

PRODUCT MONOGRAPH

PrTARO-CEFPROZIL

cefprozil tablets

(250 mg and 500 mg of cefprozil as cefprozil monohydrate)

USP

Antibiotic

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets, 250 mg and 500 mg	None <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

TARO-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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of TARO-CEFPROZIL and other antibacterial drugs, TARO-CEFPROZIL should be used only to treat 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.

CONTRAINDICATIONS

TARO-CEFPROZIL (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 AND PRECAUTIONS

Hypersensitivity

Serious Warnings and Precautions

Before therapy with TARO-CEFPROZIL (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 TARO-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.

General

Prolonged use of TARO-CEFPROZIL 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.

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

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCAR) such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported in association with beta-lactam treatment. When SCAR is suspected, TARO-CEFPROZIL should be discontinued and appropriate therapy and/or measures should be taken.

Gastrointestinal

Clostridium difficile-associated disease

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including TARO-CEFPROZIL (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

TARO-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 to 3 weeks subsequent to the administration of TARO-CEFPROZIL (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).

Renal

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 TARO-CEFPROZIL (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 TARO-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 TARO-CEFPROZIL 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.

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

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

Special Populations

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/m², 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 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

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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.

Most Common Clinical Trial Adverse Drug Reactions (> 1%)

Body System	Adverse Events considered likely to be Drug-Related (n = 4227)	
	Event	Percentage of Patients with ADR
Gastrointestinal System	Diarrhea	2.7
	Nausea	2.3
	Vomiting	1.4
Skin/Hypersensitivity	Rash	1.2

Less Common Clinical Trial Adverse Drug Reactions (<1%)

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

Hypersensitivity: 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.

Gastrointestinal: Abdominal pain (0.9%)

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%).

Abnormal Hematologic and Clinical Chemistry Findings

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.

Post Market Adverse Drug Reactions

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 pseudomembranous 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 TARO-CEFPROZIL administration is unknown.

Hepatotoxicity, including hepatitis, has been reported during post-marketing surveillance, including cases in which a causal role of cefprozil could not be excluded.

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.

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing TARO-CEFPROZIL in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

DRUG INTERACTIONS

Drug-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 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.

DOSAGE AND ADMINISTRATION

TARO-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

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 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.

OVERDOSAGE

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

Since no case of overdose has been reported to date, no specific information on symptoms or treatment of overdose 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 overdose, especially in patients with compromised renal function, hemodialysis will aid in the removal of cefprozil from

the body.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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 co-administered 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.

Special Populations and Conditions

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 WARNINGS AND PRECAUTIONS and DOSAGE

AND ADMINISTRATION).

Hepatic Insufficiency

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

Geriatrics

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.

Pediatrics

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.

STORAGE AND STABILITY

Store at room temperature (15 to 30°C). Protect from light and excessive humidity.

DOSAGE FORMS, COMPOSITION AND PACKAGING

In addition to the active ingredient, cefprozil, each tablet also contains the non-medicinal ingredients hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, talc and titanium dioxide.

TARO-CEFPROZIL (cefprozil) tablets 250 mg are white to off-white oval, film coated tablets debossed with 'RB 41' on one side and plain on the other side.

TARO-CEFPROZIL tablets 500 mg are white to off-white oval, film coated tablets debossed with 'RB 42' on one side and plain on the other side.

TARO-CEFPROZIL 250 mg and 500 mg tablets are available in bottles of 100.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

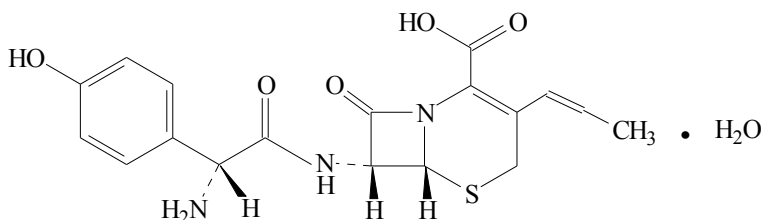
Drug Substance

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 (molecular mass): C₁₈H₁₉N₃O₅S•H₂O (407.45) g/mol

Structural Formula:



Physicochemical properties: Cefprozil is a cis and trans isomeric mixture in a 9:1 ratio. It is a white to yellow colored crystalline powder with a melting point of 197°C. It is slightly soluble in water, practically insoluble in alcohol. Cefprozil has an apparent octanol / water partition coefficient of 0.01 at pH6 and 22°C.

