26)	(6.39)	(2.70)		(0.21)
adults (n = 12)	1000 mg	11.99	16.95	8.36	2.79	1.27
		(4.67)	(4.07)	(4.13)	(1.77)	(0.12)

*n = 11; *n = 5; *n = 9; *n = 11.

Microbiology

Cefprozil has *in vitro* activity against a broad range of gram-positive and gram-negative bacteria. The bactericidal action of cefprozil results from inhibition of cell-wall synthesis. Cefprozil has been shown 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.

Aerobic gram-positive microorganisms:

Staphylococcus aureus (including β-lactamase-producing strains)
NOTE: Cefprozil is inactive against methicillin-resistant staphylococci.
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic gram-negative microorganisms:

Haemophilus influenzae (including β-lactamase-producing strains)
Moraxella (Branhamella) catarrhalis (including β-lactamase-producing strains)

The following *in vitro* data are available; however, their clinical significance is unknown. Cefprozil exhibits *in vitro* minimum inhibitory concentrations (MICs) of 8 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of cefprozil in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms:

Enterococcus durans
Enterococcus faecalis
Listeria monocytogenes
Staphylococcus epidermidis
Staphylococcus saprophyticus
NOTE: Cefprozil is inactive against *Enterococcus faecium*.

Aerobic gram-negative microorganisms:

Citrobacter diversus
Escherichia coli
Klebsiella pneumoniae
Neisseria gonorrhoeae (including β-lactamase-producing strains)
NOTE: Cefprozil is inactive against most strains of *Acinetobacter*, *Enterobacter*, *Morganella morganii*, *Proteus vulgaris*, *Providencia*, *Pseudomonas*, and *Serratia*.

Anaerobic microorganisms:

<i>Prevotella (Bacteroides) melaninogenicus</i>	<i>Fusobacterium</i> spp.
<i>Clostridium difficile</i>	<i>Peptostreptococcus</i> spp.
<i>Clostridium perfringens</i>	<i>Propionibacterium acnes</i>

NOTE: Most strains of the *Bacteroides fragilis* group are resistant to cefprozil.

Susceptibility Tests

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method^{1,2} (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefprozil powder. The MIC values should be interpreted according to the following criteria:

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

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

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard cefprozil powder should provide the following MIC values:

Microorganism	MIC (µg/mL)
<i>Enterococcus faecalis</i> ATCC 29212	4-16
<i>Escherichia coli</i> ATCC 25922	1-4
<i>Haemophilus influenzae</i> ATCC 49766	1-4
<i>Staphylococcus aureus</i> ATCC 29213	0.25-1
<i>Streptococcus pneumoniae</i> ATCC 49619	0.25-1

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure³ requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 µg cefprozil to test the susceptibility of microorganisms to cefprozil.

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

Zone diameter (mm)	Interpretation
≥ 18	Susceptible (S)
15-17	Intermediate (I)
≤ 14	Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefprozil.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30 µg cefprozil disk should provide the following zone diameters in these laboratory test quality control strains.

Microorganism	Zone diameter (mm)
<i>Escherichia coli</i> ATCC 25922	21-27
<i>Haemophilus influenzae</i> ATCC 49766	20-27
<i>Staphylococcus aureus</i> ATCC 25923	27-33
<i>Streptococcus pneumoniae</i> ATCC 49619	25-32

INDICATIONS AND USAGE

CEFZIL (cefprozil) is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

UPPER RESPIRATORY TRACT

Pharyngitis/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 route. Cefprozil is generally effective in the eradication of *Streptococcus pyogenes* from the nasopharynx; however, substantial data establishing the efficacy of cefprozil in the subsequent prevention of rheumatic fever are not available at present.

Otitis Media caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including β-lactamase-producing strains), and *Moraxella (Branhamella) catarrhalis* (including β-lactamase-producing strains). (See CLINICAL STUDIES.)

NOTE: In the treatment of otitis media due to β-lactamase producing organisms, cefprozil had bacteriologic eradication rates somewhat lower than those observed with a product containing a specific β-lactamase inhibitor. In considering the use of cefprozil, lower overall eradication rates should be balanced against the susceptibility patterns of the common microbes in a given geographic area and the increased potential for toxicity with products containing β-lactamase inhibitors.

Acute Sinusitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including β-lactamase-producing strains), and *Moraxella (Branhamella) catarrhalis* (including β-lactamase-producing strains).

LOWER RESPIRATORY TRACT

Secondary Bacterial Infection of Acute Bronchitis and Acute Bacterial Exacerbation of Chronic Bronchitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including β-lactamase-producing strains), and *Moraxella (Branhamella) catarrhalis* (including β-lactamase-producing strains).

SKIN AND SKIN STRUCTURE

Uncomplicated Skin and Skin-Structure Infections caused by *Staphylococcus aureus* (including penicillinase-producing strains) and *Streptococcus pyogenes*. Abscesses usually require surgical drainage.

Culture and susceptibility testing should be performed when appropriate to determine susceptibility of the causative organism to cefprozil.

CONTRAINDICATIONS

CEFZIL (cefprozil) is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFZIL IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFZIL, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-SENSITIVITY AMONG β-LACTAM ANTI-BIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFZIL OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefprozil, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated" colitis.

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General

In patients with known or suspected renal impairment (see DOSAGE AND ADMINISTRATION), careful clinical observation and appropriate laboratory studies should be done prior to and during therapy. The total daily dose of CEFZIL should be reduced in these patients because high and/or prolonged plasma antibiotic concentrations can occur in such individuals from usual doses. Cephalosporins, including CEFZIL, should be given with caution to patients receiving concurrent treatment with potent diuretics since these agents are suspected of adversely affecting renal function.

