PRODUCT MONOGRAPH

PrORELOX®

(cefpodoxime proxetil tablets)

100 mg cefpodoxime/tablet

Antibiotic

sanofi-aventis Canada Inc.
2150 St. Elzear Blvd. West
Laval, Quebec H7L 4A8

Date of Preparation:
May 9, 2006

Submission Control No. 105718

s-a Version 1.0 dated

PRODUCT MONOGRAPH

NAME OF DRUG

^{Pr}ORELOX®

(cefpodoxime proxetil tablets)

100 mg cefpodoxime/tablet

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION AND CLINICAL PHARMACOLOGY

Cefpodoxime proxetil is the prodrug of cefpodoxime, a semi-synthetic oral β-lactam antibiotic belonging to the third-generation cephalosporin group of antibiotics.

The bactericidal activity of cefpodoxime results from its inhibition of bacterial cell wall synthesis through its binding to penicillin-binding proteins (PBPs). Specifically, cefpodoxime binds to PBP 3 as well as to PBPs 1a, 1b and 1c. Cefpodoxime is highly stable in the presence of β-lactamases, both plasmid- and chromosomally-mediated. Cefpodoxime has shown a low potential for inducing β-lactamases.

Following oral administration, cefpodoxime proxetil is absorbed in the intestine where it is rapidly hydrolyzed by non-specific esterases to cefpodoxime. When administered to fasting subjects, approximately 50% of a cefpodoxime dose is absorbed. As absorption is increased by food intake, it is recommended that ORELOX® (cefpodoxime proxetil tablets) be taken with food (see PHARMACOLOGY section).

After single oral dosing in fasted healthy volunteers, peak serum levels of cefpodoxime are attained in 2 to 3 hours. The maximum plasma concentrations range from 1.0 to 1.2 mg/L and from 2.2 to 2.5 mg/L for the 100 mg and 200 mg dose, respectively. Cefpodoxime, the main metabolite of cefpodoxime proxetil, is very slightly metabolized.

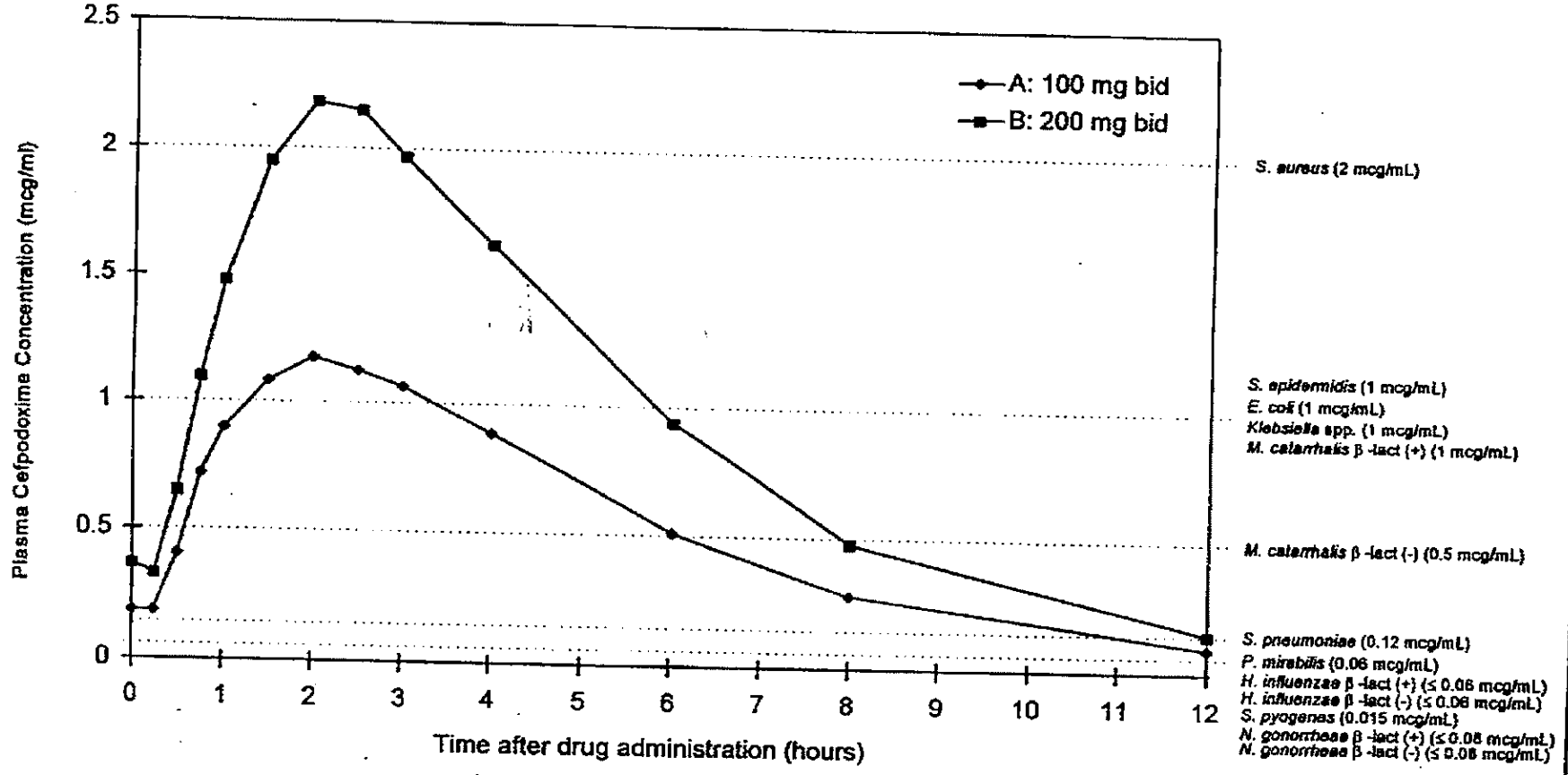
After intravenous administration of cefpodoxime, 80% of the active cefpodoxime moiety is excreted unchanged in the urine over 24 hours. The mean elimination half-life of cefpodoxime is 2.4 hours.

Plasma concentration versus time curve in relation to minimum inhibitory concentrations (MIC_{90})

The plasma concentrations of cefpodoxime on Day 15 of twice daily administration of doses of 100 mg and of 200 mg to fasted subjects, in relation to MIC_{90} for various bacterial organisms, are illustrated by the figure below.

Refer to MICROBIOLOGY section for susceptibility breakpoints of pathogens and to PHARMACOLOGY section for tissue levels of drug.

Comparison of Plasma Cefpodoxime Concentrations at Steady State and MIC_{90} Values on Day 15 of Administration



INDICATIONS AND CLINICAL USE

ORELOX ® (cefpodoxime proxetil tablets) is indicated for the treatment of patients with mild to moderate infections when caused by susceptible strains of the designated organisms, in the conditions listed below:

Lower respiratory tract infections

Community-acquired pneumonia caused by *Streptococcus pneumoniae* and by *Haemophilus influenzae**.

Secondary bacterial infection of acute bronchitis and acute exacerbations of chronic bronchitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae** and *Moraxella catarrhalis**.

* Typing of these pathogens with respect to β-lactamase production was not carried out for these clinical trials.

Upper respiratory tract infections

Pharyngitis and tonsillitis caused by *Streptococcus pyogenes*.

NB: Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. ORELOX® is as effective as penicillin in the eradication of susceptible strains of streptococci from the oropharynx; however, data establishing the efficacy of ORELOX® in the subsequent prevention of rheumatic fever are not available.

Urinary tract infections

Uncomplicated urinary tract infections (cystitis) caused by *Escherichia coli*.

Sexually transmitted diseases

Uncomplicated urethral gonococcal infections in males and uncomplicated cervical and ano-rectal gonococcal infections in females (including penicillinase-producing strains).

Skin and skin structure infections

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus*.

NB: Abscesses should be surgically drained as indicated.

Appropriate cultures should be taken for susceptibility testing before initiating treatment with ORELOX ®. Therapy may be started before results are available. Once these are obtained, the antibiotic treatment should be adjusted if required.

CONTRAINDICATIONS

ORELOX ® (cefpodoxime proxetil tablets) is contraindicated in patients who have shown Type I hypersensitivity to cefpodoxime proxetil or to any of the cephalosporin group of antibiotics.

