PRODUCT MONOGRAPH

Pr AVA-CEFPROZIL

(cefprozil)

Tablets, 250 mg and 500 mg

Powder For Oral Suspension, 125 mg/5 mL and 250 mg/5 mL, when reconstituted

USP Standard

Antibiotic

Avanstra Inc.
10761-25th street NE, Suite 110,
Calgary, Alberta, Canada
T3N 0A4

Date of Revision: June 12, 2012

Submission Control No: 155846

[Pr] AVA-CEFPROZIL

(cefprozil)

Tablets, 250 mg and 500 mg
Powder For Oral Suspension, 125 mg/5 mL and 250 mg/5 mL, when reconstituted

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION AND CLINICAL PHARMACOLOGY

Cefprozil is a semi synthetic broad-spectrum cephalosporin antibiotic intended for oral administration. It 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.

Pharmacokinetics
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 coadministered with antacid. Average plasma concentrations after administration of cefprozil to fasting subjects are shown in the following table. Urinary recovery accounts for 60% of the administered dose.

Dosage	**Mean Plasma Cefprozil* Concentrations (mcg/mL)**			**8-hour Urinary Excretion**
	Peak ~ 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.

During the first four-hour period after drug administration, the average urine concentrations following the 250 mg, 500 mg, and 1 g doses were approximately 170 mcg/mL, 450 mcg/mL and 600 mcg/mL, respectively.

The average plasma half-life in normal subjects is 1.3 hours. Plasma protein binding is approximately 36% and is independent of concentration in the range of 2 mcg/mL to 20 mcg/mL. 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 renal insufficiency
In patients with reduced renal function, the plasma half-life prolongation is related to the degree of the renal dysfunction and may be prolonged up to 5.2 hours. In patients with complete absence

of renal function, the plasma half-life of cefprozil averaged 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).

In patients with hepatic insufficiency
In patients with impaired hepatic function, no differences in pharmacokinetic parameters were observed, when compared to normal control subjects.

In elderly subjects
Following administration of a single 1 g dose of cefprozil, the average AUC observed in healthy elderly subjects (≥ 65 years of age) was approximately 35-60% higher than that of healthy young adults and the average AUC in females was 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 necessitate dosage adjustments.

In pediatric subjects
Comparable pharmacokinetic parameters of cefprozil are observed between pediatric patients (6 months-12 years) and adults following oral administration. The maximum plasma concentrations are achieved at 1-2 hours after dosing. The plasma elimination half-life is approximately 1.5 hours. The AUC of cefprozil to pediatric patients after 7.5, 15 and 30 mg/kg doses is similar to that observed in normal adult subjects after 250, 500 and 1000 mg doses, respectively.

INDICATIONS AND CLINICAL USE

Ava-Cefprozil (cefprozil) is indicated for the treatment of the following infections caused by susceptible strains of the designated microorganisms:

UPPER RESPIRATORY TRACT

Pharyngitis/tonsillitis caused by group A β-hemolytic (GABHS) *Streptococcus pyogenes*.

Substantial data establishing the efficacy of cefprozil in the subsequent prevention of rheumatic fever are not available at present, although no case was reported during its evaluation in over 978 pediatric and 831 adult patients in controlled clinical trials.

Otitis media caused by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella (Branhamella) catarrhalis.*

Acute sinusitis caused by *Streptococcus pneumoniae, Haemophilus influenzae*, (beta-lactamase positive and negative strains), and *Moraxella (Branhamella) catarrhalis*.

SKIN AND SKIN STRUCTURE

Uncomplicated skin and skin-structure infections caused by *Staphylococcus aureus* (including penicillinase-producing strains) and *Streptococcus pyogenes*.

URINARY TRACT

Uncomplicated urinary tract infections (including acute cystitis) caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis.*

Cultures and susceptibility studies should be performed when appropriate.

CONTRAINDICATIONS

Ava-Cefprozil is contraindicated in patients with known allergy to the cephalosporin class of antibiotics or to any component of the cefprozil preparations (see PHARMACEUTICAL INFORMATION, Composition).

WARNINGS

Hypersensitivity

BEFORE THERAPY WITH AVA-CEFPROZIL IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFPROZIL, CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. IF THIS 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 Ava-Cefprozil 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.

Gastrointestinal

Clostridium difficile-associated disease

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including cefprozil. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see ADVERSE REACTIONS).

Hemolytic Anemia

AVA-CEFPROZIL SHOULD NOT BE USED IN PATIENTS WITH A HISTORY OF CEPHALOSPORIN-ASSOCIATED HEMOLYTIC ANEMIA SINCE THE RECURRENCE OF HEMOLYSIS IS MUCH MORE SEVERE.