CLINICAL TRIALS

Comparative Bioavailability Studies

A blinded, randomized, single-dose, crossover comparative bioequivalence study was performed in 24 healthy male and female volunteers under fasting conditions for TARO-CEFPROZIL Tablets. The study compared the rate and extent of absorption of a single oral dose (1 x 500 mg) of TARO-CEFPROZIL tablets or Cefzil[®] (cefprozil) (Bristol-Myers Squibb Canada Inc.) tablets. A summary of the pharmacokinetic parameters is given in the tables below:

Cefprozil (1 x 500 mg) Tablets From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means**	90% Confidence Interval
AUC _T (mcg·h/mL)	28.588 28.79 (13.6)	27.730 27.96 (14.0)	103.1	100.7 – 105.6
AUC _I (mcg·h/mL)	28.790 28.99 (13.7)	27.913 28.14 (14.0)	103.1	100.7 – 105.6
C _{max} (mcg/mL)	9.337959 9.42750 (15.2)	9.308089 9.39833 (15.9)	100.3	94.8 – 106.2
T _{max} [§] (h)	1.595 (35.0)	1.523 (31.5)		
T _½ [§] (h)	1.244 (9.5)	1.262 (8.7)		
kel [§] (1/h)	0.5620 (9.7)	0.5532 (8.5)		

* TARO-CEFPROZIL Tablets 500 mg Sun Pharma Canada Inc.

† CEFZIL[™] (cefprozil) Tablets 500 mg Bristol-Myers Squibb Canada Inc.

§ Expressed as the arithmetic mean (CV%) only.

**Based on least square estimate.

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
<i>Corynebacterium Sp.</i>	13	≤ 0.008	4.000	< 0.008	0.104
<i>S. faecalis</i>	77	0.500	16.000	5.369	8.211
<i>Strep. (Group A)</i>	309	≤ 0.008	1.000	0.015	0.088
<i>Strep. (Beta hemolytic)</i>	1	0.016	0.016		
<i>S. agalactiae</i>	1	0.250	0.250		
<i>S. intermedius</i>	1	0.125	0.125		
<i>Strep. (Group G)</i>	32	≤ 0.008	0.500	0.025	0.150
<i>Strep. (Group C)</i>	28	0.016	0.500	0.018	0.339
<i>Enterococcus</i>	2	8.000	8.000		
<i>Strep. (Group F)</i>	8	0.064	1.000	0.157	
<i>S. salivarius</i>	1	0.064	0.064		
<i>Strep. (Group B)</i>	48	0.016	0.500	0.084	0.287
<i>S. mitis</i>	13	≤0.008	2.000	0.117	0.451
<i>S. constellatus</i>	1	0.500	0.500		
<i>S. sanguis</i>	17	0.064	2.000	0.149	1.110
<i>S. aureus</i>	344	0.064	8.000	0.863	2.109
<i>S. epidermidis</i>	145	0.016	32.000	0.341	3.123
<i>S. saprophyticus</i>	21	0.500	4.000	0.728	1.653
<i>S. hominis</i>	21	0.032	> 128.000	0.375	1.932
<i>S. capitis</i>	9	0.016	0.125	0.025	
<i>S. simulans</i>	6	0.032	0.500	0.125	
<i>S. haemolyticus</i>	15	0.032	>128.000	0.445	3.364
<i>S. cohnii</i>	3	0.250	1.000		
<i>S. warneri</i>	8	0.016	0.500	0.091	
<i>S. xylosus</i>	2	0.250	0.500		
<i>Micrococcus Sp.</i>	2	0.032	0.250		
<i>Aerococcus Sp.</i>	1	1.000	1.000		
<i>S. pneumoniae</i>	126	≤ 0.008	1.000	0.042	0.316
<i>P. aeruginosa</i>	35	> 128.000	> 128.000	> 128.000	>128.000
<i>P. maltophilia</i>	9	> 128.000	> 128.000	>128.000	
<i>P. fluorescens</i>	2	> 128.000	> 128.000		