WARNINGS

Before therapy with ORELOX ® (cefpodoxime proxetil tablets) is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefpodoxime proxetil, other cephalosporins, penicillins or other drugs. ORELOX ® should be administered with caution to patients who have demonstrated some form of allergy, particularly to drugs. Serious and potentially fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving these two types of compounds. There is some clinical and laboratory evidence of partial cross-allergenicity of the cephalosporins and penicillins (5 to 10% of cases). Special care is indicated in patients who have experienced anaphylactic reactions to penicillins: strict supervision is necessary for the first administration. If an allergic reaction to ORELOX ® occurs, treatment should be discontinued. Serious acute hypersensitivity reactions may require treatment with standard agents (e.g. epinephrine, antihistamines, corticosteroids) as clinically indicated.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ORELOX®, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of ORELOX®. Extreme caution should be observed when using ORELOX® in patients at increased risk for antibiotic-induced pseudomembranous colitis because of exposure to institutional settings such as nursing homes or hospitals with endemic *C. difficile.*

Treatment with broad-spectrum antibiotics, such as ORELOX ®, can alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile* or other Clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of colitis may respond to drug discontinuation alone. Moderate to severe cases should be managed with fluids, electrolytes, and protein supplementation as indicated. When the colitis is severe or not relieved by discontinuing treatment with ORELOX®, consideration should be given to the administration of oral vancomycin or other suitable therapy. Other possible causes of colitis should also be considered.

PRECAUTIONS

General

Broad-spectrum antibiotics, including ORELOX® (cefpodoxime proxetil tablets), should be administered with caution to individuals with a history of lower gastrointestinal disease, particularly colitis.

The possibility of the emergence of resistant organisms which might result in bacterial overgrowth should be kept in mind, particularly during prolonged treatment. In such situations, careful observation of the patient is essential. If superinfection occurs, therapy with ORELOX® should be discontinued and appropriate measures taken.

Use in the elderly

Dose adjustment in elderly patients with normal renal function is not necessary.

Use in renal impairment

ORELOX ® may be administered in the presence of impaired renal function, but dose modification is recommended for patients with moderate to severe renal impairment (< 40 mL/min/1.73m^2) (see DOSAGE AND ADMINISTRATION).

Use in children

The efficacy and safety of ORELOX® in children under 16 years of age has not yet been documented.

Use in pregnancy

The safety of ORELOX® in pregnant women has not yet been established. It is therefore advisable not to administer the product during pregnancy.

Nursing mothers

Because cefpodoxime is excreted in human milk, consideration should be given to discontinuing nursing temporarily during treatment with ORELOX® (see PHARMACOLOGY section).

Drug interactions

The H_2-antagonists and antacids, by reducing gastric acidity, decrease the bioavailability of ORELOX ® compared with that of the fasting state. A delay of at least 2 hours before administration of ORELOX ®

tablets is therefore recommended in patients receiving concomitant H_2-antagonist or antacid therapy (see PHARMACOLOGY section).

Impairment of renal function has been observed with other cephalosporin antibiotics, in particular with concomitant administration of cephalosporins and compounds such as aminoglycosides and loop diuretics. Close monitoring of renal function is therefore advised when ORELOX ® is administered with compounds with a known nephrotoxic potential.

Concomitant administration of probenecid competitively inhibits renal tubular secretion of cefpodoxime resulting in increased peak plasma levels and area under concentration curve (AUC) (see PHARMACOLOGY section).

Drug - laboratory interactions

A positive direct and indirect Coomb's test has been described during treatment with cephalosporins which may cause interference with cross-matching of blood.

During urine testing for glucose with reducing agents (Benedict's or Fehling's solution or with Clinitest®* tablets), a false-positive reaction may occur in patients treated with ORELOX®. It is therefore recommended that tests based on enzymatic glucose oxidase reactions (e.g. Clinistix®* or Tes-Tape®**) be used.

ADVERSE REACTIONS

Clinical Trials

The majority of adverse events observed in clinical trials involving 6780 patients treated with ORELOX ® (cefpodoxime proxetil tablets) were of a mild and transient nature.

Therapy was discontinued in 1.9% of patients because of drug-related adverse events (adverse reactions).

In single dose studies (N=548), diarrhea (1.3%) and nausea (1.3%) were the most frequently reported adverse reactions.

* Reg. Trademark of Ames company, Division of Miles Laboratories Ltd.
** Reg. Trademark of Eli Lilly.

The following possibly- or probably-related reactions were reported in controlled multiple dose clinical trials (N=6566). Incidence rates for individual reactions were less than 1% except where otherwise noted.

Body system	Adverse reactions
Body as a whole	abdomen enlarged, asthenia, chills, fever, malaise, pain
Cardiovascular system	cerebrovascular disorder, chest pain, hypotension, migraine, palpitation, vascular purpura
Gastrointestinal system	abdominal pain, abnormal stools, anorexia, colitis (unspecified), constipation, diarrhea (3.6% - 200 mg/day / 6.3% - 400 mg/day), dry mouth, dyspepsia, fecal incontinence, flatulence, gastritis, gastroenteritis, liver function tests abnormal, mouth ulceration, nausea (2%), oral moniliasis, sore mouth, stool culture positive for *C. difficile**, tenesmus, vomiting
Hemic & lymphatic system	anemia, ecchymosis
Metabolic/Nutritional	edema, excessive thirst, gout
Musculoskeletal system	muscle cramps, joint stiffness
Nervous system	abnormal dreams, anxiety, apathy, confusion, depression, dizziness, headache, hot flushes, increased sweating, insomnia, somnolence, paresthesia, tremor
Respiratory system	bronchospasm, cough increased
Skin & appendages	acne, alopecia, breast pain, erythema nodosum, fungal dermatitis, Herpes simplex, maculopapular rash, pruritus, skin disorder, rash, urticaria, vesiculobullous rash
Special senses	abnormal vision, eye disorder, taste loss, taste perversion, tinnitus
Urogenital system	dysuria, female genital pain, hematuria, increased urinary frequency, increased urination, labial edema, leukorrhea, menstrual disorder, nocturia, yeast infection penis/groin, urinary tract infection, vaginal fungal infection, vaginitis and/or vulvitis

* Of patients with diarrhea, 10% had *C. difficile* organism or toxin in the stools (The Upjohn Company safety database for VANTIN®)

Laboratory changes

Laboratory changes that have been reported in clinical trials, irrespective of drug relationship, were the following:

Hematologic: Decreased hemoglobin, direct Coombs' test positive, eosinophilia, leucocytosis, leukopenia, lymphocytosis, neutrophilia, prothrombin increased, thrombocytopenia, thrombocytosis

Hepatic: Increases and decreases in bilirubin, increases in SGOT, SGPT, GGT, LDH and alkaline phosphatase

Serum chemistry: Hypercalcemia, hyperglycemia, hyperkalemia, hyperlipemia, hyponatremia

Renal: Increases in BUN and creatinine, decreases in creatinine

Most of these abnormalities were transient and not clinically significant.

Post-Marketing Surveillance

The following serious possibly or probably drug-related adverse events have been reported in post-marketing surveillance: diarrhea, bloody diarrhea, *C. difficile* diarrhea, pseudomembranous colitis (rarely resulting in fatality), ulcerative colitis, angioedema/rash, anaphylactic shock, interstitial pneumonia, acute hepatocellular injury, mixed acute liver injury.

Very rare cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and pancreatitis, acute nephritis with vascular purpura, eosinophilic myalgia syndrome, hemolytic anemia, serum sickness, tachycardia, neuropathy and eyelid dermatitis were also reported. For these events, no specific relationship to the drug product was ascertained.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Since no case of overdosage has been reported to date with ORELOX ® (cefpodoxime proxetil tablets), no specific information on symptoms or treatment is available. As there is no specific antidote, treatment of overdosage should be symptomatic. Hemodialysis may aid in the removal of cefpodoxime from the body, particularly if renal function is compromised.