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

Cefprozil should be prescribed with caution in individuals with a history of gastrointestinal disease particularly colitis.

Positive direct Coombs' tests have been reported during treatment with cephalosporin antibiotics.

Information for Patients

Phenylketonurics: CEFZIL (cefprozil) for oral suspension contains phenylalanine 28 mg per 5 mL (1 teaspoonful) constituted suspension for both the 125 mg/5 mL and 250 mg/5 mL dosage forms.

Drug Interactions

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporin antibiotics. Concomitant administration of probenecid doubled the AUC for cefprozil.

The bioavailability of the capsule formulation of cefprozil was not affected when administered 5 minutes following an antacid.

Drug/Laboratory Test Interactions

Cephalosporin antibiotics may produce a false positive reaction for glucose in the urine with copper reduction tests (Benedict's or Fehling's solution or with Clinitest® tablets), but not with enzyme-based tests for glycosuria (e.g., Tes-Tape®). A false negative reaction may occur in the ferricyanide test for blood glucose. The presence of cefprozil in the blood does not interfere with the assay of plasma or urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long term *in vivo* studies have not been performed to evaluate the carcinogenic potential of cefprozil.

Cefprozil was not found to be mutagenic in either the Ames *Salmonella* or *E. coli* WP2 *uvrA* reversion assays or the Chinese hamster ovary cell HGPRT forward gene mutation assay and it did not induce chromosomal abnormalities in Chinese hamster ovary cells or unscheduled DNA synthesis in rat hepatocytes *in vitro*. Chromosomal aberrations were not observed in bone marrow cells from rats dosed orally with over 30 times the highest recommended human dose based upon mg/m².

Impairment of fertility was not observed in male or female rats given oral doses of cefprozil up to 18.5 times the highest recommended human dose based upon mg/m².

Pregnancy: Teratogenic Effects. Pregnancy Category B

Reproduction studies have been performed in rabbits, mice, and rats using oral doses of cefprozil of 0.8, 8.5, and 18.5 times the maximum daily human dose (1000 mg) based upon mg/m², and have revealed no harm to the fetus. 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

Cefprozil has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers

Small amounts of cefprozil (< 0.3% of dose) have been detected in human milk following administration of a single 1 gram dose to lactating women. The average levels over 24 hours ranged from 0.25 to 3.3 µg/mL. Caution should be exercised when CEFZIL is administered to a nursing woman, since the effect of cefprozil on nursing infants is unknown.

Pediatric Use: (See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION.)

The safety and effectiveness of cefprozil in the treatment of otitis media have been established in the age groups 6 months to 12 years. Use of CEFZIL (cefprozil) for the treatment of otitis media is supported by evidence from adequate and well-controlled studies of cefprozil in pediatric patients. (See CLINICAL STUDIES.)

The safety and effectiveness of cefprozil in the treatment of pharyngitis/tonsillitis or uncomplicated skin and skin structure infections have been established in the age groups 2 to 12 years. Use of CEFZIL for the treatment of these infections is supported by evidence from adequate and well-controlled studies of cefprozil in pediatric patients.

The safety and effectiveness of cefprozil in the treatment of acute sinusitis have been established in the age groups 6 months to 12 years. Use of CEFZIL in these age groups is supported by evidence from adequate and well-controlled studies of cefprozil in adults.

Safety and effectiveness in pediatric patients below the age of 6 months have not been established for the treatment of otitis media or acute sinusitis or below the age of 2 years for the treatment of pharyngitis/tonsillitis or uncomplicated skin and skin structure infections. However, accumulation of other cephalosporin antibiotics in newborn infants (resulting from prolonged drug half-life in this age group) has been reported.

Geriatric Use

Of the more than 4500 adults treated with CEFZIL in clinical studies, 14% were 65 years and older, while 5% were 75 years and older. When geriatric patients received the usual recommended adult doses, their clinical efficacy and safety were comparable to clinical efficacy and safety in nongeriatric adult patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals to the effects of CEFZIL cannot be excluded (see CLINICAL PHARMACOLOGY).

CEFZIL is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function. See DOSAGE AND ADMINISTRATION for dosing recommendations for patients with impaired renal function.

ADVERSE REACTIONS

The adverse reactions to cefprozil are similar to those observed with other orally administered cephalosporins. Cefprozil was usually well tolerated in controlled clinical trials. Approximately 2% of patients discontinued cefprozil therapy due to adverse events.

The most common adverse effects observed in patients treated with cefprozil are:

Gastrointestinal: Diarrhea (2.9%), nausea (3.5%), vomiting (1%), and abdominal pain (1%).

Hepatobiliary: Elevations of AST (SGOT) (2%), ALT (SGPT) (2%), alkaline phosphatase (0.2%), and bilirubin values (<0.1%). As with some penicillins and some other cephalosporin antibiotics, cholestatic jaundice has been reported rarely.

Hypersensitivity: Rash (0.9%), urticaria (0.1%). Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy.

CNS: Dizziness (1%). Hyperactivity, headache, nervousness, insomnia, confusion, and somnolence have been reported rarely (<1%). All were reversible.

Hematopoietic: Decreased leukocyte count (0.2%), eosinophilia (2.3%).

Renal: Elevated BUN (0.1%), serum creatinine (0.1%).

Other: Diaper rash and superinfection (1.5%), genital pruritus and vaginitis (1.6%).

The following adverse events, regardless of established causal relationship to CEFZIL, have been rarely reported during postmarketing surveillance: anaphylaxis, angioedema, colitis (including pseudomembranous colitis), erythema multiforme, fever, serum-sickness like reactions, Stevens-Johnson syndrome, and thrombocytopenia.

