# PRODUCT MONOGRAPH

**[PR] PRO-CEFADROXIL - 500**

**Cefadroxil Capsules USP**

**(as cefadroxil monohydrate)**

**500 mg**

**Antibiotic**

**PRO DOC LTÉE**
2925, boul. Industriel
Laval, Quebec
H7L 3W9

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# PRODUCT MONOGRAPH

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**(as cefadroxil monohydrate)**

**500 mg**

## THERAPEUTIC CLASSIFICATION

Antibiotic

## ACTIONS AND CLINICAL PHARMACOLOGY

Cefadroxil is a cephalosporin with bactericidal activity. In *vitro* studies have shown that the antibacterial activity of the cephalosporins results from their ability to inhibit mucopeptide synthesis in the bacterial cell wall.

### Comparative Bioavailability

A randomized, two-way, cross-over, single-dose bioavailability study was conducted in healthy, adult, male subjects. The bioavailability of PRO-CEFADROXIL-500 capsules relative to Duricef® 500 mg capsules was determined following a single oral dose of 1000 mg (2 x 500 mg capsules). The average values of the pharmacokinetic parameters determined for each of the formulations are listed in the following table for the 14 subjects completing the study.

| Summary Table of the Comparative Bioavailability Data<br>Cefadroxil (Dose: 2 x 500 mg) From Measured Data | | | |
|---|---|---|---|
| Parameter | Geometric Mean**<br>Arithmetic Mean (CV%) | | Ratio of Geometric Means (%) |
| | PRO-CEFADROXIL-500 | Duricef®† | |
| $AUC_T$<br>(mcg·hr/mL) | 90.925<br>94.173 (18) | 92.068<br>95.462 (18) | 98.8 |
| $AUC_I$<br>(mcg·hr/mL) | 92.703<br>95.851 (18) | 93.405<br>96.814 (18) | 99.2 |
| $C_{max}$<br>(mcg/mL) | 29.730<br>31.135 (17) | 28.554<br>29.444 (15) | 104.1 |
| $T_{max}$ (hr)* | 1.39 (39) | 1.64 (42) | -- |
| $T_{1/2}$ (hr)* | 1.60 (11) | 1.61 (9) | -- |

* Arithmetic means (CV%).
** The least squares estimate of the geometric means for $AUC_T$, $AUC_I$ and $C_{max}$ parameters.
† Duricef® is manufactured by Bristol-Myers Squibb Inc., and was purchased in Canada.

## INDICATIONS AND CLINICAL USE

PRO-CEFADROXIL-500 (cefadroxil) may be indicated for the treatment of the following infections when caused by susceptible strains of the organisms indicated:

- Acute uncomplicated urinary tract infections when caused by E. coli, Klebsiella species and some strains of Proteus *mirabilis*.
- Skin and skin structure infections caused by *Staphylococcus aureus* and/or group A β-hemolytic streptococci.
- Acute pharyngitis-tonsillitis, when caused by group A β-hemolytic streptococci.
- Lower respiratory tract infections, including pneumonia, caused by S. *pneumoniae* (D. *pneumoniae*), S. pyogenes (Group A β-hemolytic streptococci), K. *pneumoniae* and S. *aureus.*

Appropriate bacteriological studies should be performed prior to and during therapy in order to identify and determine the susceptibility of the causative organism(s).

## CONTRAINDICATIONS

PRO-CEFADROXIL (cefadroxil) capsules are contraindicated in patients with a known hypersensitivity to the cephalosporin group of antibiotics.

## WARNINGS

In patients with known hypersensitivity to the penicillins, cephalosporin antibiotics [including PRO-CEFADROXIL-500 (cefadroxil)] should be administered with great caution. There is clinical and laboratory evidence of cross-allergenicity between the penicillin and cephalosporin groups of antibiotics. There are instances of patients who have had reactions to both classes of antibiotics (including fatal anaphylactoid reactions after parenteral administration).

PRO-CEFADROXIL-500 should be administered with caution and then only when absolutely necessary to any patient who has a history of some form of allergy, particularly to drugs.

