PRODUCT MONOGRAPH

Pr DURICEF*

(cefadroxil)

Capsules, 500 mg

ANTIBIOTIC

Bristol-Myers Squibb Canada
2365 Cote de Liesse
St. Laurent PQ
H4N 2M7

Date of Preparation:
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Control#: 094706

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DURICEF*

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THERAPEUTIC CLASSIFICATION

ANTIBIOTIC

ACTION AND CLINICAL PHARMACOLOGY

DURICEF (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.

INDICATIONS AND CLINICAL USE

DURICEF (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 beta-hemolytic streptococci.

- Acute pharyngitis-tonsillitis, when caused by group A beta-hemolytic streptococci.

- Lower respiratory tract infections, including pneumonia, caused by *S. pneumoniae (D. pneumoniae), S. Pyogenes* (Group A-beta 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

DURICEF (cefadroxil) is contraindicated in patients with a known hypersensitivity to the cephalosporin group of antibiotics or to any component of the formulation.

WARNINGS

Before therapy with DURICEF is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to DURICEF, other 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 raction to DURICEF occurs, discontinue the drug. Serious acute hypersensitivity reactions may require emergency treatment measures.

Colitis

Pseudomembranous colitis has been reported with the use of cephalosporins and other broad spectrum antibiotics, and may range from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. After the diagnosis of colitis has been established, therapeutic measures should be initiated. Treatment with broad spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. 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 BETA-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 DURICEF (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 DURICEF can result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, the administration of DURICEF should be discontinued and appropriate measures taken. If an organism becomes resistant during treatment with DURICEF alternate therapy should be instituted.

DURICEF 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/1.73m² (50 mL/min/1.73m^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 DURICEF can accumulate in serum and tissues.

If DURICEF 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 DURICEF, 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.

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

Pregnancy

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

Nursing Mothers

Cefadroxil is distributed into breast milk; therefore, this drug should be used with caution in nursing women.

ADVERSE REACTIONS

The adverse events observed with cefadroxil are similar to those observed with other cephalosporins.

Gastrointestinal

Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment. Nausea, vomiting, and dyspepsia have been reported rarely. Administration with food decreases nausea. Diarrhea has also occurred.

Hypersensitivity

In common with other cephalosporins, allergic reactions, including fever, pruritus, rash, swollen and running eyes, urticaria, and angioedema have been observed. These reactions usually subside upon discontinuation of the drug. Erythema multiforme, Stevens-Johnson syndrome, serum sickness, and anaphylaxis have been reported rarely.

CNS

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

Miscellaneous

Vaginitis, genital pruritus, genital candidiasis, cramps in side and legs, arthralgia, moderate transient neutropenia, eosinophilia, positive direct Coombs test,elevations in BUN, alkaline phosphatase and, elevations in serum transaminase.

In common with other cephalosporins, thrombocytopenia and agranulocytosis have been reported rarely.

During postmarketing experience, hepatic dysfunction, including cholestasis has been reported, and rare reports of idiosyncratic hepatic failure have been received; because of the uncontrolled nature of these spontaneous reports, a causal relationship to DURICEF has not been established.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Data from a study of children under six years of age who had ingested a maximum of 250 mg/kg

of penicillin or a cephalosporin derivative suggested that ingestion of less than 250 mg/kg of cephalosporins (i.e., 5 to 10 times recommended dose) is not associated with significant outcomes. No treatment is required other than general support and observation. During the 72-hour evaluation period, most of the children remained asymptomatic. Gastrointestinal disturbances and rash were reported in some children. For amounts greater than 250 mg/kg, induce gastric emptying (emesis induction or gastric lavage).

For information on removal of drug by hemodialysis, see "Dosage and Administration" section.

DOSAGE AND ADMINISTRATION

DURICEF (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 in diminishing potential gastrointestinal complaints occasionally associated with oral cephalosporin therapy.

A MINIMUM OF 10 DAYS TREATMENT IS RECOMMENDED FOR INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI.

ADULTS

Normal Renal Function

The recommended dose is 1 to 2 g per day.

