PRODUCT MONOGRAPH

PrRAN-CEFPROZIL

cefprozil for oral suspension USP
(125 mg/5 mL and 250 mg/5 mL of cefprozil as cefprozil monohydrate, when reconstituted)

USP

Antibiotic

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Date of Revision:
February 10, 2010

Submission Control No: 135101

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Powder for Oral Suspension, 125 mg/5 mL and 250 mg/5 mL	Sucrose *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

RAN-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 ß-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.

Geriatrics: RAN-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.

Pediatrics: The use of RAN-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.

CONTRAINDICATIONS

RAN-Cefprozil is contraindicated in patients with known allergy to the cephalosporin class of antibiotics or to any component of the Cefprozil preparations (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Before therapy with RAN-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 (see WARNINGS AND PRECAUTIONS, Hypersensitivity).

General
Prolonged use of RAN-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.

Carcinogenesis and Mutagenesis
No data is available.

Cardiovascular
No data is available.

Dependence/Tolerance
No data is available.

Ear/Nose/Throat
No data is available.

Endocrine and Metabolism
No data is available.

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).

Genitourinary
No data is available.

Hematologic
No data is available.

Hepatic/Biliary/Pancreatic
No data is available.

Immune
No data is available.

Neurologic
No data is available.

Ophthalmologic
No data is available.

Peri-Operative Considerations
No data is available.

Psychiatric
No data is available.

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 RAN-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 RAN-CEFPROZIL, should be given with caution to patients receiving concurrent treatment with potent diuretics since these agents are suspected of adversely affecting renal function.

Respiratory
No data is available.

Hypersensitivity
If an allergic reaction to RAN-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 (See WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions).

Sexual Function/Reproduction
No data is available.

Skin
No data is available.

Special Populations

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

Pediatrics: The use of RAN-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.

Geriatrics: RAN-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

Adverse Drug Reaction Overview

The adverse reactions to RAN-CEFPROZIL (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.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse 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 approximate rates.

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%).

Abnormal Hematologic and Clinical Chemistry Findings

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, angioedema, serum sickness, colitis including pseudomembraneous colitis, 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 Cefzil 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, 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.

DRUG INTERACTIONS

Overview

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-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

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

Dosing Considerations

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

Recommended Dose and Dosage Adjustment

RAN-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 and skin structure	250 mg q12h or 500 mg q24h
Uncomplicated urinary tract	500 mg q24h

Children (2 years – 12 years)					
Skin and skin structure			20 mg/kg q24h		
Age* (years)	Weight (kg)	Multi-dose 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)	Multi-dose bottle			
		125 mg/5 mL		250 mg/5 mL	
		tsp/dose	mL/dose	tsp/dose	mL/dose
6 mos. – 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

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

Infants and children (6 months – 12 years)					
Upper respiratory tract (pharyngitis/tonsillitis)		7.5 mg/kg q12h			
Age* (years)	Weight (kg)	Multi-dose bottle			
		125 mg/5 mL		250 mg/5 mL	
		tsp/dose	mL/dose	tsp/dose	mL/dose
6 mos. – 1 yr	7-9	0.5	2.5	---	---
2-6	11-21	1.0	5.0	0.5	2.5
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.	

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 RAN-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.

Administration

Reconstitution:
Powder for Oral Suspension

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

RAN-CEFPROZIL powder for oral suspension	Bottle size (mL)	Diluent (water) added to bottle (mL)	Approximate available volume (mL)	Final concentration
125 mg/5 mL	50	40	50	125 mg/5 mL
	75	60	75	125 mg/5 mL
	100	80	100	125 mg/5 mL
250 mg/5 mL	50	36	50	250 mg/5 mL
	75	54	75	250 mg/5 mL
	100	72	100	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.

OVERDOSAGE

For management of suspected overdose, consult 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 ceprozil 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

Absorption: 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.

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

Excretion: The average plasma half-life in normal subjects is 1.3 hours. 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 (µg/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 µg/mL, 450 µg/mL and 600 µg/mL, respectively.

Special Populations and Conditions

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.

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.

Gender: No data is available.

Race: No data is available.

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

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).

Genetic Polymorphism: No data is available.

STORAGE AND STABILITY

RAN-CEFPROZIL Powder for Oral Suspension:
Temperature: Store the dry powder at room temperature (15 to 30°C).
Light: Protect from light.
Moisture: Protect from excessive humidity.