DOSAGE AND ADMINISTRATION

Since absorption is enhanced with food, it is recommended that ORELOX® (cefpodoxime proxetil tablets) be given with meals. (See PHARMACOLOGY section)

The usual daily dose of ORELOX ® is 100 mg to 200 mg orally twice daily, as follows:

Infection	Description	Dose frequency
Lower respiratory tract infections	Pneumonia	200 mg BID
	Secondary bacterial infection of acute bronchitis	100 mg to 200 mg BID*
	Acute exacerbations of chronic bronchitis	200 mg BID
Upper respiratory tract infections	Pharyngitis, tonsillitis	100 mg BID
Urinary tract infections	Uncomplicated cystitis	100 mg BID
Sexually transmitted diseases	Uncomplicated urethral, ano-rectal and cervical gonococcal infections	200 mg single dose
Skin and skin structure infections	Uncomplicated	200 mg BID

* According to severity

Duration of therapy in clinical trials was 5 to 14 days. The duration of treatment should be guided by the patient's clinical and bacteriological response. In the treatment of gonococcal infections, a single 200 mg dose is recommended.

Dosage modification in patients with renal insufficiency

Dosage should be adjusted in patients with a creatinine clearance value of less than 40 mL/min, as follows:

Creatinine clearance (mL/min)	Unit dose* (mg)	Dosage interval
≥ 40	100 or 200	12 hours
10-39	100 or 200	24 hours
< 10	100 or 200	48 hours
Patients on hemodialysis	100 or 200	after each dialysis session

* According to the type of infection

When only the serum creatinine is known, the following formula may be used to estimate creatinine clearance.

Men: Creatinine clearance (mL/min) = $\frac{\text{Weight (kg) x (140-age)}}{\text{72 x serum creatinine (mg/dL)}}$

SI units:

Men: Creatinine clearance (mL/s) = $\frac{\text{Weight (kg) x (140-age).}}{\text{49 x serum creatinine (µmol/L)}}$

Women: 0.85 x the value calculated for men.

The serum creatinine should represent a steady-state of renal function.

Dosage modification in patients with hepatic insufficiency

There is no need for dosage modification in patients with liver impairment.

PHARMACEUTICAL INFORMATION

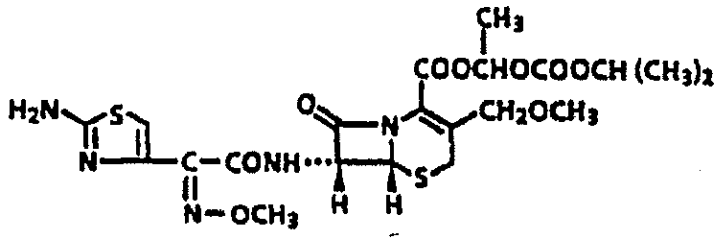
DRUG SUBSTANCE

Trade Name ORELOX ®

Proper Name Cefpodoxime Proxetil Tablets

Chemical Name (RS)-1-isopropoxycarbonyloxy)ethyl(6R,7R)-7-[2-(2-amino-4-thiazolyl)-(Z)-2-(methoxyimino)acetamido]-3-methoxy-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylate.

Structural Formula



Molecular Formula	$C_{21}H_{27}N_5O_9S_2$	(cefpodoxime proxetil)
	$C_{15}H_{17}N_5O_6S_2$	(cefpodoxime, i.e. active acid)
Molecular Weight	557.61	(cefpodoxime proxetil)
	427.47	(cefpodoxime)

Description

Cefpodoxime proxetil is a white to light brownish-white powder. It is odorless or has a slight characteristic odor and has a bitter taste. Cefpodoxime proxetil is freely soluble in many organic solvents (acetone, methanol, ethylacetate, anhydrous ethanol), but practically insoluble in water.

DOSAGE FORM

Presentation

ORELOX ® 100 mg is available as a round, biconvex, white tablet, 9 mm in diameter. A broken tablet shows a pale yellow core surrounded by a white film-coating. 208 A is engraved on one side of the tablet.

Composition

Each ORELOX ® tablet contains 100 mg of cefpodoxime (active acid) introduced as 130.45 mg of cefpodoxime proxetil (drug substance i.e., ester form of the active acid). Non-medicinal ingredients are: calcium carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, lactose monohydrate (21.55 mg/100 mg tablet), magnesium stearate, sodium laurylsulfate, talc, titanium dioxide.

Availability

ORELOX ® (cefpodoxime proxetil tablets) is available as 100 mg cefpodoxime film-coated tablets. ORELOX ® tablets are packaged in white opaque high density polyethylene bottles with a press-on white opaque polyethylene cap and in aluminum blister-packs. Bottles of 50 and unit-dose packages of 30.

Stability and Storage Recommendations

ORELOX ® tablets should be kept at room temperature, between 15-25°C.

INFORMATION FOR THE PATIENT

HOW TO MAKE ORELOX ® WORK BEST FOR YOU

Your doctor has decided that ORELOX ® is appropriate treatment for you. Remember that the chances of successfully treating your infection are greater if you cooperate fully with your doctor and try to become well informed about your condition.

This leaflet is meant to supplement what your doctor or pharmacist may have told you. If you have any questions after reading this information leaflet, be sure to ask your doctor or pharmacist.

WHAT IS ORELOX ® AND HOW DOES IT WORK?

ORELOX ® is the product name for cefpodoxime proxetil. It belongs to a family of medicines called cephalosporins, which are antibiotics.

Your doctor has prescribed ORELOX ® because you have an infection. ORELOX ® is used to kill the bacteria or 'germs' which cause your infection.

WHAT DOES ORELOX ® LOOK LIKE?

ORELOX ® is available as white, round film-coated tablets.

HOW SHOULD YOU TAKE ORELOX ® TO MAKE IT WORK BEST FOR YOU?

Your doctor has chosen the strength (dose) that he or she thinks will be most effective in treating your infection.

The usual dose of ORELOX ® tablets is one or two 100 mg tablet(s) taken twice a day. ORELOX ® tablets are more effective if taken with food: take one dose with breakfast and one dose with dinner.

You should take ORELOX ® only as directed by your doctor. Do not take it more often and do not take it for a shorter period of time than your doctor has ordered.

During the course of treatment, all tablets must be taken to make sure that all germs have been killed. Continue taking the tablets until they are finished, even if you begin to feel better.

WHAT TO DO IF YOU MISS A DOSE?

If you miss a dose of ORELOX ® tablets, take it as soon as possible then continue with the normal dose.

DOES ORELOX ® HAVE SIDE EFFECTS?

After taking your medicine

As with other similar agents such as penicillins, ORELOX ® may cause allergic reactions. If you experience wheeziness and tightness of chest, swelling of eyelids, face or lips, or develop skin lumps or hives, tell your doctor immediately. Do not take any more medicine unless your doctor tells you to do so. He may decide to stop your treatment.

Should you experience diarrhea, skin rash (red spots) or any other unusual symptoms, advise your doctor as soon as possible and follow his additional instructions.

If you feel worse or you have taken all the tablets and do not feel better, notify your doctor as soon as possible.

WHAT SHOULD I REMEMBER?

Before taking this medication tell your doctor and pharmacist if you:

- are allergic to any drugs particularly antibiotics of the penicillin or cephalosporin family;
- have a history of gastrointestinal disease, particularly colitis;
- have a history of kidney disease;
- are pregnant or intend to become pregnant while taking this medication;
- are breast feeding;
- are taking any other medication (either prescription or non-prescription, such as antacids). This is important because some medicines can interact with each other and cause some unwanted effects;
- have any other medical problem(s).

While taking this medication:

- report any unusual reactions to your doctor.This is important as it will aid in the early detection and prevention of potential complications.

- DO NOT share your medication with other members of your family or friends since it may not be appropriate for them, even if their symptoms are the same as yours.

- Keep your medication out of children's reach and protect it from excessive light or humidity.

- If you require more information on this drug, consult your doctor or pharmacist.