Cephalosporin class paragraph

In addition to the adverse reactions listed above which have been observed in patients treated with cefprozil, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Aplastic anemia, hemolytic anemia, hemorrhage, renal dysfunction, toxic epidermal necrolysis, toxic nephropathy, prolonged prothrombin time, positive Coombs' test, elevated LDH, pancytopenia, neutropenia, 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

Single 5000 mg/kg oral doses of cefprozil caused no mortality or signs of toxicity in adult, weanling, or neonatal rats, or adult mice. A single oral dose of 3000 mg/kg caused diarrhea and loss of appetite in cynomolgus monkeys, but no mortality.

Cefprozil is eliminated primarily by the kidneys. In case of severe overdosage, especially in patients with compromised renal function, hemodialysis will aid in the removal of cefprozil from the body.

DOSAGE AND ADMINISTRATION

CEFZIL (cefprozil) is administered orally.

Population/Infection	Dosage (mg)	Duration (days)
ADULTS (13 years and older)		
UPPER RESPIRATORY TRACT		
Pharyngitis/Tonsillitis	500 q 24h	10 ^a
Acute Sinusitis	250 q 12h or 500 q 12h	10
(For moderate to severe infections, the higher dose should be used)		
LOWER RESPIRATORY TRACT		
Secondary Bacterial Infection of Acute Bronchitis and Acute Bacterial Exacerbation of Chronic Bronchitis	500 q 12h	10
SKIN AND SKIN STRUCTURE		
Uncomplicated Skin and Skin Structure Infections	250 q 12h or 500 q 24h or 500 q 12h	10
CHILDREN (2 years - 12 years)		
UPPER RESPIRATORY TRACT^b		
Pharyngitis/Tonsillitis	7.5 mg/kg q 12h	10 ^a
SKIN AND SKIN STRUCTURE^b		
Uncomplicated Skin and Skin Structure Infections	20 mg/kg q 24h	10
INFANTS & CHILDREN (6 months - 12 years)		
UPPER RESPIRATORY TRACT^b		
Otitis Media (See INDICATIONS AND USAGE and CLINICAL STUDIES)	15 mg/kg q 12h	10
Acute Sinusitis (For moderate to severe infections, the higher dose should be used)	7.5 mg/kg q 12h or 15 mg/kg	10

^a In the treatment of infections due to *Streptococcus pyogenes*, CEFZIL should be administered for at least 10 days.

^b Not to exceed recommended adult doses.

Renal Impairment

Cefprozil may be administered to patients with impaired renal function. The following dosage schedule should be used.

Clinitest® is a registered trademark of the Bayer Corporation.

Tes-Tape® is a registered trademark of Eli Lilly and Company.

Creatinine Clearance (mL/min)	Dosage (mg)	Dosing Interval
30-120	standard	standard
0-29*	50% of standard	standard

* Cefprozil is in part removed by hemodialysis; therefore, cefprozil should be administered after the completion of hemodialysis.

Hepatic Impairment

No dosage adjustment is necessary for patients with impaired hepatic function.

HOW SUPPLIED

CEFZIL® (cefprozil) Tablets

Each light orange film-coated tablet, imprinted with "7720" on one side and "250" on the other, contains the equivalent of 250 mg anhydrous cefprozil.

Bottles of 100 Tablets NDC 0087-7720-60

Each white film-coated tablet, imprinted with "7721" on one side and "500" on the other, contains the equivalent of 500 mg anhydrous cefprozil.

Bottles of 50 Tablets NDC 0087-7721-50

Bottles of 100 Tablets NDC 0087-7721-60

Store at controlled room temperature, 59° to 86° F (15° to 30° C).

CEFZIL® (cefprozil) For Oral Suspension

Each 5 mL of constituted suspension contains the equivalent of 125 mg anhydrous cefprozil.

50 mL Bottle NDC 0087-7718-40

75 mL Bottle NDC 0087-7718-62

100 mL Bottle NDC 0087-7718-64

Each 5 mL of constituted suspension contains the equivalent of 250 mg anhydrous cefprozil.

50 mL Bottle NDC 0087-7719-40

75 mL Bottle NDC 0087-7719-62

100 mL Bottle NDC 0087-7719-64

All powder formulations for oral suspension contain cefprozil in a bubble-gum flavored mixture.

Reconstitution Directions for Oral Suspension

Prepare the suspension at the time of dispensing; for ease in preparation, add water in two portions and shake well after each aliquot.

Total Amount of Water Required for Reconstitution

Bottle Size	Final Concentration 125 mg/5 mL	Final Concentration 250 mg/5 mL
50 mL	36 mL	36 mL
75 mL	54 mL	54 mL
100 mL	72 mL	72 mL

After mixing, store in a refrigerator and discard unused portion after 14 days.

Store at 59° to 77° F (15° to 25° C) prior to constitution.

U.S. Patent No. 4,520,022

CLINICAL STUDIES

Study One:

In a controlled clinical study of acute otitis media performed in the United States where significant rates of β -lactamase-producing organisms were found, cefprozil was compared to an oral antimicrobial agent that contained a specific β -lactamase inhibitor. In this study, using very strict evaluability criteria and microbiologic and clinical response criteria at the 10-16 days post-therapy follow-up, the following presumptive bacterial eradication/clinical cure outcomes (i.e. clinical success) and safety results were obtained:

U.S. Acute Otitis Media Study

Cefprozil vs β -lactamase inhibitor-containing control drug

EFFICACY:

Pathogen	% of Cases with Pathogen (n = 155)	Outcome
<i>S. pneumoniae</i>	48.4%	cefprozil success rate 5% better than control
<i>H. influenzae</i>	35.5%	cefprozil success rate 17% less than control
<i>M. catarrhalis</i>	13.5%	cefprozil success rate 12% less than control
<i>S. pyogenes</i>	2.6%	cefprozil equivalent to control
Overall	100.0%	cefprozil success rate 5% less than control

SAFETY:

The incidences of adverse events, primarily diarrhea and rash*, were clinically and statistically significantly higher in the control arm versus the cefprozil arm.