The constituted RAN-CEFPROZIL oral suspension must be stored in the refrigerator (2°C - 8°C) for up to 14 days. Keep container tightly closed. Discard unused portion after 14 days.

DOSAGE FORMS, COMPOSITION AND PACKAGING

RAN-CEFPROZIL Powder for Oral Suspension:
RAN-CEFPROZIL powder for oral suspension contains cefprozil monohydrate equivalent to 125 mg or 250 mg of cefprozil per 5 mL of constituted solution.

RAN-CEFPROZIL powder for oral suspension is available as yellowish pink colored granular powder forming yellowish pink colored suspension on constitution with water. The resulting suspension has a characteristic fruity flavor.

RAN-CEFPROZIL powder for oral suspension also contains: aspartame, citric acid anhydrous, colloidal silicon dioxide, FD&C Red # 40 aluminium lake, FD&C yellow # 6 aluminium lake, flavor fruit gum 912, flavor cherry 594 SD, glycine, polysorbate 80, simethicone emulsion, sodium benzoate, sodium chloride, microcrystalline cellulose & carboxymethylcellulose sodium, carboxymethyl cellulose sodium and sucrose.

RAN-CEFPROZIL 125 mg/5mL and 250 mg/5 mL Powder for Oral Suspension are available in bottles of 50 mL, 75 mL and 100 mL.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

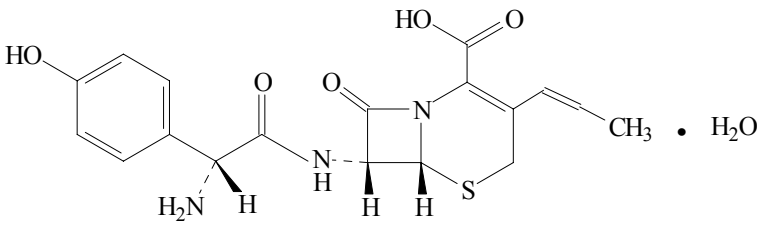
Drug Substance

Proper name: cefprozil

Chemical name: (6R,7R)-7-[(R)-2-amino-2-(p-hydroxyphenyl) acetamido]-8-oxo-3-propenyl-5-thia-l-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid

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

Structural formula:



Physicochemical properties: 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 demethyl sulfoxide. Cefprozil has an apparent octanol / water partition coefficient of 0.01 at pH6 and 22°C.

CLINICAL TRIALS

A blinded, randomized, single-dose, crossover comparative bioequivalence study was performed in 35 healthy male and female volunteers under fasting conditions for RAN-CEFPROZIL Powder for Oral Suspension. The study compared the rate and extent of absorption of a single oral dose of cefprozil powder for oral suspension following the administration of RAN-CEFPROZIL (250 mg cefprozil/5mL) or Cefzil® (250 mg cefprozil/5 mL). A summary of the pharmacokinetic parameters is given in the tables below:

Cefprozil
(A single 250 mg dose: 5 mL of 250 mg/5 mL)
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (mcg x hr/mL)	13.6470 14.198 (29.7%)	12.3294 12.754 (28.7%)	111	108 – 114
AUC_I (mcg x hr/mL)	13.9462 14.491 (29.3%)	12.6137 13.039 (28.5%)	111	108 – 114
C_{max} (mcg/mL)	4.9396 5.138 (30.0%)	4.7046 4.884 (28.9%)	105	101 – 109
T_{max} § (hrs)	1.194 (25.5%)	1.164 (20.1%)		
$T_{½}$ § (hrs)	1.401 (16.4%)	1.360 (17.7%)		

*RAN-Cefprozil 250 mg/5 mL Powder for Oral Suspension (Ranbaxy Laboratories, Ltd.).
†CEFZIL™ 250 mg/5 mL Powder for Oral Suspension (Bristol-Myers Squibb Canada Inc.).
§ 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	High MIC	MIC_{50} µg/mL	MIC_{90} µg/mL
Corynebacterium Sp.	13	≤ 0.008	4.000	< 0.008	0.104
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	31000	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. haemolyticus	15	0.032	>128.000	0.445	3.364
S. cohnii	3	0.250	1.000		
S. warneri	8	0.016	0.500	0.091	
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. aeruginosa	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