Treatment with broad spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Closfridium dificile* is one primary cause of antibiotic-associated colitis.

Pseudomembranous colitis has been reported with the use of cephalosporins and other broad spectrum antibiotics. Therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis. Other causes of colitis should also be considered.

## PRECAUTIONS

**A minimum of 10 days treatment is recommended for infections caused by group A β-hemolytic streptococci.**

Patients should be carefully monitored to detect the development of any adverse effect or other manifestations of drug idiosyncrasy. If an allergic reaction to PRO-CEFADROXIL-500 (cefadroxil) occurs, its administration should be discontinued and the patient treated with the usual agents (e.g. epinephrine, other pressor amines, or corticosteroids).

Prolonged use of PRO-CEFADROXIL-500 can result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, the administration of PRO-CEFADROXIL-500 should be discontinued and appropriate measures taken. If an organism becomes resistant during treatment with PRO-CEFADROXIL-500, alternate therapy should be instituted.

PRO-CEFADROXIL-500 should be used with caution in the presence of markedly impaired renal function [i.e. a creatinine clearance rate of less than 0.85 mL/sec/1.73 $m^2$ (50 mL/min/1.73 $m^2$) - see DOSAGE AND ADMINISTRATION]. In patients with known or suspected renal impairment, careful clinical evaluation and appropriate laboratory studies should be performed prior to and during therapy, since cefadroxil can accumulate in serum and tissues.

If PRO-CEFADROXIL-500 is to be used for long-term therapy, hematologic, renal and hepatic functions should be monitored periodically.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures, when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

During treatment with cefadroxil, false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest tablets, but not with enzyme-based tests such as Clinistix or Tes-Tape.

Pregnancy

The safety of PRO-CEFADROXIL-500 in the treatment of infections during pregnancy has not been established. The administration of PRO-CEFADROXIL-500 is not recommended during pregnancy. If, in the opinion of the attending physician, the administration of PRO-CEFADROXIL-500 is considered to be necessary, its use requires that the anticipated benefits be weighed against the possible hazards to the fetus.

Nursing Mothers

Cephalosporin antibiotics are excreted in human breast milk, and therefore would be ingested by the neonate during breast feeding. Nursing mothers receiving PRO-CEFADROXIL-500 should, therefore, discontinue breast feeding.

## ADVERSE REACTIONS

Adverse reactions observed during the use of cefadroxil include:

Gastrointestinal: The most frequently observed have been nausea and vomiting. The incidence and severity are dose dependent and the latter has been severe enough to warrant cessation of therapy, but infrequently.

Other reactions reported were abdominal cramps, gastric upset, heartburn, gas and diarrhea.

Hypersensitivity: Rash, swollen and running eyes, urticaria, eosinophilia, angioedema and positive direct Coombs test.

CNS: Dizziness, weakness, drowsiness, vertigo, nervousness and headaches.

Miscellaneous: Vaginitis, monilial vaginitis, vaginal itching, cramps in side and legs, transient neutropenia and elevations in BUN, alkaline phosphatase and SGOT.

These adverse reactions were seen during clinical trials with cefadroxil in 43 out of a total of 737 patients (5.8%).

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no specific antidote, therefore, treatment should be symptomatic.

## DOSAGE AND ADMINISTRATION

PRO-CEFADROXIL-500 (cefadroxil) is administered orally and may be taken without regard to meals.

The incidence and severity of gastrointestinal complaints is dose dependent. Administration with food may be helpful to diminish potential intestinal complaints.

**A minimum of 10 days treatment is recommended for infections caused by group A β-hemolytic streptococci.**

ADULTS

Normal Renal Function: The recommended dose is 1 to 2 grams per day.

Urinary Tract Infections: The recommended daily dose is 1 to 2 grams. This may given as a single dose at bedtime or divided into 500 mg to 1 gram doses for twice-a-day administration (every 12 hours). The usual duration of therapy is 10 days. While shorter or longer courses may be appropriate for some patients, cefadroxil should be administered for a sufficient period of time to render the urine sterile. The sterility of the urine should be re-evaluated 2 to 4 weeks after cessation of therapy.