Age Group	Cefprozil	Control
6 months-2 years	21%	41%
3-12 years	10%	19%

*The majority of these involved the diaper area in young children.

Study Two:

In a controlled clinical study of acute otitis media performed in Europe, cefprozil was compared to an oral antimicrobial agent that contained a specific β -lactamase inhibitor. As expected in a European population, this study population had a lower incidence of β -lactamase-producing organisms than usually seen in U.S. trials. In this study, using very strict evaluability criteria and microbiologic and clinical response criteria at the 10-16 days post-therapy follow-up, the following presumptive bacterial eradication/clinical cure outcomes (i.e. clinical success) were obtained:

European Acute Otitis Media Study

Cefprozil vs β -lactamase inhibitor-containing control drug

EFFICACY:

Pathogen	% of Cases with Pathogen (n = 47)	Outcome
<i>S. pneumoniae</i>	51.0%	cefprozil equivalent to control
<i>H. influenzae</i>	29.8%	cefprozil equivalent to control
<i>M. catarrhalis</i>	6.4%	cefprozil equivalent to control
<i>S. pyogenes</i>	12.8%	cefprozil equivalent to control
Overall	100.0%	cefprozil equivalent to control

SAFETY:

The incidence of adverse events in the cefprozil arm was comparable to the incidence of adverse events in the control arm (agent that contained a specific β -lactamase inhibitor).

REFERENCES

- National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*—Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December 1993.
- National Committee for Clinical Laboratory Standards. *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria*—Third Edition. Approved Standard NCCLS Document M11-A3, Vol. 13, No. 26, NCCLS, Villanova, PA, December 1993.
- National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests*—Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.

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ATTACHMENT 2

CEFPROZIL TABLETS FOR ORAL SUSPENSION

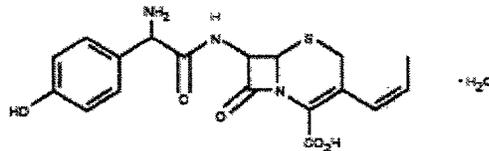
Rx only

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

DESCRIPTION

Cefprozil is a semi-synthetic broad-spectrum cephalosporin antibiotic.

Cefprozil is a cis and trans isomeric mixture ($\geq 90\%$ cis). The chemical name for the monohydrate is (6R, 7R)-7-[(R)-2-amino-2-(p-hydroxyphenyl)acetamido]-8-oxo-3-propenyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate, and the structural formula is:



Cefprozil is a white to yellowish powder with a molecular formula for the monohydrate of $C_{18}H_{19}N_3O_5S \cdot H_2O$ and a molecular weight of 407.45.

Cefprozil tablets for oral suspension are intended for oral administration. Cefprozil tablets for oral suspension contain cefprozil equivalent to 125 mg or 250 mg of anhydrous cefprozil. The inactive ingredients will be furnished when the ANDA is submitted.

CLINICAL PHARMACOLOGY

The pharmacokinetic data were derived from the capsule formulation; however, bioequivalence has been demonstrated for the oral solution, capsule, tablet, and suspension formulations under fasting conditions.

Following oral administration of cefprozil to fasting subjects, approximately 95% of the dose was absorbed. The average plasma half-life in normal subjects was 1.3 hours, while the steady state volume of distribution was estimated to be 0.23 L/kg. The total body clearance and renal clearance rates were approximately 3 mL/min/kg and 2.3 mL/min/kg, respectively.

Average peak plasma concentrations after administration of 250 mg, 500 mg, or 1 g doses of cefprozil to fasting subjects were approximately 6.1, 10.5, and 18.3 mcg/mL, respectively, and were obtained within 1.5 hours after dosing. Urinary recovery accounted for approximately 60% of the administered dose. (See Table.)

Dosage (mg)	Mean Plasma Cefprozil Concentrations (mcg/mL)*			8 hour Urinary Excretion (%)
	Peak appx. 1.5 h	4 h	8 h	
250 mg	6.1	1.7	0.2	60%
500 mg	10.5	3.2	0.4	62%
1000 mg	18.3	8.4	1.0	54%

*Data represent mean values of 12 healthy volunteers.

During the first 4-hour period after drug administration, the average urine concentrations following 250 mg, 500 mg, and 1 g doses were approximately 700 mcg/mL, 1000 mcg/mL, and 2900 mcg/mL, respectively.

Administration of Cefprozil tablet formulation with food did not affect the extent of absorption (AUC) or the peak plasma concentration (C_{max}) of cefprozil. However, there was an increase of 0.25 to 0.75 hours in the time to maximum plasma concentration of cefprozil (T_{max}).

The bioavailability of the capsule formulation of cefprozil was not affected when administered 5 minutes following an antacid.

Plasma protein binding is approximately 36% and is independent of concentration in the range of 2 mcg/mL to 20 mcg/mL.

There was no evidence of accumulation of cefprozil in the plasma in individuals with normal renal function following multiple oral doses of up to 1000 mg every 8 hours for 10 days.

In patients with reduced renal function, the plasma half-life may be prolonged up to 5.2 hours depending on the degree of the renal dysfunction. In patients with complete absence of renal function, the plasma half-life of cefprozil has been shown to be as long as 5.9 hours. The half-life is shortened during hemodialysis. Excretion pathways in patients with markedly impaired renal function have not been determined. (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**.)

In patients with impaired hepatic function, the half-life increases to approximately 2 hours. The magnitude of the changes does not warrant a dosage adjustment for patients with impaired hepatic function.