An immune mediated hemolytic anemia has been observed in patients receiving cephalosporin class antibacterials. Severe cases of hemolytic anemia, including fatalities, have been reported in both adults and children. If a patient develops anemia anytime during, or within 2-3 weeks subsequent to the administration of cefprozil, the diagnosis of a cephalosporin-associated anemia should be considered and the drug discontinued until the etiology is determined.

Patients may benefit from periodic monitoring for signs and symptoms of hemolytic anemia, including measurement of hematological parameters or drug-induced antibody testing, where appropriate (see ADVERSE REACTIONS).

PRECAUTIONS

General

Evaluation of renal status before and during therapy is recommended, especially in seriously ill patients. 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 should be reduced in patients with creatinine clearance values ≤ 30 mL/min because high and/or prolonged plasma antibiotic concentrations can occur from usual doses in such individuals. Cephalosporins, including cefprozil, 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 may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

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

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

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 for cefprozil.

If an aminoglycoside is used concurrently with cefprozil, especially if high dosages of the former are used or if therapy is prolonged, renal function should be monitored because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics.

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.

Use in pregnancy

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

Nursing Mothers

Less than 1.0% of a maternal dose is excreted in human milk. Caution should be exercised when Ava-Cefprozil is administered to a nursing mother. Consideration should be given to temporary discontinuation of nursing and use of formula feeding.

Pediatric Use

The use of cefprozil in the treatment of acute sinusitis in these age groups is supported by evidence from adequate and well-controlled studies of cefprozil in adults and from pediatric pharmacokinetic studies.

Safety and effectiveness in children below the age of 6 months have not been established. Accumulation of other cephalosporin antibiotics in newborn infants (resulting from prolonged drug half-life in this age group) has been reported.

Geriatric Use

Cefprozil has not been studied in the chronically ill or institutionalized elderly subjects. In these subjects, drug clearance by the kidney may be reduced even with normal serum creatinine clearance. Reduction of dose or of frequency of administration may be indicated.

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 events (of probable or unknown relationship to study drug) observed in 4227 patients treated with cefprozil in clinical efficacy trials are:

Gastrointestinal: Diarrhea (2.7%), nausea (2.3%), vomiting (1.4%) and abdominal pain (0.9%).

Hepatobiliary: As with some penicillins and some other cephalosporin antibiotics, cholestatic jaundice has been reported rarely.

Hypersensitivity: Rash (1.2%), erythema (0.1%), pruritus (0.3%) and urticaria (0.07%). 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, hyperactivity, headache, nervousness, insomnia, confusion and drowsiness have been reported rarely (<1%) and causal relationship is uncertain. All were reversible.

Other: Genital pruritus (0.8%) and vaginitis (0.7%).

Laboratory abnormalities
Transitory abnormalities in clinical laboratory test results of uncertain etiology have been reported during clinical trials as follows:

Hepatobiliary: Elevations of AST, ALT, alkaline phosphatase, and bilirubin.

Hematopoietic: Transiently decreased leukocyte count and eosinophilia.

Renal: Slight elevations in BUN and serum creatinine.

Adverse reactions reported from post-marketing experience and which were not seen in the clinical trials include anaphylaxis (see WARNINGS), angioedema, serum sickness, colitis including pseudomembraneous colitis (see WARNINGS), erythema multiforme, fever, Stevens-Johnson syndrome, thrombocytopenia and exfoliative dermatitis. Tooth discoloration has been reported during post-marketing surveillance. The association between these events and cefprozil administration is unknown.

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. Toxic epidermal necrolysis, renal dysfunction, toxic

nephropathy, aplastic anemia, hemolytic anemia (see WARNINGS), hemorrhage, prolonged prothrombin time, positive Coombs's tests, 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.

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Since no case of overdosage has been reported to date, no specific information on symptoms or treatment of overdosage is available. In animal toxicology studies, single doses as high as 5000 mg/kg 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

Recommended Dose and Dosage Adjustment

Ava-Cefprozil (cefprozil) is administered orally (with or without food), in the treatment of infections due to susceptible bacteria in the following doses:

Adults (13 years and older)

Upper respiratory tract (pharyngitis/tonsillitis)	500 mg q24h
Acute sinusitis	250 mg or 500 mg q12h
Skin & skin structure	250 mg q12h or 500 mg q24h
Uncomplicated urinary tract	500 mg q24h

Children (2 years-12 years)

Skin & skin structure	20 mg/kg q24h

Age * (years)	Weight (kg)	Multidose Bottle			
		125 mg/5 mL		250 mg/5 mL	
		tsp/dose	mL/dose	tsp/dose	mL/dose
2-3	11-14	2.0	10.0	1.0	5.0
4-6	15-21	3.0	15.0	1.5	7.5
7-8	22-26	---	---	2.0	10.0
9-10	28-31	---	---	2.5	12.5
11	35	---	---	3.0	15.0

* Ages given are a useful guide only. Correct dosage should be determined by weight.

