CENTER FOR DRUG EVALUATION AND RESEARCH

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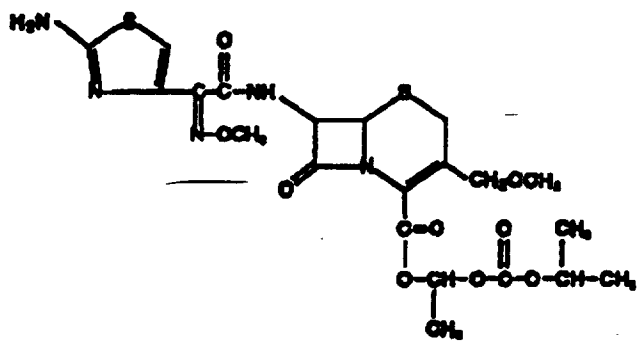
BANAN®
Tablets and Oral Suspension
CEFPODOXIME PROXETIL
Brand of cefpodoxime proxetil tablets and cefpodoxime proxetil for oral suspension- For Oral Use Only

DESCRIPTION

Cefpodoxime proxetil is an orally administered, extended spectrum, semi-synthetic antibiotic of the cephalosporin class. The chemical name is (RS)-1-(isopropoxycarbonyloxy)ethyl (+)-(6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-{(Z)-methoxyimino}acetamido]-3-methoxymethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. Its empirical formula is $C_{21}H_{27}N_5O_9S_2$ and its structural formula is represented below:



The molecular weight of cefpodoxime proxetil is 557.6. Cefpodoxime proxetil is a prodrug; its active metabolite is cefpodoxime. All doses of cefpodoxime proxetil in this insert are expressed in terms of the active cefpodoxime moiety. The drug is supplied both as film-coated tablets and as flavored granules for oral suspension.

BANAN Tablets contain cefpodoxime proxetil equivalent to 100 mg or 200 mg of cefpodoxime activity and the following inactive ingredients: carboxymethylcellulose calcium, carnauba wax, FD&C Yellow No. 6, hydroxypropylcellulose, hydroxypropylmethylcellulose, lactose hydrous, magensium stearate, propylene glycol, sodium lauryl sulfate and titanium dioxide. In addition, the 100 mg film-coated tablets contain D&C Yellow No. 10 and the 200 mg film-coated tablets contain FD&C Red No. 40.

Each 5 ml of BANAN for Oral Suspension contains cefpodoxime proxetil equivalent to 50 mg or 100 mg of cefpodoxime activity after constitution and the following inactive ingredients: artificial flavorings, butylated hydroxy anisole (BHA), carboxymethylcellulose sodium, microcrystalline cellulose, carrageenan, citric acid, colloidal silicon dioxide, croscarmellose sodium, hydroxypropylcellulose, lactose, maltodextrin, natural flavorings, propylene glycol alginate, sodium citrate, sodium benzoate, starch, sucrose, and vegetable oil.

CLINICAL PHARMACOLOGY

Absorption and Excretion:

Cefpodoxime proxetil is a prodrug that is absorbed from the gastrointestinal tract and de-esterified to its active metabolite, cefpodoxime. Following oral administration of 100 mg of cefpodoxime proxetil to fasting subjects, approximately 50% of the administered cefpodoxime dose was absorbed systemically. Over the recommended dosing range (100 to 400 mg), approximately 29 to 33% of the administered cefpodoxime dose was excreted unchanged in the urine in 12 hours. There is minimal metabolism of cefpodoxime *in vivo*.

Effects of food:

The extent of absorption (mean AUC) and the mean peak plasma concentration increased when film-coated tablets were administered with food. Following a 200 mg tablet dose taken with food, the AUC was 21 to 33% higher than under fasting conditions, and the peak plasma concentration averaged 3.1 mcg/mL in fed subjects versus 2.6 mcg/mL in fasted subjects. Time to peak concentration was not significantly different between fed and fasted subjects.

When a 200 mg dose of the suspension was taken with food, the extent of absorption (mean AUC) and mean peak plasma concentration in fed subjects were not significantly different from fasted subjects, but the rate of absorption was slower with food (48% increase in T_{max}).