Healthy geriatric volunteers (≥ 65 years old) who received a single 1 g dose of cefprozil had 35% to 60% higher AUC and 40% lower renal clearance values compared with healthy adult volunteers 20 to 40 years of age. The average AUC in young and elderly female subjects was approximately 15 to 20% higher than in young and elderly male subjects. The magnitude of these age- and gender-related changes in the pharmacokinetics of cefprozil is not sufficient to necessitate dosage adjustments.

Adequate data on CSF levels of cefprozil are not available.

Comparable pharmacokinetic parameters of cefprozil are observed between pediatric patients (6 months to 12 years) and adults following oral administration of selected matched doses. The maximum concentrations are achieved at 1 to 2 hours after dosing. The plasma elimination half-life is approximately 1.5 hours. In general, the observed plasma concentrations of cefprozil in pediatric patients at the 7.5, 15, and 30 mg/kg doses are similar to those observed within the same time frame in normal adult subjects at the

250, 500 and 1000 mg doses, respectively. The comparative plasma concentrations of cefprozil in pediatric patients and adult subjects at the equivalent dose level are presented in the table below.

Population	Dose	Mean (SD) Plasma Cefprozil Concentrations (mcg/mL)				T _{1/2} (h)
		1 h	2 h	4 h	6 h	
children (n = 18)	7.5 mg/kg	4.70 (1.57)	3.99 (1.24)	0.91 (0.30)	0.23 ^a (0.13)	0.94 (0.32)
adults (n = 12)	250 mg	4.82 (2.13)	4.92 (1.13)	1.70 ^b (0.53)	0.53 (0.17)	1.28 (0.34)
children (n = 19)	15 mg/kg	10.86 (2.55)	8.47 (2.03)	2.75 (1.07)	0.61 ^c (0.27)	1.24 (0.43)
adults (n = 12)	500 mg	8.39 (1.95)	9.42 (0.98)	3.18 ^d (0.76)	1.00 ^d (0.24)	1.29 (0.14)
children (n = 10)	30 mg/kg	6.69 (4.26)	17.61 (6.39)	8.66 (2.70)	--	2.06 (0.21)
adults (n = 12)	1000 mg	11.99 (4.67)	16.95 (4.07)	8.36 (4.13)	2.79 (1.77)	1.27 (0.12)

^an = 11; ^bn = 5; ^cn = 9; ^dn = 11.

Microbiology

Cefprozil has *in vitro* activity against a broad range of gram-positive and gram-negative bacteria. The bactericidal action of cefprozil results from inhibition of cell-wall synthesis. Cefprozil has been shown 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.

Aerobic gram-positive microorganisms:

Staphylococcus aureus (including β -lactamase-producing strains)
NOTE: Cefprozil is inactive against methicillin-resistant staphylococci.
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic gram-negative microorganisms:

Haemophilus influenzae (including β -lactamase-producing strains)
Moraxella (Branhamella) catarrhalis (including β -lactamase-producing strains)

The following *in vitro* data are available; however, their clinical significance is unknown. Cefprozil exhibits *in vitro* minimum inhibitory concentrations (MICs) of 8 mcg/mL or less against most ($\geq 90\%$) strains of the following microorganisms; however, the safety and effectiveness of cefprozil in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms:

<i>Enterococcus durans</i>	<i>Staphylococcus warneri</i>
<i>Enterococcus faecalis</i>	<i>Streptococcus agalactiae</i>
<i>Listeria monocytogenes</i>	<i>Streptococci</i> (Groups C, D, F, and G)
<i>Staphylococcus epidermidis</i>	viridans group <i>Streptococci</i>
<i>Staphylococcus saprophyticus</i>	

NOTE: Cefprozil is inactive against *Enterococcus faecium*.

Aerobic gram-negative microorganisms:

<i>Citrobacter diversus</i>	<i>Proteus mirabilis</i>
<i>Escherichia coli</i>	<i>Salmonella</i> spp.
<i>Klebsiella pneumoniae</i>	<i>Shigella</i> spp.
<i>Neisseria gonorrhoeae</i>	<i>Vibrio</i> spp.

(including β -lactamase-producing strains)

NOTE: Cefprozil is inactive against most strains of *Acinetobacter*, *Enterobacter*, *Morganella morganii*, *Proteus vulgaris*, *Providencia*, *Pseudomonas*, and *Serratia*.

Anaerobic microorganisms:

<i>Prevotella (Bacteroides) melaninogenicus</i>	<i>Fusobacterium</i> spp.
<i>Clostridium difficile</i>	<i>Peptostreptococcus</i> spp.
<i>Clostridium perfringens</i>	<i>Propionibacterium acnes</i>

NOTE: Most strains of the *Bacteroides fragilis* group are resistant to cefprozil.

Susceptibility Tests

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method^{1,2} (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefprozil powder. The MIC values should be interpreted according to the following criteria:

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

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of

“Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard cefprozil powder should provide the following MIC values:

<u>Microorganism</u>	<u>MIC (mcg/mL)</u>
<i>Enterococcus faecalis</i> ATCC 29212	4 to 16
<i>Escherichia coli</i> ATCC 25922	1 to 4
<i>Haemophilus influenzae</i> ATCC 49766	1 to 4
<i>Staphylococcus aureus</i> ATCC 29213	0.25 to 1
<i>Streptococcus pneumoniae</i> ATCC 49619	0.25 to 1

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure³ requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg cefprozil to test the susceptibility of microorganisms to cefprozil.

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

<u>Zone diameter (mm)</u>	<u>Interpretation</u>
≥ 18	Susceptible (S)
15 to 17	Intermediate (I)
≤ 14	Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefprozil.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30 mcg cefprozil disk should provide the following zone diameters in these laboratory test quality control strains.