Organism	Number of Isolates	Low MIC	High MIC	MIC_{50} µg/mL	MIC_{90} µg/mL
K. ozaenae	1	4.000	4.000		
K. oxytoca	11	0.125	32.000	1.122	7.464
E. cloacae	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. geroviae	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. influenzae	11	0.125	8.000	0.771	3.864
H. influenzae (P+)	14	1.000	16.000	2.692	6.964
H. influenzae (P -)	77	0.250	32.000	0.887	4.550
H. parainfluenzae	9	0.016	1.000	0.223	
H. parainfluenzae (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. haemolyticus	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 µg 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-µg 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 (µg/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 (µg/mL)
Enterococcus faecalis ATCC 29212	4-16
Escherichia coli ATCC 25922	1-4
Pseudomonas aeruginosa ATCC 27853	> 32
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)	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 = carboxymethylcelIulose

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, 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 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 carboxymcthylcellulose 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.

Mutagenicitv 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 clastogenecity 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

RAN-CEFPROZIL
cefprozil for oral suspension USP

(125 mg/5 mL and 250 mg/5 mL of cefprozil as cefprozil monohydrate, when reconstituted)

This leaflet is part III of a three-part "Product Monograph" published when RAN-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 RAN-CEFPROZIL. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
RAN-CEFPROZIL is used for the treatment of infections caused by bacteria (germs) such as bronchitis and infections of the ears, sinuses, skin, throat and urinary tract.

What it does:
RAN-CEFPORZIL helps prevent the growth of the bacterial cell wall, which kills the bacteria that cause infections.

When it should not be used:
You should not use RAN-CEFPROZIL if you have had any allergies to cefprozil, cephalosporins class of antibiotics or to any ingredient in the formulation or component of the container (see *What the important non-medicinal ingredients are*).

What the medicinal ingredient is:
cefprozil as cefprozil monohydrate

What the important nonmedicinal ingredients are:

RAN-CEFPROZIL Powder for Oral Suspension: aspartame, citric acid anhydrous, colloidal silicon dioxide, FD&C Red # 40 aluminium lake, FD&C yellow # 6 aluminium lake, flavor fruit gum 912, flavor cherry 594 SD, glycine, polysorbate 80, simethicone emulsion, sodium benzoate, sodium chloride, microcrystalline cellulose & carboxymethylcellulose sodium, carboxymethyl cellulose sodium and sucrose.

What dosage forms it comes in:
Powder for Oral Suspension (125 mg/5 mL or 250 mg/5mL when reconstituted).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Before taking RAN-CEFPROZIL, you must let your doctor know if you have had an allergic reaction to cefprozil, cephalosporins, penicillins, or other drugs as you are at a higher risk of developing an allergic reaction to RAN-CEFPROZIL.

BEFORE you use RAN-CEFPROZIL talk to your doctor or pharmacist if:

- You have had any allergies to this drug or its ingredients or components of the container.
- Are pregnant or nursing your baby.
- You have kidney problems.

Stop taking RAN-CEFPROZIL if you develop an allergic reaction to the drug (see Table for SERIOUS SIDE EFFECTS).

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with RAN-CEFPROZIL include: aminoglycoside antibiotics, probenecid.

PROPER USE OF THIS MEDICATION

Usual dose:
You must take this medicine as told by your doctor. The usual dose depends on your age, weight and the type of infection that you have.

It is important that you take all the medicine that your doctor has given you. Even if you start to feel better, all the medicine must be taken to make sure that all the germs have been killed.

RAN-CEFPROZIL may be taken with or without food.

Overdose:
It is important to follow the instructions from your doctor or pharmacist.

If you or someone has taken a large quantity of suspension at once contact your doctor, nearest hospital emergency department or regional poison control centre immediately.

Missed Dose:

If a dose of this medication is missed, it should be taken as soon as possible. This will help to keep a constant amount of medication in the blood. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Talk to your doctor or pharmacist if you experience diarrhea, nausea, vomiting or stomach pain. Also, talk to your doctor or pharmacist if you develop a rash.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Allergic Reaction: - Trouble breathing - Swelling of face, mouth - Red or itchy skin - Severe skin rash			✓

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

HOW TO STORE IT

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

Store the reconstituted RAN-CEFPROZIL Oral Suspension in the refrigerator (2°C - 8°C) for up to 14 days. Keep container tightly closed. Throw out the remaining suspension after 14 days.

Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

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 0701C
    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 the side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.ranbaxy.ca or by contacting the sponsor, Ranbaxy Pharmaceuticals Canada Inc. at: 1.866.840.1340.

This leaflet was prepared by Ranbaxy Pharmaceuticals Canada Inc.

Last revised: February 10, 2010