CEFZIL®

CEFPROZIL
(Tablets & Oral Suspension)

DESCRIPTION

CEFZIL (cefprozil) is a semi-synthetic broad-spectrum cephalosporin antibiotic 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 contains FD&C yellow No. 6.

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

CLINICAL PHARMACOLOGY

Cefprozil is well absorbed following oral administration in both fasting and non-fasting subjects. The oral bioavailability of cefprozil is about 90%. The pharmacokinetics of cefprozil are not altered when administered with meals, or when co-administered with antacid. Average plasma concentrations after administration of cefprozil to fasting subjects are shown in the following table.
Urinary recovery accounts for approximately 60% of the administered dose.

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

*Data represent mean values from 12 healthy, young male volunteers.
Pharmacokinetic data were derived from a capsule dosage form; however, bioequivalence has been demonstrated for oral solution, capsule, tablet and suspension formulations under fasting conditions.

During the first four-hour period after drug administration, the average urine concentrations following the 250 mg, 500 mg and 1 g doses are approximately 170 mcg/ml, 450 mcg/ml and 600 mcg/ml, respectively.
Plasma protein binding is approximately 36% and is independent of concentration in the range of 2 mcg/ml to 20 mcg/ml. The average plasma half-life in normal subjects is 1.3 hours.
After administration of single 7.5 or 20 mg/kg doses to pediatric patients, concentrations of cefprozil ranged from 0.5 to 4.3 mcg/g in tonsillar tissue and ranged from 0.4 to 4.9 mcg/g in adenoidal tissue. Concentrations in tonsillar and adenoidal tissue over 3.2 hour after dosing are higher than the MICs for common pathogens which cause pharyngitis or tonsillitis.
Peak concentrations of cefprozil in skin blister fluid were 3.0 and 5.8 mcg/ml in subjects receiving a single 250 mg or 500 mg dose of cefprozil respectively.
Skin blister fluid half-life (2.3 hours) is longer than that observed in plasma.
After administration of single 15 or 20 mg/kg doses to patients with chronic otitis media, concentrations of cefprozil in middle ear fluid ranged from 0.06 to 8.7 mcg/ml. Cefprozil concentrations in middle ear fluid remained above the MIC for most common bacteria associated with otitis media for over 6 hours after administration of cefprozil.
There is no evidence of accumulation of cefprozil in the plasma in individuals with normal renal function following multiple oral doses of up to 1 g every 8 hours for 10 days.
In patients with reduced renal function, the plasma half-life prolongation is related to 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 to 2.1 hours. Excretion pathways in patients with markedly impaired renal function have not been determined. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).
The average AUC observed in elderly subjects (≥ 65 years of age) is approximately 35-60% higher than that of young adults and the average AUC in females is approximately 15-20% higher than in males.
The magnitude of these age and gender-related variations in the pharmacokinetics of cefprozil are not sufficient to necessiate dosage adjustments.
In patients with impaired hepatic function, no statistically significant differences in pharmacokinetic parameters are observed, when compared to normal control subjects.

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 is usually active against most strains of the following organisms *in Vitro*

Aerobes, gram-positive:

- Staphylococci including Staphylococcus aureus (including penicillinase-producing strains); *S. epidermidis; S. saprophyticus; S. warneri.* NOTE: Cefprozil is inactive against methicillin-resistant staphylococci.
- Streptococci including *streptococcus pyogenes* (Group A streptococci); *S. agalactiae* (Group B streptococci); *S. pneumoniae* (including intermediate penicillin-resistant strains with penicillin MIC of 0.1 to 1 mcg/ml); Group C, D, F, & G streptococci; Viridans group streptococci.
- *Enterococcus durans; E. faecalis;* NOTE: Cefprozil is inactive against *E. faecium.*
- Other: *Listeria monocytogenes.*

Aerobes, gram-negative:

- *Moraxella catarrhalis* (including beta-lactamase-producing strains).
- *Haemophilus influenzae* (including beta-lactamase-producing strains).
- *Citrobacter diversus.*
- *Escherichia coli.*
- *Klebsiella pneumoniae.*
- *Neisseria gonorrhoeae* (including penicillinase-producing strains).
- *Proteus mirabilis.*
- *Salmonella sp.*
- *Shigella sp.*
- *Vibrio sp.*

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

Anaerobes:

- *Bacteroides melaninogenicus*; NOTE: Most strains of the *Bacteroides fragilis* group are resistant to cefprozil.
- *Clostridium difficile; C. perfringens.*
- *Fusobacterium sp.*
- *Peptostreptococcus sp.*
- *Propionibacterium acnes.*

Susceptibility tests:

Quantitative methods that require measurement of zone diameters give the most precise estimate of the susceptibility of bacteria to antimicrobial agents. Interpretation involves correlation of the diameter obtained in the disk test with the minimum inhibitory concentration (MIC) for cefprozil.
The class disc for cephalosporin susceptibility testing (the cephalothin disk) is not appropriate because of spectrum differences with cefprozil. The 30 mcg cefprozil disk should be used in all Vitro testing of isolates.
Reports from the laboratory giving results of the standard susceptibility test with a 30 mcg cefprozil disk should be interpreted according to the following criteria:

Zone diameter (mm)	Interpretation	MIC correlate
≥ 18	(S) Susceptible	≤ 8 mcg/ml
15 - 17	(MS) Moderately Susceptible	16 mcg/ml
≤ 14	(R) Resistant	≥ 32 mcg/ml

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood concentrations. A report of "Moderately Susceptible" indicated that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained. A report of "Resistant" indicates that the achievable concentration of the antibiotic is unlikely to be inhibitory.
Standardized procedures require the use of laboratory control organisms.