Infants and children (6 months-12 years)

Otitis media	15 mg/kg q12h

Age * (years)	Weight (kg)	Multidose Bottle			
		125 mg/5 mL		250 mg/5 mL	
		tsp/dose	mL/dose	tsp/dose	mL/dose
6 mths-1 yr	7-9	1.0	5.0	0.5	2.5
2	11-12	1.5	7.5	0.75	3.75
3-4	14-15	---	---	1.0	5.0
5-6	17-21	---	---	1.25	6.25
7-8	22-26	---	---	1.5	7.5
9-10	28-31	---	---	1.75	8.75
11-12	35-39	---	---	2.0	10.0

Upper respiratory tract (pharyngitis/tonsillitis) 7.5 mg/kg q12h

Age * (years)	Weight (kg)	Multidose Bottle			
		125 mg/5 mL		250 mg/5 mL	
		tsp/dose	mL/dose	tsp/dose	mL/dose
6 mths-1 yr	7-9	0.5	2.5	---	---
2-6	11-21	1.0	5.0	0.5	2.5

Age * (years)	Weight (kg)	Multidose Bottle			
		125 mg/5 mL		250 mg/5 mL	
		tsp/dose	mL/dose	tsp/dose	mL/dose
7-9	22-28	---	---	0.75	3.75
10-11	31-35	---	---	1.0	5.0
12	41	---	---	1.25	6.25

* Ages given are a useful guide only. Correct dosage should be determined by weight.

Acute sinusitis 7.5 mg/kg q12h or 15 mg/kg q12h

Follow dosing instructions as for otitis media and upper respiratory tract presented above.

The maximum pediatric daily dose should not exceed the maximum daily dose recommended for adults (i.e. 1 g per day).

Duration of Therapy

Duration of therapy in the majority of clinical trials was 10 to 15 days. The duration of treatment should be guided by the patient's clinical and bacteriological response. In the treatment of acute uncomplicated cystitis, a 7 day oral therapy is usually sufficient. In the treatment of infections due to *Streptococcus pyogenes*, a therapeutic dosage of Ava-Cefprozil should be administered for at least 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, 50% of the standard dose 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.

AVAILABILITY OF DOSAGE FORMS

Dosage forms

Ava-Cefprozil (cefprozil) 250 mg tablets are oval, unscored, white to cream tinged tablets, embossed "347" on one side and "250" on the other side.

Ava-Cefprozil (cefprozil) 500 mg tablets are oval, unscored, beige tablets, embossed "348" on one side and "500" on the other side.

Ava-Cefprozil for oral suspension contains cefprozil, in an orange-flavoured mixture, equivalent to 125 mg or 250 mg cefprozil per 5 mL of constituted solution.

Packaging

Ava-Cefprozil (cefprozil) 250 mg and 500 mg tablets are available in bottles of 100.

Ava-Cefprozil for oral suspension 125 mg/5 mL and 250 mg/5 mL are available in bottles of 75 mL and 100 mL.

PHARMACEUTICAL INFORMATION

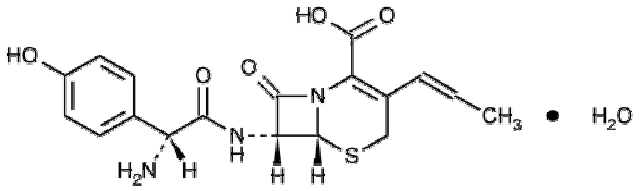
Drug Substance

Proper Name: Cefprozil

Chemical Name: (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

Molecular formula and molecular mass: $C_{18}H_{19}N_3O_5S \cdot H_2O$, 407.45

Structural Formula:



Physicochemical properties: The following solubilities of cefprozil milled were found:

Solvent	Results of Analysis
Methanol	Slightly soluble
Water	Slightly soluble
Acetone	Practically insoluble
Dichloromethane	Practically insoluble

Cefprozil is a cis and trans isomeric mixture in a 9:1 ratio. It is a white to yellowish crystalline powder with a melting point of 197°C. It is poorly soluble (< 1 mg/mL) in acetone, chloroform, ethanol and isopropanol and has an approximate solubility of 11 mg/mL in methanol and 1.6 mg/mL in dimethyl sulfoxide. It is slightly soluble in water. Cefprozil has an apparent octanol/water partition coefficient of 0.01 at pH 6 and 22°C. pH and pKa values are between 3.5 and 6.5, in a solution containing 5 mg per mL.