MICROBIOLOGY

The minimum inhibitory concentrations (MIC_{50} and MIC_{90}) against various organisms *in vitro* are presented below:

Table 1 - Antibacterial activity of Cefpodoxime

Organisms	n	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	% susceptible[1]	
Citrobacter diversius	52	0.25	2	0.15 - > 16	94	
Citrobacter freundii	158	2	> 16	0.12 - > 16	52	
Enterobacter aerogenes	116	1	> 16	0.015 - > 16	54	
Enterobacter agglomerans	15	2	16	≤ 0.008 - > 16	53	
Enterobacter cloacae	322	4	> 16	0.06 - > 16	48	
Escherichia coli	1014	0.25	1	≤ 0.003 - > 16	97	
Haemophilus influenzae	30	0.06	0.12	≤ 0.008 - 1	100	
β–lactamase (-)	24	≤ 0.06	≤ 0.06	≤ 0.06		
β–lactamase (+)	24	≤ 0.06	≤ 0.06	≤ 0.06 - 0.12		
Haemophilus parainfluenzae	19	0.03	1	< 0.008 - > 16	95	
Klebsiella oxytoca	122	0.12	1	0.015 - > 16	91	
Klebsiella pneumoniae	395	0.12	1	≤ 0.008 - > 16	94	
Moraxella catarrhalis	40	0.5	1	0.12 - 1	100	
β–lactamase (-)	21	0.25	0.5	0.12 - 1		
β–lactamase (+)	33	0.5	1	0.25 - 1		
Morganella morganii	71	8	> 16	0.015 - > 16	41	
Neisseria gonorrhoeae	34	0.015	0.06	0.002 - 0.06	100	
β–lactamase (-)	42	≤ 0.008	≤ 0.008	≤ 0.008 - 0.015		
β–lactamase (+)	42	≤ 0.008	≤ 0.008	≤ 0.008 - 0.03		
Neisseria meningitidis	20	≤ 0.06	≤ 0.06	≤ 0.06 - 0.25		
Proteus mirabilis	236	0.03	0.06	≤ 0.008 - 16	99	
Proteus vulgaris	21	0.12	16	≤ 0.008 - > 16	71	
Providencia rettgeri	18	0.015	> 16	≤ 0.008 - > 16	83	
Providencia stuartii	20	≤ 0.06	2	≤ 0.06 - 2		
Pseudomonas aeruginosa	654	> 16	> 16	2 - > 16	1	
Salmonella spp. Ampicillin-R	15	0.25	1	0.12 - 2		
Serratia marcescens	88	2	16	0.25 - > 16	63	
Shigella spp. Ampicillin-R	15	0.5	1	0.25 - 4		
Yersinia enterocolitica	20	0.25	1	0.03 - 2		
Staphylococcus aureus	25	2	2	2 - 4		
Oxa-S	578	2	2	0.12 - 4	98	
Oxa-R*	193	> 16	> 16	1 - > 16	0	(5)
Staphylococcus epidermidis	20	0.5	1	0.5 - 2		
Oxa-S	38	0.5	1	0.28 - 8	97	
Oxa-R*	108	16	> 16	0.25 - > 16	0	(1)
Staphylococcus saprophyticus	20	4	8	4 - 8		
Staphylococcus coagulase (-)						
Oxa-S	157	1	2	0.25 - 16	92	
Oxa-R*	183	16	> 16	1 - > 16	0	(3)
Streptococcus pneumoniae	30	0.015	0.12	≤ 0.008 - 4	97	
Streptococcus pyogenes	57	≤ 0.008	0.015	≤ 0.008 - 0.03	100	
Streptococcus agalactiae	92	0.015	0.03	≤ 0.008 - 0.5	100	
Streptococcus viridans	20	0.25	32	0.015 - 64		
Enterococcus faecalis	103	> 16	> 16	4 - > 16	0	

Table 1 - Antibacterial activity of Cefpodoxime **(Continued)**

Organisms	n	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	% susceptible[1]
Bacteroides fragilis	43	> 8	> 8	8 - > 8	0
Fusobacterium sp.	10	0.25	8	0.125 - 128	
Peptostreptococcus sp.	26	0.5	8	≤ 0.12 - > 8	69
Clostridium spp.	10	4	> 8	4 - > 8	0

[1] Susceptibility defined as MIC ≤ 2mg/L (NCCLS, 1990)

* Staphylococci exhibiting resistance to Oxacillin should be reported as also resistant to other β-lactamase (NCCLS, 1990). In parenthesis are the percentage of isolates that demonstrated apparent *in vitro* susceptibility.

Stability to β-lactamases

Plasmid-mediated enzymes: Cefpodoxime is highly stable to the hydrolytic activity of TEM-1, TEM-2 and SHV-1 enzymes. It is also stable to hydrolysis by the CARB-2 and PSE-1 type enzymes. It has also been shown that cefpodoxime is not hydrolyzed by the β-lactamases of the PSE-2, PSE-4 and OXA-6 types. The OXA-1 enzyme have showed slightly reduced stability in some of the studies.

Chromosome-mediated enzymes: Cefpodoxime is generally stable to types Ia and Ib enzymes. It is however significantly hydrolyzed by the cefuroximases belonging to the Richmond-Sykes group Inc.

Effects on fecal flora

Cefpodoxime proxetil showed a relatively minimal effect on the normal fecal flora in healthy volunteers. In one study, *C. difficile* was detected in 6 subjects out of 6 treated with cefpodoxime proxetil while this organism was not detected in pretreatment specimens. One (1) of the 6 subjects developed diarrhea. Neither the presence of *C. difficile* enterotoxin nor Toxin A was detected after end of treatment. Results of this study showed that there is no obvious correlation between the presence of *C. difficile* or its toxin in stools and the existence of diarrhea/loose stools.

Susceptibility testing

Diffusion techniques: Quantitative methods that require measurement of zone diameters give a good estimate of the susceptibility of bacteria to antimicrobial agents.

One such standardized procedure recommended for use with 10 mcg cefpodoxime disk is the National Committee for Clinical Laboratory Standards (NCCLS) approved procedure.

Interpretation involves correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) of cefpodoxime.

Reports from the laboratory giving results of the standardized single disk susceptibility test using a 10 mcg cefpodoxime disk should be interpreted according to the following criteria:

• For organisms other than *Haemophilus* and *N. gonorrhoeae* (M100-S5 [M2-A5-Table 2])

Zone diameter (mm)	Interpretation
≥ 21	(S) Susceptible
18-20	(I) Intermediate
≤ 17	(R) Resistant

A report of 'Susceptible' indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of 'Intermediate' indicates that the results should be considered equivocal, and, if the organism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of 'Resistant' indicates that achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

• For *Haemophilus* (M100-S5 [M2-A5-Table 2A])

Zone diameter (mm)	Interpretation
≥ 21	(S) Susceptible
_[1]	(I) Intermediate
_[1]	(R) Resistant

[1] For this antimicrobial agent, the current absence of resistant strains precludes defining any results categories other than "susceptible". Strains yielding results suggestive of a "non susceptible" category should be submitted to a reference laboratory for further testing.

• For *N. gonorrhoeae* (M100-S5 [M2-A5 - Table 2B])

Zone diameter (mm)	Interpretation
≥ 29	(S) Susceptible
_[1]	(M) Moderately susceptible
_[1]	(I) Intermediate
_[1]	(R) Resistant

[1] For this antimicrobial agent, the current absence of resistant strains precludes defining any results categories other than "susceptible". Strains yielding results suggestive of a "non susceptible" category should be submitted to a reference laboratory for further testing.

Standardized procedures require the use of laboratory control organisms. The 10 mcg disk should give the following zone diameters:

Organism	Zone diameter (mm)
Escherichia coli ATCC 25922	23-28
Staphylococcus aureus ATCC 25923	19-25
Haemophilus influenzae ATCC 49247	25-31
Neisseria gonorrhoeae ATCC 49226	35-43

Cephalosporin 'class disks' should not be used to test for susceptibility to cefpodoxime.

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

- For organisms other than *Haemophilus* and *N. gonorrhoeae* (M100-SA [M7-A2-Table 2])

MIC (mg/L)	Interpretation
≤ 2	(S) Susceptible
4	(I) Intermediate
≥ 8	(R) Resistant

- For *Haemophilus* species (M100-S5 [M7-A3 - Table 2A])

MIC (mg/L)	Interpretation
≤ 2	(S) Susceptible
_[1]	(I) Intermediate
_[1]	(R) Resistant

[1] For this antimicrobial agent, the absence of resistant strains precludes defining any results categories other than "susceptible". Strains yielding results suggestive of a "non susceptible" category should be submitted to a reference laboratory for further testing.

- For *N. gonorrhoeae* (M100-S5 [M7-A3 - Table 2B])

MIC (mg/L)	Interpretation
≤ 0.5	(S) Susceptible
_[1]	(M) Moderately susceptible
_[1]	(I) Intermediate
_[1]	(R) Resistant

[1] For this antimicrobial agent, the absence of resistant strains precludes defining any results categories other than "susceptible". Strains yielding results suggestive of a "non susceptible" category should be submitted to a reference laboratory for further testing.