Urinary Tract Infections

The recommended daily dose is 1 to 2 g. This may be given as a single dose at bedtime or divided into 500 mg to 1 g 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, DURICEF 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 g 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 DURICEF should be adjusted according to creatinine clearance rates to prevent

drug accumulation.

In adults, the initial dose is 1 g as 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 (HOURS)
(mL/sec/1.73m^2)	**(mL/min/1.73m^2)**	
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 50 mL/min/1.73m^2 may be dosed as for those patients with normal renal function.

In five adult anuric patients, it was demonstrated that an average of 63% of a 1-g oral dose is extracted from the body during a 6 to 8 hour hemodialysis session.

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 equally divided doses given for 10 days.

PHARMACEUTICAL INFORMATION

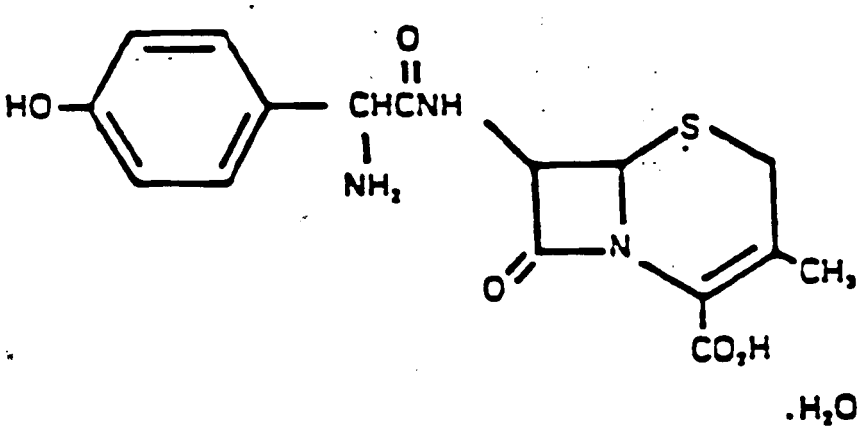
I. DRUG SUBSTANCE

Proper Name: Cefadroxil Monohydrate

Chemical Name: (6R,7R)-7-((R)-2-Amino-2-(p-hydroxyphenyl) acetamido)-3-methyl-8-oxo-5-thia-l-azabicyclo (4.2.0)oct-2-ene-2-carboxylic acid monohydrate.

Empirical Formula: $C_{16}H_{17}N_3O_5SH_20$

Structural Formula:



Molecular Weight: 381.40

Description: Cefadroxil monohydrate is a white to yellow white powder and is soluble in water.

II. COMPOSITION

DURICEF capsules contain 500 mg of cefadroxil monohydrate, magnesium stearate and may also contain lactose and silicon dioxide. The capsule shell has the following composition: D & C yellow no. 10 and red no. 33, FD & C blue no. 1 and red no. 3, gelatin, printing ink, titanium dioxide.

III. STABILITY AND STORAGE RECOMMENDATION

DURICEF capsules should be stored at controlled room temperature (15-30°C).

AVAILABILITY OF DOSAGE FORM

Capsules

DURICEF (Cefadroxil) is available in maroon and white hard gelatin capsules containing 500 mg of cefadroxil (as monohydrate) in bottles 100 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. Many strains of *H. influenzae* and most strains of enterococci species (*Enterococcus faecalis* and *Enterococcus faecium*), Enterobacter species, indole-positive Proteus species, *Morganella morganii, Providencia stuartii* and Serratia species are resistant to cefadroxil. Cefadroxil has no activity against Pseudomonas and *Acinetobacter calcoaceticus*.

TABLE I

Cumulative Percentage of Strains Inhibited at Indicated Concentrations (mcg/mL)

Organisms (No. of Strains)	0.13	0.25	0.5	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) (non-penicillinase producing)	---	---	---	11.7	100							
S. aureus (70) (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 spp. (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)	---	---	---	---	---	---	3.9	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

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 II.