Composition

In addition to the active ingredient cefprozil, Ava-Cefprozil tablets contain the following inactive ingredients: hypromellose, magnesium stearate, methylcellulose, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, titanium dioxide. The 500 mg strength also contains ferric oxide yellow.

In addition to the active ingredient cefprozil, Ava-Cefprozil for oral suspension also contains: aspartame, citric acid, colloidal silicone dioxide, flavours (natural and artificial), FD&C Yellow no. 6, microcrystalline cellulose, sodium benzoate, sodium carboxymethylcellulose, sodium chloride, simethicone, sucrose, polysorbate 80 and glycine.

STORAGE AND STABILITY

Ava-Cefprozil tablets and powder for oral suspension must be stored between 15 and 30°C and protected from light and excessive humidity.

RECONSTITUTION

Prior to dispensing, the pharmacist must constitute the dry powder with water as follows:

Ava-Cefprozil for oral suspension	Bottle size (mL)	Diluent (water) added to bottle (mL)	Approximate available volume (mL)	Final concentration
125 mg/5 mL	75 100	54 72	75 100	l25 mg/5 mL l25 mg/5 mL
250 mg/5 mL	75 100	54 72	75 100	250 mg/5 mL 250 mg/5 mL

For ease in preparation, the water can be added in two portions. Shake well after each addition and prior to use.

STORAGE OF RECONSTITUTED SUSPENSION

The constituted Ava-Cefprozil oral suspension must be refrigerated between 2 and 8°C for up to 14 days. Keep container tightly closed. Discard unused portion after 14 days.

CLINICAL TRIALS

Comparative Bioavailability Studies

A single dose, crossover bioavailability study of cefprozil 500 mg tablets was conducted on a total of 25 healthy male (11) and female (14) volunteers (aged 18-55 years) under fasting conditions. The study results are based on data from 22 healthy adult volunteers.

Cefprozil in Plasma (Dose 1 x 500 mg cefprozil tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Cefprozil 500 mg tablet (A)	Cefzil® 500 mg tablet [1] (B)	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (mcg·h/mL)	33.671 34.19 (18.5)	33.936 34.53 (19.4)	99	97-102
AUC_{INF} (mcg·h/mL)	33.903 34.43 (18.6)	34.355 34.98 (19.8)	99	97-102
C_{max} (mcg /mL)	11.877794 12.11500 (21.1)	11.622830 11.81000 (18.9)	102	99-107
T_{max} [2] (h)	1.320 (22.1)	1.600 (36.7)		
$T_{½}$ [2] (h)	1.331 (9.5)	1.313 (8.1)		

1[2] Cefzil® 500 mg (cefprozil) tablets (Bristol-Myers Squibb Company, US), were purchased in the US

[2] Expressed as arithmetic mean (CV%) only.

A single dose, randomised, 2-way crossover bioequivalence study of cefprozil powder for oral suspension versus Bristol-Myers Squibb's Cefzil, each administered as 10 mL x 125 mg/5 mL (total dose of 250 mg) oral suspension, was conducted on a total of 18 healthy male and female volunteers (10 males and 8 females, aged 18-55 years) under fasting conditions.

Total Cefprozil in Plasma (Dose 10 mL of 125 mg/5 mL cefprozil as oral suspension) From measured data (total cefprozil) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Cefprozil	Cefzil™ †	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	13580.57 13785.72 (18.34)	14468.01 14674.27 (17.69)	93.87	91.82-95.96
AUC_I (ng·h/mL)	13872.45 14077.21 (18.17)	14735.18 14940.43 (17.46)	94.15	92.21-96.12
C_{max} (ng/mL)	5703.71 5814.29 (20.32)	6058.30 6178.08 (21.28)	94.15	90.75-97.67

Total Cefprozil in Plasma (Dose 10 mL of 125 mg/5 mL cefprozil as oral suspension) From measured data (total cefprozil) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Cefprozil	Cefzil™ †	% Ratio of Geometric Means	90% Confidence Interval
T_{max} ▯ (h)	1.03 (20.25)	1.04 (16.97)		
$T_{½}$ ▯ (h)	1.33 (20.28)	1.30 (13.78)		

† Cefzil® 125 mg/5 mL (cefprozil) Powder for Oral Suspension (Bristol-Myers Squibb Canada Inc), purchased in Canada

▯ Expressed as the arithmetic mean (CV%) only

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 more stable than cefaclor to beta lactamase hydrolysis by plasmid-encoded penicillinases including TEM and *S. aureus* enzymes as well as class Ia, Ib, Ic and Id enzymes.