Pharmacokinetics of Cefpodoxime Proxetil Film-coated Tablets:

Over the recommended dosing range, (100 to 400 mg), the rate and extent of cepfodoxime absorption exhibited dose-dependency; dose-normalized C_{max} and AUC decreased by up to 32% with increasing dose. Over the recommended dosing range, the T_{max} was approximately 2 to 3 hours and the $T_{1/2}$ ranged from 2.09 to 2.84 hours. Mean C_{max} was 1.4 mcg/mL for the 100 mg dose, 2.3 mcg/mL for the 200 mg dose, and 3.9 mcg/mL for the 400 mg dose. In patients with normal renal function, neither accumulation nor significant changes in other pharmacokinetic parameters were noted following multiple oral doses of up to 400 mg Q 12 hours.

CEFPODOXIME PLASMA LEVELS (mcg/mL) IN FASTED ADULTS AFTER FILM –COATED TABLET ADMINISTRATION (Single Dose)

Dose (cefpodoxime equivalents)	Time after oral ingestion 1hr	2hr	3hr	4hr	6hr	8hr	12hr
100 mg	0.98	1.4	1.3	1.0	0.59	0.29	0.08
200 mg	1.5	2.2	2.2	1.8	1.2	0.62	0.18
400 mg	2.2	3.7	3.8	3.3	2.3	1.3	0.38

Pharmacokinetics of Cefpodoxime Proxetil Suspension:

In adult subjects, a 100 mg dose of oral suspension produced an average peak cefpodoxime concentration of approximately 1.5 mcg/mL (range: 1.1 to 2.1 mcg/mL), which is equivalent to that reported following administration of the 100 mg tablet. Time to peak plasma concentration and area under the plasma concentration-time curve (AUC) for the oral suspension were also equivalent to those produced with film-coated tablets in adults following a 100 mg oral dose.

The pharmacokinetics of cefpodoxime were investigated in 29 patients aged 1 to 17 years. Each patient received a single, oral, 5 mg/kg dose of cefpodoxime oral suspension. Plasma and urine samples were collected for 12 hours after dosing. The plasma levels reported from this study are as follows:

CEFPODOXIME PLASMA LEVELS (mcg/mL) IN FASTED PATIENTS
(1 to 17 years of age) AFTER SUSPENSION ADMINISTRATION

Dose (cefpodoxime equivalent)	Time after oral ingestion 1hr	2hr	3hr	4hr	6hr	8hr	12hr
5 mg/kg[1]	1.4	2.1	2.1	1.7	0.90	0.40	0.090

[1]Dose did not exceed 200 mg.

Distribution:

Protein binding of cefpodoxime ranges from 22 to 33% in serum and from 21 to 29% in plasma:

Skin Blister: Following multiple-dose administration every 12 hours for 5 days of 200 mg or 400 mg cefpodoxime proxetil, the mean maximum cefpodoxime concentration in skin blister fluid averaged 1.6 and 2.8 mcg/mL, respectively. Skin blister fluid cefpodoxime levels at 12 hours after dosing averaged 0.2 and 0.4 mcg/mL for the 200 mg and 400 mg multiple-dose regimens, respectively.

Tonsil Tissue: Following a single, oral 100 mg cefpodoxime proxetil film-coated tablet, the mean maximum cefpodoxime concentration in tonsil tissue averaged 0.24 mcg/g at 4 hours post-dosing and 0.09 mcg/g at 7 hours post-dosing. Equilibrium was achieved between plasma and tonsil tissue within 4 hours of dosing. No detection of cefpodoxime in tonsillar tissue was reported 12 hours after dosing. These results demonstrated that concentrations of cefpdoxime exceeded the MIC_{90} of *S. pyogenes* for at least 7 hours after dosing of 100 mg of cefpodoxime proxetil.

Lung Tissue: Following a single, oral 200 mg cefpodoxime proxetil film-coated tablet, the mean maximum cefpodoxime concentration in lung tissue averaged 0.63 mcg/g at 3 hours post-dosing, 0.52 mcg/g at 6 hours post-dosing, and 0.19 mcg/g at 12 hours post-dosing. The results of this study indicated that cefpodoxime penetrated into lung tissue and produced sustained drug concentrations for at least 12 hours after dosing at levels that exceeded the MIC_{90} for *S. pneumoniae* and *H. influenzae*.