<u>Microorganism</u>	<u>Zone diameter (mm)</u>
<i>Escherichia coli</i> ATCC 25922	21 to 27
<i>Haemophilus influenzae</i> ATCC 49766	20 to 27
<i>Staphylococcus aureus</i> ATCC 25923	27 to 33
<i>Streptococcus pneumoniae</i> ATCC 49619	25 to 32

INDICATIONS AND USAGE

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

Cefprozil tablets for oral suspension are indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

UPPER RESPIRATORY TRACT

Pharyngitis/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 route. Cefprozil is generally effective in the eradication of *Streptococcus pyogenes* from the nasopharynx; however, substantial data establishing the efficacy of cefprozil in the subsequent prevention of rheumatic fever are not available at present.

Otitis Media caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including β -lactamase-producing strains), and *Moraxella (Branhamella) catarrhalis* (including β -lactamase-producing strains). (See **CLINICAL STUDIES**.)

NOTE: In the treatment of otitis media due to β -lactamase producing organisms, cefprozil had bacteriologic eradication rates somewhat lower than those observed with a product containing a specific β -lactamase inhibitor. In considering the use of cefprozil, lower overall eradication rates should be balanced against the susceptibility patterns of the common microbes in a given geographic area and the increased potential for toxicity with products containing β -lactamase inhibitors.

Acute Sinusitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including β -lactamase-producing strains), and *Moraxella (Branhamella) catarrhalis* (including β -lactamase-producing strains).

LOWER RESPIRATORY TRACT

Secondary Bacterial Infection of Acute Bronchitis and Acute Bacterial

Exacerbation of Chronic Bronchitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including β -lactamase-producing strains), and *Moraxella (Branhamella) catarrhalis* (including β -lactamase-producing strains).

SKIN AND SKIN STRUCTURE

Uncomplicated Skin and Skin-Structure Infections caused by *Staphylococcus aureus* (including penicillinase-producing strains) and *Streptococcus pyogenes*.

Abscesses usually require surgical drainage.

Culture and susceptibility testing should be performed when appropriate to determine susceptibility of the causative organism to cefprozil.

CONTRAINDICATIONS

Cefprozil tablets for oral suspension are contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFPROZIL TABLETS FOR ORAL SUSPENSION IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFPROZIL TABLETS, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE

CROSS-SENSITIVITY AMONG β -LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFPROZIL TABLETS FOR ORAL SUSPENSION OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefprozil, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated" colitis.

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General

Prescribing cefprozil tablets for oral suspension 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.

In patients with known or suspected renal impairment (see **DOSAGE AND ADMINISTRATION**), careful clinical observation and appropriate laboratory studies should be done prior to and during therapy. The total daily dose of cefprozil tablets for oral suspension should be reduced in these patients because high and/or prolonged plasma antibiotic concentrations can occur in such individuals from usual doses. Cephalosporins, including cefprozil tablets for oral suspension, should be given with caution to patients receiving concurrent treatment with potent diuretics since these agents are suspected of adversely affecting renal function.

Prolonged use of cefprozil tablets for oral suspension may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Cefprozil should be prescribed with caution in individuals with a history of gastrointestinal disease particularly colitis.

Positive direct Coombs' tests have been reported during treatment with cephalosporin antibiotics.

Information for Patients

Patients should be counseled that antibacterial drugs including cefprozil tablets for oral suspension should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When cefprozil tablets for oral suspension are prescribed to treat a bacterial 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 bacteria will develop resistance and will not be treatable by cefprozil tablets for oral suspension or other antibacterial drugs in the future.

Drug Interactions

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporin antibiotics. Concomitant administration of probenecid doubled the AUC for cefprozil.

The bioavailability of the capsule formulation of cefprozil was not affected when administered 5 minutes following an antacid.

Drug/Laboratory Test Interactions

Cephalosporin antibiotics may produce a false positive reaction for glucose in the urine with copper reduction tests (Benedict's or Fehling's solution or with Clinitest[®] tablets), but not with enzyme-based tests for glycosuria (e.g., Tes-Tape[®]). A false negative reaction may occur in the ferricyanide test for blood glucose. The presence of cefprozil in the blood does not interfere with the assay of plasma or urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long term *in vivo* studies have not been performed to evaluate the carcinogenic potential of cefprozil.

Cefprozil was not found to be mutagenic in either the Ames *Salmonella* or *E. coli* WP2 *uvrA* reversion assays or the Chinese hamster ovary cell HGPRT forward gene mutation assay and it did not induce chromosomal abnormalities in Chinese hamster ovary cells or unscheduled DNA synthesis in rat hepatocytes *in vitro*. Chromosomal aberrations were not observed in bone marrow cells from rats dosed orally with over 30 times the highest recommended human dose based upon mg/m².

Impairment of fertility was not observed in male or female rats given oral doses of cefprozil up to 18.5 times the highest recommended human dose based upon mg/m².

Pregnancy: Teratogenic Effects. Pregnancy Category B

Reproduction studies have been performed in rabbits, mice, and rats using oral doses of cefprozil of 0.8, 8.5, and 18.5 times the maximum daily human dose (1000 mg) based upon mg/m², and have revealed no harm to the fetus. 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

Cefprozil has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

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Nursing Mothers

Small amounts of cefprozil (< 0.3% of dose) have been detected in human milk following administration of a single 1 gram dose to lactating women. The average levels over 24 hours ranged from 0.25 to 3.3 mcg/mL. Caution should be exercised when cefprozil tablets for oral suspension are administered to a nursing woman, since the effect of cefprozil on nursing infants is unknown.

Pediatric Use: (See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION.)