Acute Pharyngitis and Tonsillitis: The recommended dose is 1 gram per day in single (q.d.) or divided doses (b.i.d.). Treatment should be for a minimum of 10 days and continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained.

Lower Respiratory Tract Infections: The recommended dose is 500 mg to 1 g two times per day (every 12 hours).

Skin and Skin Structure Infections: 1 g daily in a single dose.

Impaired Renal Function: The dosage of PRO-CEFADROXIL-500 should be adjusted according to creatinine clearance rates to prevent drug accumulation.

In adults, the dose is 1 g for a patient with normal renal function (see above) and the maintenance dose (based on the creatinine clearance rate) is 500 mg at the time intervals listed below:

| Creatinine Clearance | | Dose Interval |
|---|---|---|
| (mL/sec/1.73 $m^2$) | (mL/min/1.73 $m^2$) | (hours) |
| 0 - 0.17 | 0 - 10 | 36 |
| 0.17 - 0.43 | 10 -25 | 24 |
| 0.43 - 0.85 | 25 - 50 | 12 |

Patients with creatinine clearance rates greater than 0.85 mL/sec/1.73 $m^2$ (50 mL/min/1.73 $m^2$) may be dosed as for those patients with normal renal function.

CHILDREN

There is clinical experience for the treatment of urinary tract, and integumentary infections and acute pharyngitis-tonsillitis in children 6 weeks of age and over.

Clinical studies for the treatment of lower respiratory tract infections have been carried out in children one year of age and over.

Recommended dose is 30 mg/kg/day in two divided doses given for 10 days.

## PHARMACEUTICAL INFORMATION

Drug Substance

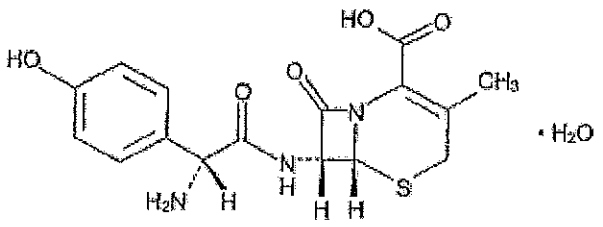
Common Name: Cefadroxil

Chemical Names:

1) 5-Thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid, 7-[[amino(4-hydroxyphenyl)-acetyl]amino]-3-methyl-8-oxo-, monohydrate, [6*R*-[6α, 7β(*R**)]]-

2) (6*R*,7*R*)-7-[(*R*)-2-Amino-2-(*p*-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2- carboxylic acid monohydrate.

Structural Formula:




Molecular Formula: $C_{16}H_{17}N_3O_5S \cdot H_2O$

Molecular Weight: 381.40

Description: A white or off-white crystalline powder. Slightly soluble in water; practically insoluble in alcohol, in chloroform and in ether.

Composition

PRO-CEFADROXIL-500 (cefadroxil) capsules contain cefadroxil monohydrate equivalent to 500 mg cefadroxil, along with the following non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, stearic acid, talc.

The capsule shell contains the following non-medicinal ingredients: FD&C blue #1, FD&C red #40, gelatin, grey ink, silicon dioxide, sodium lauryl sulphate and titanium dioxide.

The edible grey ink on the capsule shells contains the non-medicinal ingredient black iron oxide.

Stability and Storage Recommendations

Store at room temperature (15°-30°C), in tightly-closed containers.

## AVAILABILITY OF DOSAGE FORMS

PRO-CEFADROXIL (cefadroxil) is available as off-white powder in white body, maroon cap hard gelatin capsules imprinted '500', containing 500 mg of cefadroxil (as monohydrate).

Available in bottles of 100, 250 and 500 capsules.

## MICROBIOLOGY

The antibacterial activity of cefadroxil was determined *in vitro* on 555 strains of gram-negative and gram-positive organisms. Table 1 outlines these results in terms of cumulative percentage as determined by the agar dilution method.