The *in vitro* activity of cefprozil against clinical isolates is shown below:

Organism	**Number of Isolates**	**Low MIC (mcg/mL)**	**High MIC (mcg/mL)**	**MIC_{50} (mcg/mL)**	**MIC_{90} (mcg/mL)**
Corynebacterium sp.	13	≤0.008	4.000	<0.008	1.04
S. faecalis	77	0.500	16.000	5.369	8.211
Strep. (Group A)	309	≤0.008	1.000	0.015	0.088
Strep. (Beta hemolytic)	1	0.016	0.016		
S. agalactiae	1	0.250	0.250		
S. intermedius	1	0.125	0.125		
Strep. (Group G)	32	≤0.008	0.500	0.025	0.150
Strep. (Group C)	28	0.016	0.500	0.018	0.339
Enterococcus	2	8.000	8.000		
Strep. (Group F)	8	0.064	1.000	0.157	
S. salivarius	1	0.064	0.064		
Strep. (Group B)	48	0.016	0.500	0.084	0.287
S. mitis	13	≤0.008	2.000	0.117	0.451
S. constellatus	1	0.500	0.500		
S. sanguis	17	0.064	2.000	0.149	1.110
S. aureus	344	0.064	8.000	0.863	2.109
S. epidermidis	145	0.016	32.000	0.341	3.123
S. saprophyticus	21	0.500	4.000	0.728	1.653
S. hominis	21	0.032	>128.000	0.375	1.932
S. capitis	9	0.016	0.125	0.025	
S. simulans	6	0.032	0.500	0.125	
S. hæmolyticus	15	0.032	>128.000	0.445	3.364
S. colinii	3	0.250	1.000		
S. warneri	8	0.016	0.500	0.091	

Organism	Number of Isolates	Low MIC (mcg/mL)	High MIC (mcg/mL)	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)
S. xylosus	2	0.250	0.500		
Micrococcus sp.	2	0.032	0.250		
Aerococcus sp.	1	1.000	1.000		
S. pneumoniae	126	≤0.008	1.000	0.042	0.316
P. æruginosa	35	>128.000	>128.000	>128.000	>128.000
P. maltophilia	9	>128.000	>128.000	>128.000	
P. fluorescens	2	>128.000	>128.000		
P. paucimobilis	1	2.000	2.000		
P. vesicularis	1	32.000	32.000		
P. putida	5	>128.000	>128.000	>128.000	
P. cepacia	1	>128.000	>128.000		
Pseudomonas Sp. VE-2	1	>128.000	>128.000		
P. mendocina	1	> 128.000	>128.000		
P. acidovorans	1	> 128.000	>128.000		
E. coli	551	0.064	>128.000	1.223	4.948
C. freundii	14	0.500	>128.000	11.314	>78.793
C. diversus	9	0.500	8.000	0.749	
K. pneumoniae	68	0.032	32.000	0.660	1.711
K. ozænæ	1	4.000	4.000		
K. oxytoca	11	0.125	32.000	1.122	7.464
E. cloacæ	38	8.000	>128.000	38.055	>128.000
E. aerogenes	15	16.000	>128.000	24.675	>76.109
E. sakazakii	1	8.000	8.000		
E. geroviæ	2	2.000	8.000		
H. alvei	1	16.000	16.000		
S. marcescens	10	4.000	>128.000	>128.000	>128.000
P. mirabilis	66	0.250	8.000	3.143	6.662
P. vulgaris	3	>128.000	>128.000		
M. morganii	7	4.000	>128.000	>128.000	
P. stuartii	1	16.000	16.000		
E. agglomerans	8	0.500	>128.000	2.000	
H. infuenzae	11	0.125	8.000	0.771	3.864
H. infuenzae (P+)	14	1.000	16.000	2.692	6.964
H. infuenzae (P-)	77	0.250	32.000	0.887	4.550
H. parainfuenzae	9	0.016	1.000	0.223	
H. parainfuenzae (P+)	1	1.000	1.000		
Flavobacterium Sp.	1	1.000	1.000		
A. anitratus	22	4.000	>128.000	84.449	>128.000
A. lwoffi	17	1.000	>128.000	8.980	>95.339
A. hæmolyticus	1	64.000	64.000		
M. catarrhalis	9	0.500	4.000	0.917	
M. catarrhalis (P+)	32	0.064	4.000	0.707	2.297
M. catarrhalis (P-)	4	0.032	2.000	0.045	
A. hydrophilia	1	1.000	1.000		

Cefprozil is inactive against methicillin resistant *Staphylococci*, *Enterococcus faecium*, most strains of *Acinetobacter*, *Enterobacter*, *Morganella morganii*, *Proteus vulgaris*, *Providencia*, *Pseudomonas* and *Serratia*.