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard cefpodoxime susceptibility powder should give the fol-lowing MIC values:

Organism	MIC range (mg/L)
Escherichia coli ATCC 25922	0.25-1
Staphylococcus aureus ATCC 29213	1-8
Haemophilus influenzae ATCC 49247	0.25-1
Neisseria gonorrhoeae ATCC 49226	0.03-0.12

NOTE: Susceptibility testing by dilution methods requires the use of cefpodoxime susceptibility powder.

PHARMACOLOGY

Animal Pharmacology

The secondary pharmacological effects of cefpodoxime proxetil have been investigated in mice, rats, rabbits, guinea pigs, cats and dogs at dose levels up to 2000 mg/kg (4000 mg/kg in influence on gross behavior testing in mice and rats) and up to 1000 mg/kg in other species. Cefpodoxime proxetil did not exert significant influence on the central nervous system, respiratory and circulatory systems, autonomic nervous system, smooth muscle, and blood. The only significant effects noted were the inhibition of gastric secretion, a decrease in urinary volume and an increased urinary osmotic pressure in rats receiving the maximum dose of 2000 mg/kg.

Human Pharmacology

Pharmacokinetics:

Cefpodoxime proxetil is a prodrug that is absorbed from the gastrointestinal tract and deesterified to its active metabolite, cefpodoxime. Following oral administration of cefpodoxime proxetil to fasting subjects, the bioavailability of cefpodoxime is 50%.

Bioavailability is increased when cefpodoxime proxetil tablets are administered with food and all types of diet (normal, high protein, low protein, high fat and low fat) and results in similar changes in pharmacokinetic parameters: increase in AUC by 27%, increase in C_{max} by 20% and no significant change in elimination half-life (single 200 mg dose in healthy volunteers).

Modifications of gastric conditions also affect the absorption of cefpodoxime: the decrease in pH increases the solubility and stability of cefpodoxime proxetil to hydrolysis, thereby optimizing absorption. Lowering gastric pH (by fasting or by pentagastrin treatment) or raising gastric pH (by H_2-antagonists or antacids) produces an inverse relationship between pH and C_{max} and AUC. The increase in pH produced by H_2-antagonists or antacids is accompanied by a significant fall in C_{max} and AUC by 33% and 30% overall, T_{max} (2.5 hours) being only affected (prolonged to 3.7 hours) by H_2-antagonist treatment.

Changes in gastric motility (induced by propantheline or metoclopramide) do not affect absorption.

The pharmacokinetics of cefpodoxime after single dosing are linear up to 200 mg. Pharmacokinetic parameters after single and repeated doses in fasted healthy volunteers are presented in the following tables:

Single oral dose (m ± sem; n=12)

Pharmacokinetic parameters		Doses			
		100 mg	200 mg	400 mg	800 mg
Obs.Cmax	mg/L	1.37 ± 0.08	2.60 ± 0.16	4.50 ± 0.27	6.95 ± 0.34
Tmax	h	2.38 ± 0.13	2.42 ± 0.15	2.50 ± 0.17	2.94 ± 0.29
C12h	mg/L	0.074 ± 0.008	0.193 ± 0.028	0.388 ± 0.041	0.894 ± 0.081
AUC	mg.h/L	7.0 ± 0.5	14.5 ± 1.0	26.5 ± 1.3	46.4 ± 1.5
Urinary recovery	mg	40.2 ± 2.0	78.5 ± 3.5	95.2 ± 7.8	223.6 ± 18.9
Cl_R	L/h	5.87 ± 0.28	5.59 ± 0.40	3.64 ± 0.30	4.75 ± 0.30
Cal. T1/2 e	h	2.11 ± 0.07	2.31 ± 0.15	2.42 ± 0.17	2.88 ± 0.21

Repeated doses (29 doses - 14.5 days) (m ± sem; n=24)

		100 mg BID		200 mg BID	
Pharmacokinetics parameters		1st dose	last dose	1st dose	last dose
Observed					
Cmax	mg/L	1.23 ± 0.18	1.19 ± 0.14	2.34 ± 0.31	2.23 ± 0.25
Tmax	h	2.25 ± 0.19	1.88 ± 0.18	2.38 ± 0.30	2.00 ± 0.10
C 12h	mg/L	0.088 ± 0.021	0.089 ± 0.020	0.197 ± 0.043	0.149 ± 0.021
AUC 0 - 12	mg.h/L	6.57 ± 0.83	6.56 ± 0.71	12.8 ± 1.7	11.8 ± 1.2
Urinary recovery	mg	29.5 ± 2.5	35.3 ± 3.4	59.1 ± 7.1	60.7 ± 5.3
Cl_R	L/h	4.75 ± 0.41	5.60 ± 0.47	4.72 ± 0.35	5.27 ± 0.34
Calculated					
T 1/2 β	h	2.28	2.28	2.29	2.32

Following administration of 100 mg and 200 mg twice daily over 14.5 days to healthy volunteers, the plasma pharmacokinetic parameters of cefpodoxime remain unchanged, reflecting the absence of accumulation of the active principle.

The volume of distribution of cefpodoxime is 30 to 35 L (0.43 L/kg) in young healthy fasting subjects, indicating good tissue distribution.

Cefpodoxime is non-saturably bound to plasma protein (mainly albumin) to about 40%.

Cefpodoxime diffuses well into lung parenchyma, bronchial mucosa, pleural fluid, tonsils, kidneys, prostatic tissue and interstitial fluid. The concentrations observed are above the MICs of sensitive microorganisms and are maintained throughout the dosage cycle. Concentrations of cefpodoxime in various tissues and secretion after a single oral dose are presented below:

DOSE TISSUE	100 mg Tonsils		200 mg Pleural fluid		200 mg Lung		200 mg Bronchial mucosa		200 mg Renal tissue		200 mg Interstitial fluid		200 mg Prostatic tissue		400 mg Prostatic tissue	
Time	T	T/P	T	T/P	T	T/P	T	T/P	T	TP	T	T/P	T	T/P	T	T/P
3h*	0.24	0.22	0.62	0.24	0.63	0.78	1.08	0.42	1.67[1] 1.61[2]	0.64[1] 0.57[2]	1.64	0.79	0.56-0.65	0.29-0.35	1.16	0.29
6h*	0.09	0.24	1.84	0.67	0.52	0.70	-		2.07[1] 3.07[2]	1.04[1] 1.49[2]	1.18	1.11	0.24-0.66	0.22-0.41	0.90	0.33
12h	ND		0.78	1.07	0.19	0.53	-		1.14[1] 1.65[2]	1.60[1] 2.19[2]	0.33	2.14	0.07-0.28	0.22-0.29	0.42	0.36

*: except tonsil: 4 and 7 h -: no sample ND: not detectable T/P: Tissue / Plasma concentrations
1. Medullary
2. Cortical
T: Tissue (in mg/kg) or secretion (in mg/L)
P: Plasma (in mg/L)

Metabolism and excretion:

After oral administration, cefpodoxime proxetil is hydrolyzed by esterases of the intestinal wall into cefpodoxime, the main active metabolite.

Cefpodoxime, which reaches the plasma, undergoes very little metabolism subsequently. After intravenous administration of cefpodoxime, 80% of cefpodoxime is excreted unchanged into the urine, over 24 hours.

Elimination half-life of cefpodoxime is 2.4 hours on average.

In a study of 3 lactating women, levels of cefpodoxime in human milk were 0%, 2%, and 6% of concomitant serum levels at 4 hours following a 200mg oral dose of cefpodoxime proxetil. At 6 hours post-dosing, milk levels were 0%, 9% and 16% of concomitant serum levels.

As with other beta-lactam antibiotics, renal excretion of cefpodoxime was inhibited by probenecid and resulted in an approximately 31% increase in AUC and 21% increase in peak cefpodoxime plasma levels.

At-risk subjects:

The pharmacokinetic parameters of cefpodoxime are very slightly modified in elderly subjects (mean age: 70.8 years [range: 67-77]) with normal renal function. The slight increases in maximum serum concentrations (by 9%) and elimination half-life (by 14%) do not justify any reduction of the dosage regimen in this patient subgroup.