Table 1

| Organism (No. of Strains) | Cumulative % of Strains Inhibited at Indicated Concentrations (μg/mL) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.13 | 0.25 | 0.50 | 1 | 2 | 4 | 8 | 16 | 32 | 63 | 125 | 250 |
| GRAM-POSITIVE | | | | | | | | | | | | |
| *Str. Pyogenes* (28) | 89.2 | 100 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| *Str. Pneumoniae* (20) | -- | 5 | 20 | 40 | 95 | 100 | -- | -- | -- | -- | -- | -- |
| *S. aureus* (17) (nonpenicillinase producing) | -- | -- | -- | 11.7 | 100 | -- | -- | -- | -- | -- | -- | -- |
| *S. aureus* (10) (penicillinase producing) | -- | -- | -- | -- | 31.4 | 85.6 | 100 | -- | -- | -- | -- | -- |
| *Str. Faecalis* (14) | -- | -- | -- | -- | -- | -- | -- | 7.1 | 7.1 | 100 | -- | -- |
| GRAM-NEGATIVE | | | | | | | | | | | | |
| *N. gonorrhoeae* (16) | -- | -- | -- | 12.5 | 18.7 | 49.9 | 81.1 | 100 | -- | -- | -- | -- |
| Shigella sp. (12) | -- | -- | -- | -- | -- | 8.3 | 74.9 | 100 | -- | -- | -- | -- |
| Salmonella (32) | -- | -- | -- | -- | -- | -- | 62.5 | 96.5 | 100 | -- | -- | -- |
| *K. pneumoniae* (62) | -- | -- | -- | -- | -- | -- | 56.4 | 90.2 | 96.6 | 98.2 | 100 | -- |
| *P. mirabilis* (51) | -- | -- | -- | -- | -- | -- | 3.90 | 64.6 | 97.9 | 100 | -- | -- |
| *E. coli* (96) | -- | -- | -- | -- | -- | 6.2 | 54.1 | 90.5 | 92.5 | 96.6 | 96.6 | 96.6 |
| *H. influenzae* (24) | -- | -- | -- | -- | -- | -- | -- | 20.9 | 95.9 | 100 | -- | -- |
| *P. stuartii* (31) | -- | -- | -- | -- | -- | -- | 3.2 | 12.8 | 38.6 | 67.0 | 96.6 | 100 |
| *P. vulgaris* (4) | -- | -- | -- | -- | -- | -- | -- | 25.0 | 50.0 | 50.0 | 75.0 | 100 |

Many strains of *H. influenzae* and most strains of enterococci species (*Strep. faecalis* and *Strep. faecium*), Enterobacter species, indole-positive Proteus species, *Providencia stuartii* and Serratia species are resistant to cefadroxil. Cefadroxil has no activity against Pseudomonas and Herella species.

*In Vivo* Studies

Male Swiss-Webster mice were fasted overnight and then challenged by the intraperitoneal injection of sufficient pathogens to kill untreated animals within 72 hours. The challenge organisms included *Str. pyogenes, Str. pneumoniae, S. aureus, E. coli, K. pneumoniae* and *P. mirabilis.* For *S. aureus* infections, cefadroxil was given orally at the time of infection and repeated 2 hours later. In the case of the other organisms, cefadroxil was given orally at 1 and 3.5 hours after injection of the bacteria. The results are shown in Table 2.

| Table 2<br>Protective Activity of Cefadroxil in Mice | | |
|---|---|---|
| Organism<br>(No. of Strains) | Challenge (Mean #<br>of organisms) | Protective $Dose_{50}$<br>(mg/kg) |
| *Str. pyogenes* (3) | $6.7 \times 10^6$ | 1.23 |
| *Str. pneumoniae* (3) | $2.0 \times 10^5$ | 22.0 |
| *S. aureus* | | |
| • lacking penicillinase (2) | $1.5 \times 10^8$ | 2.7 |
| • with penicillinase (2) | $1.0 \times 10^9$ | 18.5 |
| *E. coli* (2) | $6.0 \times 10^4$ | 14.0 |
| *K. pneumoniae* (1) | $4.0 \times 10^4$ | 85.0 |
| *P. mirabilis* (1) | $3.0 \times 10^6$ | 64.0 |