Susceptibility tests

Diffusion Techniques

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 disk for cephalosporin susceptibility testing (the cephalothin disk) is not appropriate because of spectrum differences with cefprozil. The 30 mcg cefprozil disk should be used for all *in vitro* testing of isolates and should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥18	(S) Susceptible
15-17	(MS) Moderately Susceptible
≤14	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood concentrations. A report of "Moderately Susceptible" indicates 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. The 30 mcg cefprozil disk should give the following zone diameters:

Organism	Zone Diameter (mm)
Escherichia coli ATCC 25922	21-27
Staphylococcus aureus ATCC 25923	27-33

Dilution Techniques

Use a standardized dilution method (broth, agar, microdilution) or equivalent with cefprozil powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤ 8	(S) Susceptible
16	(MS) Moderately Susceptible
≥ 32	(R) Resistant

As with standard diffusion techniques, dilution techniques require the use of laboratory control organisms. Standard cefprozil powder should give the following MIC values:

Organism	MIC (mcg/mL)
Enterococcus faecalis ATCC 29212	4-16
Escherichia coli ATCC 25922	1-4
Pseudomonas aeruginosa ATCC 27853	> 32

Organism	MIC (mcg/mL)
Staphylococcus aureus ATCC 29213	0.25-1

TOXICOLOGY

Acute toxicity

Species/Strain	Sex (N)	Route	Estimated LD_{50} (mg/kg)
Mouse Swiss-Webster	M (5) F (5)	Oral gavage (200 mg/mL suspension)	> 5000
Rat Sprague-Dawley	M (5) F (5)	Oral gavage (200 mg/mL suspension)	> 5000
Rat Sprague-Dawley	M (15)** F (15)**	Oral gavage (250 mg/mL suspension) * CMC 0.5%	> 5000
Monkey Cynomolgus	M (1) F (1)	Oral gavage (200 mg/mL suspension)	> 3000
Mouse Swiss-Webster	M (5) F (5)	IP	> 5000
Mouse Swiss-Webster	M (5) F (5)	Subcutaneous	> 5000

* CMC = Carboxymethylcellulose
** Includes 5 neonates, 5 weanlings and 5 adults

No deaths occurred.

The only sign of toxicity in mice was a decreased body weight gain in males given cefprozil by oral gavage.

There were no signs of toxicity in neonatal (5 days of age), weanling (23 days of age) or adult (7 weeks) rats following administration of cefprozil 5000 mg/kg by oral gavage.

Signs of toxicity in monkeys included soft or liquid stools and sporadically disturbed appetite.

Subacute toxicity

Species/Strain	Sex	N/Group	Cefprozil Dosage (mg/kg/day)	Route	Duration	Effects
Rat (CD/Charles River)	M F	10 10	0, 250, 750, 1500 (*CMC 0.5%)	Oral gavage	4 weeks	Slight increase in kidney weight with reduction in serum creatinine and BUN but no corresponding urinalysis or microscopic pathology in (M) given 750 or 1500 mg/kg. Minimal focal erosion of gastric mucosa for 3 of 20 rats at 1500 mg/kg. Transient soft stools during second week and gross and microscopic dilatation of colon and cecum attributed to enteral antibiotic effect.
Monkey (Cynomolgus)	M F	2 2	0, 50, 200, 600	Oral gavage	1 month	Salivation after dosing at 600 mg/kg/day. No consistent pathologic changes. Dose-related incidence of soft or liquid stools attributed to enteral antibiotic effect.
Rat (CD/Charles River)	M F	20 20	0, 250, 750, 1500 (CMC 0.5%)	Oral gavage	3 months + 1 month recovery	Reversible slight increases in serum creatine kinase and alanine transaminase and in kidney weights at 750 and 1500 mg/kg. No morphologic gross or microscopic pathology.
Monkey (Cynomolgus)	M F	3 or 4 3 or 4	0, 50, 150, 600 (CMC 0.5%)	Oral gavage	3 months + 1 month recovery	No consistent toxicologic change. Transient body weight loss for 2 males at 600 mg/kg dose level. No pathologic changes. Dose related incidence of diarrhea (reversible and attributed to enteral antibiotic effect).
Monkey (Cynomolgus)	M F	2 2	0, 25, 50 (0.9% sodium chloride)	IV	2 weeks	No consistent toxicologic change. No morphologic gross or microscopic pathology. Transient mild to moderate discolouration was noted at injection sites across all treated and control groups.