The safety and effectiveness of cefprozil in the treatment of otitis media have been established in the age groups 6 months to 12 years. Use of cefprozil tablets for oral suspension for the treatment of otitis media is supported by evidence from adequate and well-controlled studies of cefprozil in pediatric patients. (See **CLINICAL STUDIES**.)

The safety and effectiveness of cefprozil in the treatment of pharyngitis/tonsillitis or uncomplicated skin and skin structure infections have been established in the age groups 2 to 12 years. Use of cefprozil tablets for oral suspension for the treatment of these infections is supported by evidence from adequate and well-controlled studies of cefprozil in pediatric patients.

The safety and effectiveness of cefprozil in the treatment of acute sinusitis have been established in the age groups 6 months to 12 years. Use of cefprozil tablets for oral suspension in these age groups is supported by evidence from adequate and well-controlled studies of cefprozil in adults.

Safety and effectiveness in pediatric patients below the age of 6 months have not been established for the treatment of otitis media or acute sinusitis or below the age of 2 years for the treatment of pharyngitis/tonsillitis or uncomplicated skin and skin structure infections. However, accumulation of other cephalosporin antibiotics in newborn infants (resulting from prolonged drug half-life in this age group) has been reported.

Geriatric Use

Of the more than 4500 adults treated with cefprozil tablets in clinical studies, 14% were 65 years and older, while 5% were 75 years and older. When geriatric patients received the usual recommended adult doses, their clinical efficacy and safety were comparable to clinical efficacy and safety in nongeriatric adult patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals to the effects of cefprozil tablets for oral suspension cannot be excluded (see **CLINICAL PHARMACOLOGY**).

Cefprozil is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function. See **DOSAGE AND ADMINISTRATION** for dosing recommendations for patients with impaired renal function.

ADVERSE REACTIONS

The adverse reactions to cefprozil are similar to those observed with other orally administered cephalosporins. Cefprozil was usually well tolerated in controlled clinical trials. Approximately 2% of patients discontinued cefprozil therapy due to adverse events.

The most common adverse effects observed in patients treated with cefprozil are:

Gastrointestinal: Diarrhea (2.9%), nausea (3.5%), vomiting (1%), and abdominal pain (1%).

Hepatobiliary: Elevations of AST (SGOT) (2%), ALT (SGPT) (2%), alkaline phosphatase (0.2%), and bilirubin values (< 0.1%). As with some penicillins and some other cephalosporin antibiotics, cholestatic jaundice has been reported rarely.

Hypersensitivity: Rash (0.9%), urticaria (0.1%). Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy.

CNS: Dizziness (1%). Hyperactivity, headache, nervousness, insomnia, confusion, and somnolence have been reported rarely (< 1%). All were reversible.

Hematopoietic: Decreased leukocyte count (0.2%), eosinophilia (2.3%).

Renal: Elevated BUN (0.1%), serum creatinine (0.1%).

Other: Diaper rash and superinfection (1.5%), genital pruritus and vaginitis (1.6%). The following adverse events, regardless of established causal relationship to cefprozil tablets, have been rarely reported during postmarketing surveillance: anaphylaxis, angioedema, colitis (including pseudomembranous colitis), erythema multiforme, fever, serum-sickness like reactions, Stevens-Johnson syndrome, and thrombocytopenia.

Cephalosporin class paragraph

In addition to the adverse reactions listed above which have been observed in patients treated with cefprozil, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Aplastic anemia, hemolytic anemia, hemorrhage, renal dysfunction, toxic epidermal necrolysis, toxic nephropathy, prolonged prothrombin time, positive Coombs' test, elevated LDH, pancytopenia, neutropenia, 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

Single 5000 mg/kg oral doses of cefprozil caused no mortality or signs of toxicity in adult, weanling, or neonatal rats, or adult mice. A single oral dose of 3000 mg/kg caused diarrhea and loss of appetite in cynomolgus monkeys, but no mortality.

Cefprozil is eliminated primarily by the kidneys. In case of severe overdosage, especially in patients with compromised renal function, hemodialysis will aid in the removal of cefprozil from the body.

DOSAGE AND ADMINISTRATION

Directions for Cefprozil Tablets for Oral Suspension:

Dissolve one tablet in a glass with a suitable amount of water. Be sure to drink the entire mixture. Rinse the glass with an additional small amount of water and drink the contents to assure the whole dose is taken. Do not chew or swallow the tablets. Tablets will not rapidly dissolve in your mouth.

The tablet is not recommended to be mixed with any liquid other than water, as studies have only been conducted using water.

Cefprozil tablets for oral suspension are administered orally.

Population/Infection	Dosage (mg)	Duration (days)
ADULTS (13 years and older)		
UPPER RESPIRATORY TRACT		
Pharyngitis/Tonsillitis	500 q 24h	10 ^a
Acute Sinusitis (For moderate to severe infections, the higher dose should be used)	250 q 12h or 500 q 12h	10
LOWER RESPIRATORY TRACT		
Secondary Bacterial Infection of Acute Bronchitis and Acute Bacterial Exacerbation of Chronic Bronchitis	500 q 12h	10
SKIN AND SKIN STRUCTURE		
Uncomplicated Skin and Skin Structure Infections	250 q 12h or 500 q 24h or 500 q 12h	10
<hr/>		
CHILDREN (2 years to 12 years)		
UPPER RESPIRATORY TRACT^b		
Pharyngitis/Tonsillitis	7.5 mg/kg q 12h	10 ^a
SKIN AND SKIN STRUCTURE^b		
Uncomplicated Skin and Skin Structure Infections	20 mg/kg q 24h	10
<hr/>		
INFANTS & CHILDREN (6 months to 12 years)		
UPPER RESPIRATORY TRACT^b		
Otitis Media (See INDICATIONS AND USAGE and CLINICAL STUDIES)	15 mg/kg q 12h	10
Acute Sinusitis (For moderate to severe infections, the higher dose should be used)	7.5 mg/kg q 12h or 15 mg/kg	10

^a In the treatment of infections due to *Streptococcus pyogenes*, cefprozil tablets for oral suspension should be administered for at least 10 days.