Male Swiss-Webster mice were challenged by injecting P. *mirabilis* into the right hind leg muscle only (0.2 mL of a suspension containing $10^8$ organisms). Cefadroxil was administered either orally or subcutaneously immediately following the bacterial challenge, and thigh enlargement was measured 24 hours later. Cefadroxil had an $ED_{50}$ of 85 mg/kg when administered by the oral route and 80 mg/kg by the subcutaneous route.

Beta Lactamase Susceptibility

The susceptibility of cefadroxil to hydrolysis by cell-free extracts containing different β-lactamases is shown in Table 3.

| Table 3<br>Relative Susceptibility to Hydrolysis by Beta-Lactamases | | | |
|---|---|---|---|
| Enzyme | | Organism<br>(Source of Enzyme) | Relative Rate of<br>Hydrolysis* |
| Class | Type | | |
| I | a | *Enterobacter cloacae* | 595 |
| | b | *Escherichia coli* | 48 |
| II | a | *Proteus mirabilis* | <1 |
| III | a | *E. coli* | <1 |
| IV | a | *Klebsiella pneumoniae* | <1 |
| | b | *K. pneumoniae* | 2 |
| -- | -- | *Staphylococcus aureus* (A9606) | <1 |

*Benzyl penicillin = 100

## PHARMACOLOGY

### Animal

After oral administration of cefadroxil at 50 mg/kg to four groups of rats (sampling was performed at 0.5, 1, 2 and 4 hours), maximum concentrations were reached at 0.5 hours in the liver (18.9 μg/g), kidney (136 μg/g) and muscle (4.88 μg/g) and at 1.0 hour in the lungs (5.63 μg/g), spleen (3.88 μg/g) and heart (2.63 μg/g). Insignificant concentrations were seen in brain tissue (0.83 μg/g).

### Human

Cefadroxil is well absorbed following oral administration with 93% of a 500 mg dose being recovered unchanged in the urine after 24 hours. Absorption of cefadroxil from the gastrointestinal tract is not inhibited by the presence of food.

Approximately 20% of the dose of cefadroxil is bound to the serum proteins. The apparent volume of distribution is 14 to 17% of body weight.

Human volunteers were given single 500, 1000 or 2000 mg oral doses (as multiples of the 500 mg cefadroxil capsule).

The total urinary excretion following single oral doses of cefadroxil has been determined in a number of experiments and the experimental results are summarized in Table 4.

Table 4

| Dose of Cefadroxil (mg) | Cumulative Urinary Excretion (mg) | | | |
|---|---|---|---|---|
| | 0-3 hr. | 3-6 hr. | 6-12 hr. | Total 0-12 hr. |
| 500 | 290 | 115 | 44 | 449 |
| 1000 | 455 | 264 | 111 | 830 |

The following table (Table 5) shows various pharmacokinetic values for 500, 1000 and 2000 mg doses.

| Table 5<br>Pharmacokinetic Parameters in Normal Human Volunteers | | | |
|---|---|---|---|
| Parameter | Dose of Cefadroxil (mg) | | |
| | 500 | 1000 | 2000 |
| Time to peak concentration: $T_{max}$ (hr) | 1.28 | 2.00 | 2.00 |
| Peak concentration: $C_{max}$ (µg/mL) | 14.8 | 23.63 | 32.7 |
| Area under the curve: AUC (µg/hr/mL) | 45.3 | 94.20 | 167.42 |
| Half-life (hr) | 1.34 | 1.51 | -- |

Lower Respiratory Tissue Levels

Cefadroxil was administered to 7 patients as a 500 mg single dose. At 12 hours, the pleural exudate contained cefadroxil at a level of 2.1 µg/mL compared to 0.8 µg/mL in the serum. Table 6 shows the pleural fluid concentration after 8 hours and 12 hours following the administered dose.