Elimination of cefpodoxime is reduced in patients with moderate to severe renal impairment (< 40 mL/min/1.73m^2). In subjects with mild impairment of renal function (40 to 80 mL/min/1.73m^2 creatinine clearance), the elimination half-life was 4.9 hours. In subjects with a creatinine clearance ranging from 10 to 39 mL/min.1.73m^2, the half-life increased to 7.7 hours. (see DOSAGE AND ADMINISTRATION section)

When studied in subjects on hemodialysis, the dialysis clearance of cefpodoxime was established to be 6.2 L/h, a value similar to the renal clearance of subjects with normal renal function, thus suggesting that dose should be administered after each dialysis session. (see DOSAGE AND ADMINISTRATION section)

In hepatic insufficiency, the values of the pharmacokinetic parameters representative of elimination were comparable to those found in healthy volunteers after administration of 100 mg or 200 mg cefpodoxime proxetil. (see DOSAGE AND ADMINISTRATION section)

TOXICOLOGY

Acute toxicity

Toxicology studies were conducted in mice, rats, guinea pigs, dogs, rabbits and monkeys. Routes of administration included oral, subcutaneous and intraperitoneal routes with dosage periods ranging from one (1) day to one (1) year.

Species /Strain	No. Animal/ group	Route	Doses (mg/kg)	LD_{50} (mg/kg)	Length of observation Time of death	Summary toxic signs
Mouse (RFVL)	10 M, 10 F	P.O.	2000, 4000, 8000	> 8000	14 days No deaths	Slight and transitory weight loss.
Mouse (RFVL)	10 M, 10 F	I.P.	1900, 2300, 2800, 3300, 4000	M: 3502 F: 2535	14 days Deaths: d1-d3 until d6	After injection: irregular respiration, slow movement, ventral decubitus and unsteady walking. Dead animals: unabsorbed drug in the abdominal cavity, fundic erosion, decreased splenic size.
Mouse (RFVL)	10 M, 10 F	S.C.	2500, 5000, 10000	> 10000	14 days 2 deaths in first 24 h at 10000	Discoloration and edema at injection site. Death preceeded by irregular respiration and slow movement.
Rat (WI)	10 M, 10 F	P.O.	1000, 2000, 4000	> 4000	14 days No deaths	No toxic signs observed.
Rat (F344)	10 M, 10 F	P.O.	1000, 2000, 4000	> 4000	14 days No deaths	Soft stools (~ 1/2 of the rats; post-dosage days 5 to 11), body weight loss (post-dosage days 2 to 5) and retarded weight gains in higher dose group from post-dosage day 7 to 14.
Rat (WI)	10 M, 10 F	I.P.	1000, 2000, 4000	> 4000	14 days No deaths	Transient irregular respiration, slow movement (first 6 h). Transient body weight loss. Necropsy: moderate cecal distension in all treated rats. Thickened hepatic and splenic capsules with abdominal adhesion (2000 and 4000 mg/kg). Unabsorbed drug in the abdominal cavity.
Rat (WI)	10 M, 10 F	S.C.	500, 1000, 2000	> 2000	14 days No deaths	Edema at injection site (necropsy: light yellow or reddish brown edematous fluid). Necropsy: slightly distended cecum.
Dog (Beagle)	1 M, 1 F	P.O.	800	> 800	14 days No deaths	No toxic signs observed.
Dog (Beagle)	2 F	P.O.	25, 50, 100, 200, 400, 800	> 800	6 days No deaths	Slight decrease in food consumption in one dog. Small erosion of the pyloric stomach and small ulcer of the fundic stomach in the other dog.

Chronic Toxicity

In long-term studies in rats, nonspecific secondary effects were seen commonly in most dose groups. These were attributed to the sudden changes* in the intestinal (especially cecal) microbial flora induced by large oral doses of an antibiotic, which were likely associated with subsequent altered digestion and absorption of nutrients. The most common changes in rats, generally dose-related, were a marked increase in the size and the weight of the cecum and its contents, sporadic soft stools during dosing, transient loss of body weight during dosing and sometimes also after drug withdrawal, transient decreases in food consumption during the first few weeks of dosing, and slight decreases in mean total serum protein plus a slight increase in the A/G ratio at the end of the dosing period.

Study	Doses mg/kg/day	Death	Observations, results and conclusions
Rat (WI) / Oral 4/4 weeks 15/sex/group	0, 250, 500, 1000	None	Single daily oral doses of 1000 mg/kg or less for 28 consecutive days were nontoxic. Soft stools, transient body weight loss, slightly decreased total protein and SGPT, distended ceca and decreased liver weight (reversible) were seen*.
Rat (WI) / Oral 13/4 weeks 15/sex/group	0, 30, 80, 200, 500	None	Daily oral doses were well tolerated (maximum tolerated daily subchronic oral dose > 500 mg/kg). With the possible exception of some treated rats given 200 mg/kg or more of cefpodoxime proxetil having a tendency towards lower absolute neutrophil values at the end of the dosing period, the following changes* were observed in treated rats: transient soft stools, slightly decreased body weight gains, slightly decreased total serum protein, slightly increased A/G ratio [not reversed], cecal distension, increased cecal weights [not reversed], decreased liver weights [500 mg/kg males].
Rat (WI) / Oral 13/4 weeks 15/sex/group	0, 1000	None	Orally, 1000 mg/kg of cefpodoxime proxetil was very well tolerated. Changes thought to be indicative of a mild drug-related toxic effect were limited to more low absolute neutrophil (PMN) values in treated rats than in control rats and mild to moderate fat deposition in hepatocytes in treated males. Other reported changes* were as follows: soft stools, decreased cholesterol, total protein, potassium and alkaline phosphatase, increased A/G ratio [not reversed], decreased total bilirubin and calcium [males only], cecal distension and increased cecal weight [not reversed], decreased cardiac weights [males].

Study/Species/Route	Doses mg/kg/day	Death	Observations, results and conclusions
Rat (F344) / Oral 13/4 weeks 20/sex/group	0, 30, 80, 200, 500	1 M & 1 F at 30 mg/kg 6 M & 7 F at 200 mg/kg 10 M & 13 F at 500 mg/kg	Most deaths in the 200 and 500 mg/kg groups occurred between dosage days 56 and 82. The cause of death in all these rats was hemorrhagic-necrotic cecitis, most likely a *Clostridium difficile*-like enteritis that is sometimes a secondary complication of oral antibiotic therapy.** Changes* observed in survivors were mild and included transitory soft stools, variable body weights, slight blood chemistry variations, distended ceca with increased cecal weights and slightly decreased carcass weights. Changes in treated recovery rats were limited to a slightly greater food intake in 200 mg/kg females during the first week and slightly greater absolute and relative cecal weights plus contents in all treated groups at the end of the recovery period. ** In a further bacteriologic evaluation, it was shown that F344 rats were much more sensitive to *C. difficile* and its toxin than WI rats, and this explained the reason for a fatal hemorrhagic-necrotic cecitis observed in F344 but not WI rats in previous drug safety studies.
Rat (WI) / Oral 52 weeks 20/sex/group	0, 250, 500, 1000	None	Terminal absolute neutrophil counts and white blood cell counts were slightly decreased in all treated groups. These decreases were considered a possible direct toxicologic effect of cefpodoxime proxetil. Other findings* included soft stools, slightly decreased food consumption, slightly decreased body weight gain (males), slight increases or decreases in several serum chemistry parameters and cecal distension with increased absolute and relative weights of the cecum plus content.
Dog (Beagle) / Oral 28 days 3/sex/group	0, 100, 200, 400	None	The maximum nontoxic single daily oral dose in beagle dogs given drug for 4 consecutive weeks was greater than 400 mg/kg. Larger doses were not evaluated because of technical limitations. No drug-related changes were observed. A few significant differences (transient serum sodium, calcium and creatinine decreases; transient alkaline phosphatase increase) were present between treated and control group mean values and sometimes between individual dogs; however, these differences were slight, inconsistent between and within groups and were sometimes related to spontaneous lesions. Therefore, none of these changes were considered to have possible toxicologic relevance.
Dog (Beagle) / Oral 13 weeks 4/sex/group	0, 25, 100, 400	None	No evidence of drug toxicity was present in any of the parameters evaluated in any of the dogs. Therefore, the maximum nontoxic single daily oral dose in dogs treated for 13 consecutive weeks was in excess of 400 mg/kg body weight. Unabsorbed drug (white substance) was present in the feces of all high dose dogs throughout the dosage period.