TABLE II
Protective activity of cefadroxil in mice

Organism (No. of Strains)	Challenge Mean No. of Organisms	Protective $Dose_{50}$ (mg/kg)
Str. pyogenes (3)	6.7×10^6	1.23
Str. pneumoniae (3)	2.0×10^5	22.0
S. Aureus - lacking penicillinase (2) - with penicillinase (2)	 1.5×10^8 1.0×10^9	 2.7 18.5
E. coli (2)	6.0×10^4	14
K. pneumoniae (1)	4.0×10^4	85
P. mirabilis (1)	3.0×10^6	64

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 beta-lactamases is shown in Table III.

TABLE III

Relative susceptibility to hydrolysis by beta-lactamases

Enzyme[10]		Organism (Source of Enzyme)	Relative Rate of Hydrolysis*
Class	**Type**		
I	a b	*Enterobacter cloacae* *Escherichia coli*	595 48
II	a	*Proteus mirabilis*	< 1
III	a	*Escherichia coli*	< 1
IV	a b	*Klebsiella pneumoniae* *Klebsiella pneumoniae*	< 1 2
---	---	*Staphyloccus 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 mcg/g), kidney (136 mcg/g) and muscle (4.88 mcg/g) and at 1.0 hour in the lungs (5.63 mcg/g), spleen (3.88 mcg/g) and heart (2.63 mcg/g). Insignificant concentrations were seen in brain tissue (0.83 mcg/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 serum and urinary concentrations as a function of time are shown in Figures I and II.

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 IV.

TABLE IV

Dose of Cefadroxil (mg)	Cumulative Urinary Excretion (mg)			
	0 - 3 hr.	3 - 6 hr.	6 - 12 hr.	Total 0 - 12 hr.
500	290	115	4	449
1000	455	264	111	830

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

TABLE V

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} (mcg/mL)	14.8	23.63	32.7
Area under the curve; AUC (mcg/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 mcg/ml compared to 0.8 mcg/ml in the serum. Table VI shows the pleural fluid concentration after 8 hours and 12 hours following the administered dose.

TABLE VI

Pleural Fluid Concentration Following a Single 500 mg Oral Dose of Cefadroxil

No. of Cases	Cefadroxil Concentration		
	Time (hrs) Post-Dose	Pleural Fluid (mcg/mL)	Serum (mcg/mL)
7	8 12	3.6 2.1	3.4 0.8

In another study the mean pleural exudate and mean serum levels following a single 1 g 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 VII).

TABLE VII

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 Concentration	
			Fluids (mcg/mL) Tissue (mcg/g)	Serum (mcg/mL)
Sputum Pleural	9	3 - 4	1.3	Not done
Exudate	4	3 - 5	11.4	9.4
Lungs	22	2 - 4	7.4	11.5

Data from Table VI and Table VII 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/1.73m^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 and is shown in Figure III.

TOXICOLOGY

Acute Toxicity

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

TABLE VIII

Species	Age	Sex	No. of Animals	Route of Administration	LD_{50} (mg/kg)
Mouse[1]	Adult	M & F	80	Oral	> 7000
Mouse[1]	Adult	M & F	80	Intraperitoneal	> 7000
Mouse	Adult	M & F	40	Intravenous	> 1500
Mouse	Adult	M & F	60	Subcutaneous	> 5000
Rat	24 - 48 hrs.	M & F	50	Oral	> 8000
Rat[2]	Adult	M & F	60	Oral	> 8000
Rat[2]	Adult	M & F	60	Intraperitoneal	> 6000
Rat[2]	Adult	M & F	40	Intravenous	> 1000
Rat[2]	Adult	M & F	40	Subcutaneous	> 5000

[1] Swiss-Webster mice
[2] Sprague-Dawley rats

No deaths were observed in mice or in young rats. In adult rats, one death occurred following an intraperitoneal dose of 6000 mg/kg and 3 deaths following an intravenous dose of 1000 mg/kg. Ataxia, decreased activity and prostration were observed at high doses.

Two adult beagles 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 (10.5 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 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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