CSF: Adequate data on CSF levels of cefpodoxime are not available.

Effects of decreased renal function:

Elimination of cefpodoxime is reduced in patients with moderate to severe renal impairment (<50 mL/min creatinine clearance). (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION.**) In subjects with mild impairment of renal function (50 to 80 mL/min creatinine clearance), the average plasma half-life of cefpodoxime was 3.5 hours. In subjects with moderate (30 to 49 mL/min creatinine clearance) or severe renal impairment (5 to 29 mL/min creatinine clearance), the half-life increased to 5.9 and 9.8 hours, respectively. Approximately 23% of the administered dose was cleared from the body during a standard 3-hour hemodialysis procedure.

Effects of hepatic impairment (cirrhosis):

Absorption was somewhat diminished and elimination unchanged in patients with cirrhosis. The mean cefpodoxime $T_{1/2}$ and renal clearance in cirrhotic patients were similar to those derived in studies of healthy subjects. Ascites did not appear to affect values in cirrhotic subjects. No dosage adjustment is recommended in this patient population.

Pharmacokinetics in Elderly Subjects:
Elderly subjects do not require dosage adjustments unless they have diminished renal function. (See **PRECAUTIONS.**) In healthy geriatric subjects, cefpodoxime half-life in plasma averaged 4.2 hours (vs. 3.3 hours in younger subjects) and urinary recovery averaged 21% after a 400 mg dose was administered every 12 hours. Other pharmacokinetic parameters (C_{max}, AUC, and T_{max}) were unchanged relative to those observed in healthy young subjects.

Microbiology:
Cefpodoxime is active *in vitro* against a wide range of gram-positive and gram-negative bacteria. Cefpodoxime is highly stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins, due to the presence of beta-lactamases, may be susceptible to cefpodoxime.
The bactericidal activity of cefpodoxime results from its inhibition of cell wall synthesis.
Cefpodoxime is usually active against the following organisms *in vitro* and in clinical infections. (See **INDICATIONS AND USAGE.**)
Gram-positive aerobes:
Staphylococcus aureus (including penicillinase-producing strains)
NOTE: Cefpodoxime is inactive against methicillin-resistant staphylococci.
Staphylococcus saprophyticus
Streptococcus pneumoniae
Streptococcus pyogenes
Gram-negative aerobes:
Escherichia coli
Haemophilus influenzae (including ß-lactamase-producing strains)
Klebsiella pneumoniae
Moraxella (Branhamella) catarrhalis
Neisseria gonorrhoeae (including penicillinase-producing strains)
Proteus mirabilis
The following *in vitro* data are available; however, their clinical significance is unknown. Cefpodoxime exhibits *in vitro* minimum inhibitory concentrations of 2.0 mcg/mL or less against most strains of the following organisms. The safety and effectiveness of cefpodoxime proxetil in treating infections due to these organisms have not been established in adequate and well-controlled trials.
Gram-positive aerobes:
Streptococcus agalactiae
Streptococcus spp. (Groups C, F, G)
NOTE: Cefpodoxime is inactive against most strains of *Enterococcus*.
Gram-negative aerobes:
Citrobacter diversus
Haemophilus parainfluenzae
Klebsiella oxytoca
Proteus vulgaris
Providencia rettgeri
NOTE: Cefpodoxime is inactive against most strains of *Pseudomonas* and *Enterobacter*.
Anaerobes:
Peptostreptococcus magnus

SUSCEPTIBILITY TESTING

Diffusion Techniques: Quantitative methods that require measurement of zone diameters give the most precise estimate of the susceptibility of bacteria to antimicrobial agents. One such standardized procedure[1] recommended for use with the 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) for cefpodoxime.

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

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 result 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.