Study / Species / Route / Duration	Doses mg/kg/day	Death	Observations, results and conclusions
Dog (Beagle) / Oral 26 weeks 4/sex/group	0, 25, 100, 400	None	During the study period, all the animals survived without showing changes in general condition. On hematological and blood biochemical examinations, some of the animals in the treatment groups showed differences between pretreatment values and values obtained after treatment beyond a range of changes in the control group, and there were significant differences in some of the test items between the control and treatment groups. However, these changes analyzed according to individual animals or groups seemed to have no relation to the treatment with the test compound, because there was no dose dependency in any of the test items. There were no pathological changes induced by the treatment with test compound.
Monkey (Cynomolgus macaca facicularis) / Oral 13/5 weeks 4/sex/group	0, 50, 100, 200	None	The maximum tolerated dose was in excess of 200 mg/kg/day. Treatment-related effects were minimal and limited to clinical observation of changes in stool consistency, salivation and vomiting. There was a dose-related increase in the occurrence of soft stools in treated animals and some animals also had an episode of diarrhea for only one day early in the treatment period. Stools returned to normal consistency by the sixth week of treatment in most animals. These changes were attributed to secondary effects on the intestinal bacterial flora and not to primary effects of the drug. Salivation, during or shortly after dosing, was sporadically observed mainly in the early stage of the treatment period in some of the 100 and 200 mg/kg/day monkeys. Vomiting, usually more than one hour after dosing, occurred once in two 200 mg/kg/day animals and 13 times in a third during the treatment period. No changes attributed to treatment were observed in any of the other parameters evaluated.

Mutagenicity

The mutagenic potential of cefpodoxime proxetil and its sodium salt has been evaluated in a full range of *in vitro* tests and in the micronucleus test.

The following *in vitro* tests (with the maximum concentration or dose tested) were used: gene mutation in yeast (10000 µg/plate), unscheduled DNA synthesis in primary rat hepatocyte cultures (100 µg/plate), AS52/XPRT gene mutation (5000 µg/mL in absence and presence of S9 metabolic activation), chromosome aberrations in V79 fibroblasts (2710 µg/mL in absence and presence of S9) and Ames test. The Ames test was performed by the classical method (maximum concentration 100 µg/plate in the absence of S9 and 5 µg/plate in its presence for cefpodoxime proxetil and 10 µg/plate in the absence and presence of S9 for cefpodoxime sodium salt) and by a variant where cells of the TA98 and TA100 *S. typhimurium* strains were incubated for 30 minutes with a high concentration of drug (up to 2500 µg/plate for cefpodoxime proxetil and 156-312 µg/plate for cefpodoxime sodium salt) before washing and plating: this manoeuvre allowed exposure to a greater concentration of compound than would otherwise be possible.

In the micronucleus test, no evidence of mutagenicity was observed at oral doses of 1000, 2000, 4000 and 5000 mg/kg.

Overall, the results from this battery of well conducted standard mutagenic studies, with inclusion of appropriate positive controls, revealed that cefpodoxime proxetil shows no potential for mutagenic activity.

Reproduction and teratology

Fertility

Study	Maternal Toxicity	Embryo/Feto Toxicity	Teratogenicity
Modified fertility and reproductive toxicology			
Rat (WI); Oral; 0, 20, 100, 500 mg/kg; 23/sex/group; Treated animals mated with treated animals.	**Yes at 100 mg/kg:** Slight decrease in food and water consumption noted in males at 500 mg/kg. From 100 mg/kg in females, retarded body weight gain and water intake in gestation and food intake during dosing. Cecum inflation noted for 500 mg/kg females. Cefpodoxime proxetil did not adversely affect the ability of male rats to successfully inseminate their assigned females, or the ability of the dams to mate and become pregnant.	**No:** No significant difference in number of corpora lutea, number of implantation, implantation rate, body weight and sex ratio of live fetuses. No external malformation noted.	**No:** Skeletal and visceral anomalies comparable to controls.
Rat (Upj;TUC(SD)spf); Oral; 0, 10, 30, 100 mg/kg 12 M & 24 F/group; Treated animals mated with treated animals.	**Yes at 10 mg/kg:** Mild toxicity indicated by the presence of soft stools (including controls) and diarrhea in a small number of animals and for a short period of time. There were no statistically or biologically significant differences found for any of the reproductive parameters examined.	**No:** No significant difference for the mean number of corpora lutea, mean number of implantations, preimplantation loss, or live or dead embryos.	**No:** Hydronephrosis observed in 100 mg/kg. However, the incidence was not considered biologically significant.

Embryotoxicity

Study	Maternal Toxicity	Embryo/Feto Toxicity	Teratogenicity	Comments
Mouse (CD-1); Oral; 0, 40, 200, 1000 mg/kg from day 6 to 15 of gestation; 30 F/group;	**No:** No clinical signs observed. No treatment-related macroscopic changes observed at necropsy.	**No:** 200 mg/kg Slight increase of fetal mortality. No dose-relationship noted.	**No:** Skeletal and visceral anomalies comparable to controls.	
Rat (WI); Oral; 0, 125, 250, 500 mg/kg from day 7 to17 of gestation 21-22 F/group;	**Yes:** 125 mg/kg Decreased food consumption and body weight gains. Soft stools and enlarged ceca.	**Yes:** Very slight decrease in mean weight of live fetuses in all treated groups [statistically significant at 125 mg/kg only - no dose response shown]. Decrease in mean number of ossified caudal vertebrae. No dose-response: only statistically significant at 125 and 250 mg/kg.	**No:** No increase in anomalies.	In spite of the maternal toxicity and the delay in normal fetal development reported, the pregnancy rate was not affected. Not embryolethal or teratogenic in any of the groups.
Rat (WI); Oral; 0, 20, 100, 500 mg/kg from day 7 to 17 of gestation; 35-36 F/group;	**Yes:** 100 mg/kg Soft stools and diarrhea. Decreased food consumption and body weight gains.	**Yes:** 500 mg/kg Decreased number of caudal ossification centers	**No**	No embryolethal nor teratogenic effects observed. No abnormality noted in the postnatal growth of newborns.
Rabbits (Japanese white) Oral; 0, 10, 30 mg/kg from day 6-8, 9-11, 12-14 and 15-17 of gestation; 12-15 F/group/dose	**Yes:** 10 mg/kg Decreased food consumption (transient in surviving does) and death. Survival rates in the 0, 10 and 30 mg/kg groups = 100, 94.4 and 86.9%, respectively. Hyperemia/hemorrhage of the serous membrane of the cecum and erythema of the mucous membranes.	**No:** No differences in the degree of ossification.	**No**	In spite of the maternal toxicity due to extreme sensitivity of the rabbits to antibiotics, cefpodoxime did not affect the pregnancy rate and not toxic to the fetus. Not embryolethal or teratogenic effects noted in any of the groups.

Perl and post-natal toxicity

Study	Maternal Toxicity	Embryo/Feto Toxicity	Parturition/Neonatal Growth and Survival
Rat (WI); Oral; 0, 20, 100, 500 mg/kg from day 17 of gestation to day 21 of lactation; 23 F/group;	**Yes:** Reduced food consumption (at all doses). Body weight gain during lactation (100 and 500 mg/kg). Cecal enlargement at 100 mg/kg (n=2) and at 500 mg/kg (n=12). F_0 maternal, and F_1 maternal and paternal, survival up to scheduled sacrifice: 100%. In spite of the maternal toxicity reported in the dams from the 100 and 500 mg/kg groups, cefpodoxime proxetil did not appear to affect the pregnancy rate, was not embryolethal or teratogenic at any dose.	**Yes:** 500 mg/kg Reduced number of ossified caudal vertebrae attributed to the decrease in maternal food consumption.	**No:** In dams allowed to deliver, the mean length of gestation; delivery; litter size; pup survival and growth (body weight changes); and pup postnatal developmental milestones, motor function, sensory function, emotion or the ability to learn were not adversely affected. The ability of the F_1 generation pups to mate and deliver normal litters, and the sperm count or motility in F_1 males were not affected.

Other animal studies

Three aspects of potential toxicity were investigated in supplementary studies.

Acute renal toxicity was examined in rabbits following a single intravenous dose of 400 or 800 mg/kg and showed no evidence of an effect on the kidney.