Organism	Number of Isolates	Low MIC mcg/mL	High MIC mcg/mL	MIC ₅₀ mcg/mL	MIC ₉₀ mcg/mL
<i>P. paucimobilis</i>	1	2.000	2.000		
<i>P. vesicularis</i>	1	32.000	32.000		
<i>P. putida</i>	5	> 128.000	> 128.000	> 128.000	
<i>P. cepacia</i>	1	> 128.000	> 128.000		
<i>Pseudomonas Sp. VE-2</i>	1	> 128.000	> 128.000		
<i>P. mendocina</i>	1	> 128.000	> 128.000		
<i>P. acidovorans</i>	1	> 128.000	> 128.000		
<i>E. coli</i>	551	0.064	> 128.000	1.223	4.948
<i>C. freundii</i>	14	0.500	> 128.000	11.314	> 78.793
<i>C. diversus</i>	9	0.500	8.000	0.749	
<i>K. pneumoniae</i>	68	0.032	32.000	0.660	1.711
<i>K. ozaenae</i>	1	4.000	4.000		
<i>K. oxytoca</i>	11	0.125	32.000	1.122	7.464
<i>E. cloacae</i>	38	8.000	> 128.000	38.055	> 128.000
<i>E. aerogenes</i>	15	16.000	> 128.000	24.675	> 76.109
<i>E. sakazakii</i>	1	8.000	8.000		
<i>E. geroviae</i>	2	2.000	8.000		
<i>H. alvei</i>	1	16.000	16.000		
<i>S. marcescens</i>	10	4.000	> 128.000	> 128.000	> 128.000
<i>P. mirabilis</i>	66	0.250	8.000	3.143	6.662
<i>P. vulgaris</i>	3	> 128.000	> 128.000		
<i>M. morgani</i>	7	4.000	> 128.000	> 128.000	
<i>P. stuartii</i>	1	16.000	16.000		
<i>E. agglomerans</i>	8	0.500	> 128.000	2.000	
<i>H. influenzae</i>	11	0.125	8.000	0.771	3.864
<i>H. influenzae (P+)</i>	14	1.000	16.000	2.692	6.964
<i>H. influenzae (P)</i>	77	0.250	32.000	0.887	4.550
<i>H. parainfluenzae</i>	9	0.016	1.000	0.223	
<i>H. parainfluenzae (P+)</i>	1	1.000	1.000		
<i>Flavobacterium Sp.</i>	1	1.000	1.000		
<i>A. anitratus</i>	22	4.000	> 128.000	84.449	> 128.000
<i>A. lwoffii</i>	17	1.000	> 128.000	8.980	> 95.339
<i>A. haemolyticus</i>	1	64.000	64.000		
<i>M. catarrhalis</i>	9	0.500	4.000	0.917	
<i>M. catarrhalis (P+)</i>	32	0.064	4.000	0.707	2.297
<i>M. catarrhalis (P-)</i>	4	0.032	2.000	0.045	
<i>A. hydrophilia</i>	1	1.000	1.000		

Cefprozil is inactive against methicillin resistant *Staphylococci*, *Enterococcus faecium*, most strains of *Acinetobacter*, *Enterobacter*, *Morganella morgani*, *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)
<i>Escherichia coli</i> ATCC 25922	21-27
<i>Staphylococcus aureus</i> 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)
<i>Enterococcus faecalis</i> ATCC 29212	4-16
<i>Escherichia coli</i> ATCC 25922	1-4
<i>Pseudomonas aeruginosa</i> ATCC 27853	> 32
<i>Staphylococcus aureus</i> 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)	I.P.	> 5000
Mouse Swiss-Webster	M (5) F (5)	Subcutaneous	> 5000

* CMC = Carboxymethyl cellulose

** 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)	I.V.	2 weeks	No consistent toxicologic change. No morphologic gross or microscopic pathology. Transient mild to moderate discoloration 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 = carboxymethyl cellulose

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 (CrI: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 (CrI: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 CD)	35 F	0, 250, 750 and 1500 mg/kg from day 7 through 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 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).