| Table 6<br>Pleural Fluid Concentration Following a Single 500 mg Oral Dose of Cefadroxil | | | |
|---|---|---|---|
| No. of Cases | Time (hrs) Post-Dose | Cefadroxil Conc. | |
| | | Pleural Fluid (µg/mL) | Serum (µg/mL) |
| 7 | 8 | 3.6 | 3.4 |
| | 12 | 2.1 | 0.8 |

In another study the mean pleural exudate and mean serum levels following a single 1 gram dose of cefadroxil exhibited a similar pattern 3 to 5 hours post-administration, i.e. the pleural fluid concentration is higher than the serum concentration (Table 7).

| Table 7<br>Measurement of Cefadroxil in Respiratory Tissues and Fluids Following a Single 1 g Dose | | | | |
|---|---|---|---|---|
| Fluid or Tissue | No. of Cases | Time (hrs) Post-Dose | Cefadroxil Conc. | |
| | | | Fluids (µg/mL) Tissue (µg/g) | Serum (µg/mL) |
| Sputum | 9 | 3-4 | 1.3 | Not done |
| Pleural Exudate | 4 | 3-5 | 11.4 | 9.4 |
| Lungs | 22 | 2-4 | 7.4 | 11.5 |

Data from Tables 6 and 7 indicate that tissue and fluid compartments act as a depot for cefadroxil after serum concentrations have diminished.

Renal Impairment

Single 1000 mg doses of cefadroxil were administered to 20 fasting patients with varying degrees of renal impairment as determined by creatinine clearance (from anuric to 1.76 mL/sec/1.73 $m^2$ [105.7 mL/min/1.73 $m^2$]). Blood and urinary concentrations of cefadroxil were monitored for up to 48 hours post-administration. The results of this study show that as creatinine clearance decreases the elimination rate constant also decreases, but the half-life increases.

In another study, single 1000 mg doses of cefadroxil were administered to eight fasting patients with varying degrees of severe renal impairment. Creatinine clearances varied from 0.004 to 0.54 mL/sec/1.73 $m^2$ (0.24 to 32.35 mL/min/1.73 $m^2$). Blood and urinary concentrations were monitored for up to 48 hours post-administration. A linear inverse correlation between the half-life of cefadroxil and creatinine clearance was observed.

## TOXICOLOGY

Acute Toxicity

The $LD_{50}$ values (see Table 8) were determined for cefadroxil in mice and rats. The observation period after the single injection was 7 days.

No deaths were observed in mice or in young rats. In adult rats, one death occurred following an intraperitoneal dose of 600 mg/kg and 3 deaths following an intravenous dose of 1000 mg/kg. Ataxia, decreased activity and prostration were observed at high doses.

Table 8

| Species | Age | Sex | No. of Animals | Route of Admin. | LD50 (mg/kg) |
|---|---|---|---|---|---|
| Mouse* | Adult | M&F | 80 | p.o. | >7000 |
| Mouse* | Adult | M&F | 80 | i.p. | >7000 |
| Mouse | Adult | M&F | 40 | i.v. | >1500 |
| Mouse | Adult | M&F | 60 | s.c. | >5000 |
| Rat | 24-48 hrs. | M&F | 50 | p.o. | >8000 |
| Rat** | Adult | M&F | 60 | p.o. | >8000 |
| Rat** | Adult | M&F | 60 | i.p. | >6000 |
| Rat** | Adult | M&F | 40 | i.v. | >1000 |
| Rat** | Adult | M&F | 40 | s.c. | >5000 |

*Swiss-Webster mice; **Sprague-Dawley rats.

Two adult beagle dogs (one male and one female) were given cefadroxil by the oral route at a dose of 500 mg/kg. One dog exhibited emesis and slight drowsiness while the other exhibited moderate drowsiness and had a slight increase in the heart rate.