INDICATIONS AND USAGE:

CEFZIL is indicated for the treatment of patients with the following infections caused by susceptible strains of bacteria:

- Upper respiratory tract infections including pharyngitis, tonsillitis, sinusitis and otitis media.
- Lower respiratory tract infections including bronchitis and pneumonia.
- Skin and skin structure infections.

NOTE: Abscesses usually require surgical drainage.

- Uncomplicated urinary tract infections including acute cystitis.

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

CONTRAINDICATIONS

CEFZIL 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 THE PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-SENSITIVITY AMONG BETA-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 **CEFZIL** OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EMERGENCY TREATMENT MEASURES.

Pseudomembranous colitis has been reported with nearly all antibacterial agents including cefprozil, and may range 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. After the diagnosis of colitis has been established, therapeutic measures should be initiated.

PRECAUTIONS

General:

The total daily dose of **CEFZIL** should be reduced in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) because high and/or prolonged plasma antibiotic concentrations can occur 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. If superinfection occurs during therapy, appropriate measures should be taken.

positive direct combs tests have been reported during treatment with cephalosporin antibiotics.

Information for Patients:

Phenylketonurics: **CEFZIL** for Oral Suspension contains phenylalanine (from asparatame) 28 mg per 5 ml (1 teaspoon) 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 area-under-the-curve (AUC) for cefprozil.

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 (glucose oxidase) for glycosuria. 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:

No mutagenic potential of cefprozil was found in appropriate prokaryotic or eurkaryotic cells *in vitro* or *in vivo*. No *in vivo* long-term studies have been performed to evaluate carcinogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

Use In Pregnancy:

Reproduction studies have been performed in mice, rats, and rabbits at doses 14, 7 and 0.7 times the maximum daily human dose (1000 mg) based upon mg/m^2, and have revealed no evidence of harm to the fetus due to cefprozil monohydrate. 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.

Nursing Mothers:

Less than 0.3% of a maternal dose is excreted in human milk.

Caution should be exercised when **CEFZIL** is administered to a nursing mother.

Pediatric Use:

Safety and effectiveness in children below the age of 6 months have not been established.

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 in clinical trials 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 with a few days after cessation of therapy.

CNS: Dizziness (1%). Hyperactivity, headache, nervousness, inosmnia, confusion, and somnolence have been reported rarely (<1%) and causal relationship is uncertain. All were reversible.

Hematopoietic: Transiently decreased leukocyte count (0.2%), eosinophilia (2.3%). Prolonged prothrombin time also has been observed rarely.

Renal: Slight elevations in BUN (0.1%), serum creatinine (0.1%).

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

The following events known to be associated with cephalosporin antibiotics were not observed in clinical trials but rare occurrences have been reported in post-marketing experience with cefprozil: serum sickness and colitis, including pseudomembranous colitis.

* Clinitest is the trademark of Ames

OVERDOSAGE

single doses as high as 5000 mg/kg administered in animal toxicology studies were without serious or lethal consequences.

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 may be administered without regard to meals, since food has no significant effect on absorption.

Adults and children over 12 years:

CEFZIL is administered orally in the treatment of infections due to susceptible bacteria in the following doses:

Upper respiratory infections	500 mg every 24 hours.
Sinusitis	250 mg every 12 hours.
Lower respiratory infections	500 mg every 12 hours.
Uncomplicated urinary tract infections	500 mg every 24 hours.
Skin & skin structure infections	250 mg every 12 hours or 500 mg every 24 hours.

Children:

In clinical trials, **CEFZIL** has been administered to children who were at least 6 months old.

In otitis media, the recommended dose of **CEFZIL** is 15 mg/kg administered every 12 hours.

In upper respiratory infections, pharyngitis or tonsillitis, the recommended dose of **CEFZIL** is 20 mg/kg once daily or 15 mg/kg days divided into two equal doses.

In uncomplicated skin and skin structure infections, 20 mg/kg once daily is recommended.

The maximum pediatric daily dose should not exceed the maximum daily dose recommended for adults. In the treatment of ß-hemolytic streptococcal infections, a therapeutic dosage of **CEFZIL** should be administered for 10 days.

Renal Impairment:

Cefprozil may be administered to patients with impaired renal function. No dosage adjustment is necessary for patients with creatinine clearance values > 30 ml/min. For those with creatinine clearance values ≤ 30 ml/min, following administration of the first standard dose, 50% of the standard dose subsequently should be given at the standard dosing interval. 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:

Box of 10 or 8 coated tablets 250 mg.

Box of 10 or 8 coated tablets 500 mg.

Store at room temperature (15° - 30° C).

CEFZIL (cefprozil) oral suspension:

Bottles of 50 ml or 75 ml:

125 mg / 5 ml after reconstitution.

250 mg / 5 ml after reconstitution.

All powder formulations for oral suspension contain cefprozil is a pleasantly flavored mixture. Directions for mixing are included on the box. Shake well before using. Keep container tightly closed. After mixing, store in a refrigerator, and discard unused portion after 14 days.

Do not store above 25° C prior to constitution.

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