* CMC= carboxymethylcellulose

Chronic toxicity

Species/Strain	Sex	N/Group	Cefprozil Dosage (mg/kg/day)	Route	Duration	Effects
Rat (Sprague-Dawley)	M F	25 25	0, 150, 300, 900 (*CMC 0.5%)	Oral gavage	26 weeks + 12 -13 week recovery	No evidence of overt toxicity. Transient increase in food (M and F) and water (M) consumption at start of dosing and increased food consumption in (M) at end of dosing. Reversible kidney weight increase. No clinicopathologic or histopathologic changes.
Monkey (Cynomolgus)	M F	4 or 6 4 or 6	0, 50, 150, 600 (CMC 0.5%)	Oral gavage	26 weeks + 4 week recovery	Reversible diarrhea, rectal prolapse, emesis, salivation upon dosing at 600 mg/kg. Menstrual cycle, body weight and food consumption unaffected. No consistent change in clinical pathology, necropsy or histopathology. Diarrhea during first month at 50 and 150 mg/kg doses attributed to enteral antibiotic effect.

* CMC = carboxymethylcellulose

Reproduction and teratology

Species/Strain	No. of Animals and Sex/Dose	Cefprozil Doses and Frequency	Route	Results
SEGMENT I				
Rat (Sprague - Dawley)	20 M 35 F	0, 250, 750 or 1500 mg/kg as follows: M: at least 70 days before mating and during mating. F: 14 days before mating through Day 21 pregnancy or Day 21 postpartum	Oral gavage *	Gestation and parturition unaffected. Copulation index slightly lower than controls for treated rats but with no dose relationship. Minor decreases in food consumption before mating, during gestation and in body weight during lactation. No signs of teratogenicity. Higher postnatal mortality in treated groups. Slight growth inhibition in pups (M) during lactation and postweaning. No adverse effect on F_1 generation reproductive performance.
Rat (Crl: CoBS CD(SD)Br)	30 F	0, 100, 250 and 500 mg/kg as follows: F: 15 days prior to mating with untreated M through Day 20 of gestation or Day 21 postpartum	Oral gavage *	No effect on reproduction of F and their offspring. Incidence of alopecia was increased at 500 mg/kg dose level. Maternal body weight gain during gestation diminished at 250 and 500 dose levels.
SEGMENT II				
Mouse (Crl: CD(ICR) Br)	43 F	0, 250, 750 and 1500 mg/kg from Day 6 through Day 15 of gestation	Oral gavage *	No evidence of teratogenicity or embryotoxicity.
Rat (Sprague - Dawley)	35 F	0, 250, 750 and 1500 mg/kg from Day 7 through Day 17 of gestation	Oral gavage	No teratogenic or embryotoxic effects. Reduced implantation with increasing dose. No effects on fetuses, on offspring and on development of pups during lactation and post-weaning.

* Suspending vehicle: Sodium Carboxymethylcellulose 0.5%

Reproduction and teratology (cont'd)

Species/Strain	No. of Animals and Sex/Dose	Cefprozil Doses and Frequency	Route	Results
SEGMENT II (cont'd)				
Rabbit (New Zealand White)	22 F	0, 5, 20, 40 mg/kg from Day 6 through 18 of gestation	Oral gavage	Live fetuses/implantation decrease with increasing doses of cefprozil. No evidence of teratogenicity and embryotoxicity. No effect on reproductive function and body weights. No maternal toxicity.
SEGMENT III				
Rat (Sprague - Dawley CD)	22 F	0, 150, 300 and 900 mg/kg/day from Day 17 through post-partum Day 21	Oral gavage	No overt maternal toxicity. Increased postnatal mortality and slight growth inhibition for suckling pups from dams given 300 or 900 mg/kg/day. Physical development, neuromuscular, sensorial functions and reproduction of F_1 pups were unaffected.

* Suspending vehicle: Sodium carboxymethylcellulose 0.5%

Special Studies
There were no testicular changes noted in special screening studies conducted with cefprozil.

No evidence of nephrotoxicity or systemic toxicity was apparent in rabbits given cefprozil by oral gavage with single doses up to 1000 mg/kg. Cefprozil administered orally at doses up to 500 mg/kg/day to neonatal male rats on postnatal days 6 through 11 resulted in neither testicular toxicity nor systemic toxicity.