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PART III; CONSUMER INFORMATION

TARO-CEFPROZIL

cefprozil tablets
250 mg and 500 mg

This leaflet is part III of a three-part "Product Monograph" published when TARO-CEFPROZIL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TARO-CEFPROZIL. Contact your doctor or pharmacist if you have any questions about the drug.

Keep this information with your medicine in case you need to read it again.

ABOUT THIS MEDICATION

TARO-CEFPROZIL is the generic brand name for a drug called cefprozil.

What the medication is used for:

The most common uses of TARO-CEFPROZIL are:

- respiratory infections
- urinary tract infections
- skin infections
- acute sinusitis

Antibacterial drugs like TARO-CEFPROZIL treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, TARO-CEFPROZIL should be used exactly as directed. Misuse or overuse of TARO-CEFPROZIL could lead to the growth of bacteria that will not be killed by –TARO-CEFPROZIL (resistance). This means that –TARO-CEFPROZIL may not work for you in the future. Do not share your medicine.

For other possible uses, please speak to your doctor or pharmacist.

What it does:

TARO-CEFPROZIL is an antibiotic.

When it should not be used:

Do not use if allergic to cefprozil or any of the nonmedicinal ingredients present in TARO-CEFPROZIL (See "What the important non-medicinal ingredients are" section below).

What the medicinal ingredient is:

cefprozil as cefprozil monohydrate

What the important nonmedicinal ingredients are:

TARO-CEFPROZIL Tablets contain the following

nonmedicinal ingredients: hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, talc and titanium dioxide.

What dosage forms it comes in:

Tablets, 250 mg and 500 mg

WARNINGS AND PRECAUTIONS

Before starting TARO-CEFPROZIL and to get the best possible treatment, be sure to tell your doctor if you:

- Are allergic to penicillins, cephalosporins, cefprozil or any other drugs.
- Do not use if you are pregnant, plan to become pregnant or are breastfeeding.
- Do not use for children below the age of 6 months.
- Caution is required when cefprozil is used for the chronically ill or institutionalized elderly.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with TARO-CEFPROZIL include: aminoglycoside antibiotics and probenecid.

Before you use TARO-CEFPROZIL talk to your doctor or pharmacist.

PROPER USE OF THIS MEDICATION

Adults (13 years and older)

Usual dose:

Respiratory and Urinary Tract Infections: 500 mg once daily.

Skin Infections: 250 mg every 12 hours or 500 mg once daily.

Acute Sinusitis: 250 mg or 500 mg, every 12 hours.

Overdose:

Call your doctor or pharmacist right away in case of an overdose.

If you think you have taken too much TARO-CEFPROZIL contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Call your doctor or pharmacist right away in case of a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects are diarrhea, nausea, vomiting and abdominal pain.

This is not a complete list of side effects. For any unexpected effects while taking TARO-CEFPROZIL, contact your doctor or pharmacist.

Serious side effects and what to do about them			
Symptom/effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<p>Severe Cutaneous Adverse Reactions (SCAR) (severe skin reactions that may also affect other organs):</p> <ul style="list-style-type: none"> • Skin peeling, scaling, or blistering (with or without pus) which may also affect your eyes, mouth, nose or genitals, itching, severe rash, bumps under the skin, skin pain, skin color changes (redness, yellowing, purplish) • Swelling and redness of eyes or face • Flu-like feeling, fever, chills, body aches, swollen glands, cough • Shortness of breath, chest pain or discomfort 			✓

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about TARO-CEFPROZIL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this patient medication information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>) or by calling 1-866-840-1340.

This leaflet was prepared by Sun Pharma Canada Inc.

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HOW TO STORE IT

Remember to keep TARO-CEFPROZIL well out of reach and sight of children. TARO-CEFPROZIL should be stored at room temperature (15-30°C) and protect from light and excessive humidity.