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

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

Dilution Technique: Use a standardized dilution method[2] (broth, agar, microdilution) or equivalent with cefpodoxime susceptibility powder. The MIC values should be interpreted according to the following criteria:

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

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

Organism	MIC range (mcg/mL)
Escherichia coli ATCC 25922	0.25-1
Staphylococcus aureus ATCC 29213	1-8

NOTE: Susceptibility testing by dilution methods requires the use of cefpodoxime susceptibility powder. Cefpodoxime proxetil granules for oral use should **NOT** be used for *in vitro* susceptibility tests.

INDICATIONS AND USAGE

Cefpodoxime proxetil is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Recommended dosages, duration of therapy, and applicable patient populations vary among these infections. Please see DOSAGE AND ADMINISTRATION for specific recommendations.

LOWER RESPIRATORY TRACT

Community-acquired pneumonia caused by *S. pneumoniae* or *H. influenzae* (including beta-lactamase-producing strains).

Acute bacterial exacerbation of chronic bronchitis caused by *S. pneumoniae*, *H. influenzae* (non-beta-lactamase-producing strains only), or *M. catarrhalis*. Data are insufficient at this time to establish efficacy in patients with acute bacterial exacerbations of chronic bronchitis caused by beta-lactamase-producing strains of *H. influenzae*.

SEXUALLY TRANSMITTED DISEASES

Acute, uncomplicated urethral and cervical gonorrhea caused by *Neisseria gonorrhoeae* (including penicillinase-producing strains).

Acute, uncomplicated ano-rectal infections in women due to *Neisseria gonorrheae* (including penicillinase-producing strains).

NOTE: The efficacy of cefpodoxime in treating male patients with rectal infections caused by *N. gonorrheae* has not been established. Data do not support the use of cefpodoxime proxetil in the treatment of pharyngeal infections due to *N. gonorrheae* in men or women.

SKIN AND SKIN STRUCTURES

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (including penicillinase-producing strains) or *Streptococcus pyogenes*. Abscesses should be surgically drained as clinically indicated.

NOTE: In clinical trials, successful treatment of uncomplicated skin and skin structure infections was dose-related. The effective therapeutic dose for skin infections was higher than those used in other recommended indications. (See DOSAGE AND ADMINISTRATION.)

UPPER RESPIRATORY TRACT

Acute otitis media caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including ß-lactamase-producing strains), or *Moraxella (Branhamella) catarrhalis*.

Pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes*.

NOTE: Only penicillin by the intramuscular route of administration has been shown to be effective in the prophylaxis of rheumatic fever. Cefpodoxime proxetil is generally effective in the eradication of streptococci from the oropharynx. However, data establishing the efficacy of cefpodoxime proxetil for the prophylaxis of subsequent rheumatic fever are not available.

URINARY TRACT

Uncomplicated urinary tract infections (cystitis) caused by *Escherichia coli*, *Klebsiella penumoniae*, *Proteus mirabilis*, or *Staphylococcus saprophyticus*.

NOTE: In considering the use of cefpodoxime proxetil in the treatment of cystitis, cefpodoxime proxetil's lower bacterial eradication rates should be weighed against the increased eradication rates and different safety profiles of some classes of approved agents. (See CLINICAL STUDIES section.)

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibility to cefpodoxime. Therapy may be instituted while awaiting the results of these studies. Once these results become available,

antimicrobial therapy should be adjusted accordingly.

CONTRAINDICATIONS

Cefpodoxime proxetil is contraindicated in patients with a known allergy to cefpodoxime or to the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFPODOXIME PROXETIL IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFPODOXIME, OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF CEFPODOXIME IS TO BE ADMINISTERED TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFPODOXIME PROXETIL OCCURS, DISCONTINUE THE DRUG. SERIOUS ACTUE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINE, AND AIRWAY MANAGEMENT AS CLINICALLY INDICATED. PSEUDOMEMBRANOUS COLITIS HAS BEEN REPORTED WITH NEARLY ALL ANTIBACTERIAL AGENTS, INCLUDING CEFPODOXIME, 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 ANTIBACTERIAL AGENTS.

Extreme caution should be observed when using this product 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, including cefpodoxime proxetil, alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is the primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an oral antibacterial drug effective against *C. difficile*.