In rats given either cefprozil (cis/trans isomers in a 9:1 ratio), the cis isomer or the trans isomer at 1500 mg/kg/day by oral gavage for one month, alopecia, salivation, reduced body weight in males, decreased litter weight and increased kidney weight were observed. No clinical pathology or gross or microscopic pathology was observed.

There were no remarkable differences in the toxicity of the cis isomer, the trans isomer or cefprozil (the isomeric mixture) in rats given 1500 mg/kg/day by oral gavage for one month.

Mutagenicity and Genotoxicity
Cefprozil (cis isomer) was not mutagenic in the Ames Microbial mutagen test with *S. thyphimurium* and the microbial reverse mutation assay using *E. coli.* Cefprozil (cis/trans isomers) was also not mutagenic in the forward gene mutation assay using Chinese Hamster ovary cells.

Unscheduled DNA synthesis in rat hepatocytes *in vitro* and clastogenicity in Chinese Hamster ovary cells *in vitro* or in rat bone marrow cells *in vivo* were unaffected by cefprozil (cis/trans isomers).

REFERENCES

1. Arguedas AG, Zaleska M et al. Comparative Trial of Cefprozil vs Amoxicillin Clavulanate Potassium in the Treatment of Children with Acute Otitis Media with Effusion. Pediatr. Infect. Dis. J. 10:375-380, 1991.

2. Aronovitz GH, Doyle CA et al. Cefprozil vs Amoxicillin/Clavulanate in the Treatment of Acute Otitis Media. Infections in Medicine. Supplement C:19-32, January 1992.

3. Chin NX and Neu HC. Comparative Antibacterial Activity of a New Oral Cephalosporin Antimicrob. Agents Chemother. 31:480-483, 1987.

4. Doyle CA, Durham SJ et al. Cefprozil vs Cefaclor in the Treatment of Pharyngitis and Tonsillitis in Adults. Infections in Medicine. Supplement E:1-2. February 1992.

5. Gehanno P, Depondt J et al. Comparison of Cefpodoxime Proxetil with Cefaclor in the Treatment of Sinusitis. J. Antimicrobiol. Chemother. 26(E):87-91, 1990.

6. Hiraoka M, Masuyoshi S, Tomatsu K, Inoue M, Mitsuhashi S. *In Vitro* Activity and Beta-Lactamase Stability of the Oral Cephalosporin BMY 28100. Eur. J. Clin. Microbiol. 6:559-563, 1987.

7. Jones RN, Barry AL and the Collaborative Antimicrobial Testing Group. BMY 28100, a New Oral Cephalosporin: Antimicrobial Activity Against Nearly 7,000 Recent Clinical Isolates, Comparative Potency with Other Oral Agents and Activity Against Beta-Lactamase Producing Isolates. Diagn. Microbiol. Infect. Dis. 9:11-26, 1988.

8. Kessler RE and Fung-Tomc JC. *In Vitro* Activity of Cefprozil Compared with other Cephalosporins. Infections in Medicine. Supplement C:10-18. January 1992.

9. Leitner F et al. BMY 28100, a New Oral Cephalosporin. Antimicrobiol. Agents & Chemother. 31:238-243, 1987.

10. McCarty JM, Renteria A et al. Cefprozil vs Cefaclor in the Treatment of Pharyngitis and Tonsillitis. Infections in Medicine. Supplement C:33-43, January 1992.

11. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Second Edition Approved Standard NCCLS Document M7-A2 10(8), NCCLS, Villanova. PA, April 1990.

12. Nolen T, Conetta BJ et al. Safety and Efficacy of Cefprozil vs Cefaclor in the Treatment of Mild to Moderate Skin and Skin Structure Infections. Infections in Medicine. Supplement C:56-67, January 1992.

13. Nye K, O'Neill JM et al. Pharmacokinetics and Tissue Penetration of Cefprozil. J. Antimicrobiol. Chemother. 25:831-835, 1990.

14. Sáez-Llorens X et al. Pharmacokinetics of Cefprozil in Infants and Children. Antimicrobiol. Agents Chemother. 34:2152-2155, 1990.

15. Scribner RK, Marks MI and Finkhouse BD. *In Vitro* Activity of BMY 28100 Against Common Isolates from Pediatric Infections. Antimicrobiol. Agents Chemother. 31:630-631, 1987.

16. Wilber RB, Hamilton H et al. Cefprozil *vs* Cefaclor in the Treatment of Lower Respiratory Tract. Infections in Medicine. Supplement C:44-55, January 1992.

17. World Almanac® and Book of Facts 1994, Mahwab, N.J.

18. Bristol-Myers Squibb Canada Inc., Cefzil Product Monograph, Control Number 141786, Date of Revision: December 21, 2010.