^b Not to exceed recommended adult doses.

Renal Impairment

Cefprozil tablets for oral suspension may be administered to patients with impaired renal function. The following dosage schedule should be used.

Creatinine Clearance (mL/min)	Dosage (mg)	Dosing Interval
30 to 120	standard	standard
0 to 29*	50% of standard	standard

*Cefprozil is in part removed by hemodialysis; therefore, cefprozil tablets for oral suspension should be administered after the completion of hemodialysis.

Hepatic Impairment

No dosage adjustment is necessary for patients with impaired hepatic function.

HOW SUPPLIED

Description of Cefprozil Tablets for Oral Suspension to be determined.

Store at 20 - 25° C (68 - 77° F). (See USP Controlled Room Temperature).

CLINICAL STUDIES

Study One:

In a controlled clinical study of **acute otitis media** performed in the United States where significant rates of β -lactamase-producing organisms were found, cefprozil was compared to an oral antimicrobial agent that contained a specific β -lactamase inhibitor. In this study, using very strict evaluability criteria and microbiologic and clinical response criteria at the 10 to 16 days post-therapy follow-up, the following presumptive bacterial eradication/clinical cure outcomes (i.e. clinical success) and safety results were obtained:

U.S. Acute Otitis Media Study Cefprozil vs β -lactamase inhibitor-containing control drug

EFFICACY:

Pathogen	% of Cases with Pathogen (n = 155)	Outcome
<i>S. pneumoniae</i>	48.4%	cefprozil success rate 5% better than control
<i>H. influenzae</i>	35.5%	cefprozil success rate 17% less than control
<i>M. catarrhalis</i>	13.5%	cefprozil success rate 12% less than control
<i>S. pyogenes</i>	2.6%	cefprozil equivalent to control
Overall	100.0%	cefprozil success rate 5% less than control

SAFETY:

The incidences of adverse events, primarily diarrhea and rash*, were clinically and statistically significantly higher in the control arm versus the cefprozil arm.

Age Group	Cefprozil	Control
6 months to 2 years	21%	41%
3 to 12 years	10%	19%

*The majority of these involved the diaper area in young children.

Study Two:

In a controlled clinical study of **acute otitis media** performed in Europe, cefprozil was compared to an oral antimicrobial agent that contained a specific β -lactamase inhibitor. As expected in a European population, this study population had a lower incidence of β -lactamase-producing organisms than usually seen in U.S. trials. In this study, using very strict evaluability criteria and microbiologic and clinical response criteria at the 10 to 16 days post-therapy follow-up, the following presumptive bacterial eradication/clinical cure outcomes (i.e. clinical success) were obtained:

European Acute Otitis Media Study
Cefprozil vs β -lactamase inhibitor-containing control drug

EFFICACY:

Pathogen	% of Cases with Pathogen (n = 47)	Outcome
<i>S. pneumoniae</i>	51.0%	cefprozil equivalent to control
<i>H. influenzae</i>	29.8%	cefprozil equivalent to control
<i>M. catarrhalis</i>	6.4%	cefprozil equivalent to control
<i>S. pyogenes</i>	12.8%	cefprozil equivalent to control
Overall	100.0%	cefprozil equivalent to control

SAFETY:

The incidence of adverse events in the cefprozil arm was comparable to the incidence of adverse events in the control arm (agent that contained a specific β -lactamase inhibitor).

REFERENCES

1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*—Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December 1993.
2. National Committee for Clinical Laboratory Standards. *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria* —Third Edition. Approved Standard NCCLS Document M11-A3, Vol. 13, No. 26, NCCLS, Villanova, PA, December 1993.
3. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests*—Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.

Manufactured for:

Ranbaxy Pharmaceuticals Inc.
 Jacksonville, FL 32216 USA
 By: Ranbaxy Laboratories Limited
 New Delhi – 110 019, India

October 2003

FDA-1

PATIENT INFORMATION SHEET

Cefprozil Tablets for Oral Suspension

PATIENT'S DIRECTIONS FOR USE

Mix one Cefprozil Tablet for Oral Suspension in water before you take it.

1. Remove one tablet from the bottle.
2. Place the tablet in a small amount of water
3. Swirl or stir until thoroughly mixed.
4. Drink the mixture immediately after mixing.
5. Be sure to drink the entire mixture.
6. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken.

DO NOT CHEW or **SWALLOW** the Cefprozil Tablet for Oral Suspension whole. The tablet will not rapidly dissolve in your mouth.

Take all of the medicine as recommended by your doctor or other health care provider.

Do not mix the Cefprozil Tablet for Oral Suspension with any liquid other than water.

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590



ATTACHMENT 3

Search results from the "Rx" table for query on "050665."

Active Ingredient: CEFPROZIL
Dosage Form;Route: FOR SUSPENSION; ORAL
Proprietary Name CEFZIL
Applicant: BRISTOL MYERS SQUIBB
Strength: 125MG/5ML
Application Number: 050665
Product Number: 001
Approval Date: Dec 23, 1991
Reference Listed Drug: No
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: [Click Here](#)

Active Ingredient: CEFPROZIL
Dosage Form;Route: FOR SUSPENSION; ORAL
Proprietary Name CEFZIL
Applicant: BRISTOL MYERS SQUIBB
Strength: 250MG/5ML
Application Number: 050665
Product Number: 002
Approval Date: Dec 23, 1991
Reference Listed Drug: Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: [Click Here](#)

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