Subacute Toxicity

Cefadroxil was administered orally at doses of 0, 200,400 or 600 mg/kg/day to 4 groups of 30 Sprague-Dawley rats (15 males and 15 females) for 14 weeks. Liver weights in males dosed at 400 and 600 mg/kg were increased by 11% and the combined relative weights of seminal vesicles and prostate glands were decreased by 16 to 21% for all treated groups. Adrenal weights of females in the 400 and 600 mg/kg groups were decreased by 12 to 16%. No histological abnormalities were observed at autopsy.

Cefadroxil was administered by gavage to 3 groups of 10 male and 10 female weanling rats at doses of 0, 2000 or 4000 mg/kg/day, for 4 weeks. An increase in SGPT (112%) in half of the animals in the 2 treated groups; a slight decrease in serum protein levels in both treated groups; and a decrease in serum glucose values in the high dose groups were observed. At necropsy increased cecum size (1.5 to 3-fold), and decreased heart (1 0.5 to 15.9%), liver (4.9 to 6.1 %) and spleen (10.8 to 25.7%) weights were noted, although no histological changes in the organs were seen.

Four groups of young beagle dogs (3 males and 3 females per group) were given cefadroxil orally at doses of 0, 100, 200 or 400 mg/kg/day for a period of 13 weeks. The

animals in the 200 and 400 mg/kg/dose groups had a marginally lower food intake (10 to 18%) and body weight (6.8%) by the end of the study.

No histological abnormalities were observed at autopsy. However, the spleen and gonad weights in female dogs were elevated (78% and 88% respectively) in the high dose group, while relative adrenal weights were increased by 45% in the 200 mg/kg dose group. There was an increased incidence of emesis (dose related) and proteinuria at all drug dose levels.

Chronic Toxicity

Cefadroxil was administered orally (admixed in the feed) to 4 groups of 30 Charles River rats (15 males and 15 females) at doses of 0, 100, 316 or 1000 mg/kg/day for a period of 26 weeks. No deaths were observed, however, significantly increased ($p<0.05$) kidney weights in the middle (11%) and high (16%) dose group males were observed.

Four groups of beagle dogs (3 males and 3 females) were given cefadroxil at doses of 0, 200, 400 or 600 mg/kg/day for 26 weeks (once a day for the first week, then b.i.d. for the remainder of the experiment). A decrease was seen in weight gain (24.6%) in the middle dose female group and a slight decrease in total serum proteins and albumin levels in all treated groups were observed.

Renal Toxicity

Male mice were pretreated with intraperitoneal injections of furosemide (20 or 40 mg/kg) or 0.9% saline. Fifteen minutes later 0.9% saline or doses of 1396, 2792 or 5584 mg/kg of cefadroxil were injected intraperitoneally. Urine evaluation (pH, glucose and urine protein) and histological examination of kidneys were conducted 48 hours following the injections. A slight weight loss in the high dose cefadroxil group pretreated with furosemide was noted. No evidence of renal injury was seen.

Fertility and Reproduction Study

The oral administration of cefadroxil to three groups of 40 Sprague-Dawley rats per group (15 males and 25 females) at doses of 0, 200 or 400 mg/kg/day during gestation

did not modify pregnancy nor alter the percentage of resorptions. The males were dosed for 77 days prior to mating and the females for 14 days prior to mating. The percentage of stillbirths in each group was 3.3, 1.8 and 1.3 for the 400, 200 and 0 mg/kg dose groups, respectively.

Teratology Studies

The oral administration of cefadroxil at doses of 0, 100, 250 or 500 mg/kg/day given b.i.d. to pregnant Sprague-Dawley rats and Swiss mice on gestation day 6 through day 15 had no discernible effect on nidation or on maternal or fetal survival.

Perinatal - Postnatal Study

Cefadroxil was administered at doses of 0, 250 or 500 mg/kg/day given b.i.d. to pregnant Sprague-Dawley rats from day 14 of gestation to post-partum day 21. No adverse drug-related effects on fetal birth weight, survival or growth were observed.

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