Effect on spermatogenesis was investigated by treating neonatal male rats subcutaneously with 10, 100, or 1000 mg/kg/day of cefpodoxime sodium salt from days 6 to 41 of age: cephalothin and moxalactam were included in this study as comparators. Some of these rats were examined on day 41 and others mated. Overall, cefpodoxime sodium salt had no effect on any parameter whereas both the comparators had effects in reducing sperm number.

The possible antigenicity of cefpodoxime proxetil has been investigated in a number of ways examining both its propensity to induce sensitization and the likelihood of cross reactions in animals already sensitized to another antibiotic. Among a range of comparator antibiotics, cefpodoxime proxetil showed weak or no ability to induce an immune response - measured as IgE or IgG anaphylactic antibodies, hemagglutinating antibodies or a delayed hypersensitivity reaction. Cross reaction was demonstrated with cefotaxime both in

terms of challenge with cefotaxime in cefpodoxime proxetil - human gammaglobulin sensitized animals and challenge with cefpodoxime proxetil in cefotaxime sensitized animals. Weak interactions with cefmenoxime and cefmetazole were also seen in some experimental protocols. Overall, cefpodoxime proxetil was weak in terms of antigenic potential, particularly in comparison with the other agents tested, a representative sample of cephalosporins and penicillins.

BIBLIOGRAPHY

Bergogne-Berezin E. Cefpodoxime proxetil in upper respiratory tract infections. Drugs 1991; 42 (suppl 3): 25-33.

Boaretti M et al. Comparison of cefpodoxime with amoxicillin/clavulanic acid. *In vitro* activity, penicillin-binding protein affinity and stability to beta-lactamases. ICID 1990, poster, Montreal, Canada.

Borin MT. A review of the pharmacokinetics of cefpodoxime proxetil. Drugs 1991; 42 (suppl 3): 13-21.

Borin MT et al. Pharmacokinetic and tolerance studies of cefpodoxime after single- and multiple-dose oral administration of cefpodoxime proxetil. J Clin Pharmacol 1991; 31: 1137-45.

Cephalosporins. In: American Society of Hospital Pharmacists. Drug Information 93. Bethesda: American Society of Hospital Pharmacists, 1993: 92-8.

Cephalosporins (systemic). In: USP DI 1993, 13th ed. United States Pharmacopeial. Convention, Inc, 1993: 755-61.

Cephalosporins (The). In: Goodman and Gilman's, the Pharmacological Basis of. Therapeutics, 8th ed. Gilman AG, Rall TW, Nies AS, Taylor P, eds, 1990: 1085-92.

Chantot JF, Mauvais P. RU 51807 (cefpodoxime proxetil). Evaluation de l'activité. antibactérienne *in vitro* et in vivo d'une nouvelle céphalosporine active par voie orale. Path Biol 1991; 39(1): 17-27.

Chin NX, Neu HC. *In vitro* activity of an oral iminomethoxy aminothiazolyl cephalosporin, R-3746. Antimicrob Ag Chemother 1988; 32 (5): 671-7.

Couraud L et al. Concentrations of cefpodoxime in plasma and lung tissue after a single oral dose of cefpodoxime proxetil. J Antimicrob Chemother 1990; 26 (suppl E): 35-40.

Cullmann W, Dick W. Cefpodoxime: comparable evaluation with other orally active cephalosporins with a note on the role of beta-lactamases. Zbl Bakt 1990; 273: 501-17.

Dabernat H et al. *In vitro* activity of cefpodoxime against pathogens responsible for community-acquired respiratory tract infections. J Antimicrob Chemother 1990; 26 (suppl E): 1-6.

Dumont R et al. Concentrations of cefpodoxime in plasma and pleural fluid after a single oral dose of cefpodoxime proxetil. J Antimicrob Chemother 1990; 26 (suppl E): 41-6.

Fass RJ, Helsel VL. *In vitro* activity of U-76,252 (CS-807), a new oral cephalosporin. Antimicrob Ag Chemother 1988, 32 (7): 1082-5.

Frampton JE et al. Cefpodoxime proxetil - A review of its antibacterial activity, pharmacokinetic properties and therapeutic potential. Drugs 1992; 44 (5): 889-917.

Geddes AM. Cefpodoxime proxetil in the treatment of lower respiratory tract infections. Drugs 1991; 42 (suppl 3): 34-40.

Gehanno P et al. Concentrations of cefpodoxime in plasma and tonsillar tissue after single oral dose of cefpodoxime proxetil. J Antimicrob Chemother 1990; 26 (suppl E): 47-51.

Harrison TR. Principles of Internal Medicine, 11th ed. Braunwald E et al, eds, 1987: Chapter 95: Streptococcal infections: 543-50.

Höffler D et al. Cefpodoxime proxetil in patients with endstage renal failure on hemodialysis. Infection 1990; 18 (3): 157-62.

Hughes GS et al. The effects of gastric pH and food on the pharmacokinetics of a new oral cephalosporin, cefpodoxime proxetil. Clin Pharmacol Ther 1989; 46 (6): 674-85.

Hughes GS et al. Gastric emptying and the pharmacokinetics of the cephalosporin antibiotic, cefpodoxime proxetil. Meth Find Exp Clin Pharmacol 1990; 12 (3): 197-204.

Jones RN, Barry AL. Antimicrobial activity and disk diffusion susceptibility testing of U -76,253A (R-3746), the active metabolite of the new cephalosporin ester, U-76,252 (CS-807). Antimicrob Ag Chemother 1988; 32 (4): 443-9.

Naber KG. Concentrations of cefpodoxime in plasma, ejaculate and in prostatic fluid and adenoma tissue. Infection 1991; 19 (1): 30-5.

National Committee for Clinical Laboratory Standards: Performance Standards for Antimicrobial Disk Susceptibility Tests, 5th ed.; 14 (16): M2-A5, Villanova, PA, December 1994.

National Committee for Clinical Laboratory Standards: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, 3rd ed.; 14 (16): M7-A3, Villanova, PA, December 1994.

National Committee for Clinical Laboratory Standards: Performance Standards for Antimicrobial Disk Susceptibility Tests, 5th suppl.; 14 (16): M100-S5, Villanova, PA, December 1994.

O'Neill P et al. Pharmacokinetics and inflammatory fluid penetration of cefpodoxime proxetil in volunteers. Antimicrob Ag Chemother 1990; 34 (2): 232-4.

Pechere JC. Induction of chromosomal beta-lactamase by RU 51746 (sodium salt of cefpodoxime). Data on file.

Periti P et al. Efficacy and tolerance of cefpodoxime proxetil compared with co-amoxiclav in the treatment of exacerbations of chronic bronchitis. J Antimicrobf Chemother 1990; 26 (suppl E): 63-9.

Saathoff N et al. Pharmacokinetics of Cefpodoxime proxetil and interaction with anf antacid and an H_2 receptor antagonist. Antimicrob Ag Chemother 1992; 36 (4): 796-800.

Sader HS et al. *In vitro* activity of cefpodoxime compared with other oral cephalosporins tested against 5556 recent clinical isolates from five medical centers. Diagn Microbiol Infect Dis 1993; 17: 143-50.

Safran C. Cefpodoxime proxetil: dosage, efficacy and tolerance in adults suffering from respiratory tract infections. J Antimicrob Chemother 1990; 26 (suppl E): 93-101.

Schaadt RD et al. *In vitro* activity of cefpodoxime proxetil (U-76,252; CS-807) against *Neisseria gonorrhoeae*. Antimicrob Ag Chemother 1990; 3 (2): 371-2.

Stobbeeringh EE et al. *In vitro* activity of cefpodoxime, a new oral cephalosporin. Eur J Clin Microbiol Infect Dis 1989; 8: 656-8.

Surjus A et al. Absolute bioavailability of cefpodoxime after single oral administration of cefpodoxime proxetil. ICID 1990, poster, Montreal, Canada.

Tremblay D et al. Pharmacokinetics of cefpodoxime in young and elderly volunteers after single doses. J Antimicrob Chemother 1990; 26 (suppl E): 21-8.

Utsui Y, Inoue M, Mitsuhashi S. *In vitro* and *in vivo* antibacterial activities of CS-807, a new oral cephalosporin. Antimicrob Ag Chemother 1987; 31(7): 1085-92.

Zuck P et al. Efficacy and tolerance of cefpodoxime proxetil compared with ceftriaxone in vulnerable patients with bronchopneumonia. J Antimicrob Chemother 1990; 26 (suppl E): 71-7.