A concerted effort to monitor for *C. difficile* in cefpodoxime treated patients with diarrhea was undertaken because of an increased incidence of diarrhea associated with *C. difficile* in early trials in normal subjects. *C. difficile* organisms or toxin was reported in 10% of the cefpodoxime-treated adult patients with diarrhea; however, no specific diagnosis of pseudomembranous colitis was made in these patients.

In post-marketing experience outside the United States, reports of pseudomembranous colitis associated with the use of cefpodoxime proxetil have been received.

PRECAUTIONS

General

In patients with transient or persistent reduction in urinary output due to renal insufficiency, the total daily dose of cefpodoxime proxetil should be reduced because high and prolonged serum antibiotic concentrations can occur in such individuals following usual doses. Cefpodoxime, like other cephalosporins, should be administered with caution to patients receiving concurrent treatment with potent diuretics. (See DOSAGE AND ADMINISTRATION.)

As with other antibiotics, prolonged use of cefpodoxime proxetil may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Drug Interactions

Antacids: Concomitant administration of high doses of antacids (sodium bicarbonate and aluminum hydroxide) or H_2 blockers reduces peak plasma levels by 24% to 42% and the extent of absorption by 27% to 32%, respectively. The rate absorption is not altered by these concomitant medications. Oral anti-cholinergics (e.g., propantheline) delay peak plasma levels (47% increase in T_{max}), but do not affect the extent of absorption (AUC).

Probenecid: As with other beta-lactam antibiotics, renal excretion of cefpodoxime was inhibited by probenecid and resulted in an approximately 31% increase in AUC and 20% increase in peak cefpodoxime plasma levels.

Nephrotoxic Drugs: Although nephrotoxicity has not been noted when cefpodoxime proxetil was given alone, close monitoring of renal function is advised when cefpodoxime proxetil is administered concomitantly with compounds of known nephrotoxic potential.

Drug/Laboratory Test Interactions

Cephalosporins, including cefpodoxime proxetil, are known to occasionally induce a positive direct Coombs' test.

Carginogenesis, Mutagenesis, Impairment of Fertility

Long-term animal carcinogenesis studies of cefpodoxime proxetil have not been performed. Mutagenesis studies of cefpodoxime, including the Ames test both with and without metabolic activation, the chromosome aberration test, the unscheduled DNA synthesis assay, mitotic recombination and gene conversion, the forward gene mutation assay and the *in vivo* micronucleus test, were all negative. No untoward effects on fertility or reproduction were noted when 100 mg/kg/day or less (2 times the human dose based on mg/m^2) was administered orally to rats.

Pregnancy – Teratogenic Effects:

Pregnancy Category B

Cefpodoxime proxetil was neither teratogenic nor embryocidal when administered to rats during organogenesis at doses up to 100 mg/kg/day (2 times the human dose based on mg/m^2) or to rabbits at doses up to 30 mg/kg/day (1-2 times the human dose based on mg/m^2).

There are however, no adequate and well-controlled studies of cefpodoxime proxetil use in pregnant women. Because animal reproduction studies are not always predictive of human response, the drug should be used during pregnancy only if clearly needed.

Labor and Delivery:

Cefpodoxime proxetil has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers:
Cefpodoxime is excreted in human milk. 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 200 mg oral dose of cefpodoxime proxetil. At 6 hours post-dosing, levels were 0%, 9% and 16% of concomitant serum levels. Because of the potential for serious reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and efficacy in infants less than 5 months of age have not been established.

Geriatric Use
Of the 3338 patients in multiple-dose clinical studies of cefpodoxime proxetil film-coated tablets, 521 (16%) were 65 and over, while 214 (6%) were 75 and over.
No overall differences in effectiveness or safety were observed between the elderly and younger patients. In healthy geriatric subjects with normal renal function, cefpodoxime half-life in plasma averaged 4.2 hours and urinary recovery averaged 21% after a 400 mg dose was given every 12 hours for 15 days. Other pharmacokinetic parameters were unchanged relative to those observed in healthy younger subjects. Dose adjustment in elderly patients with normal renal function is not necessary.

ADVERSE REACTIONS

Clinical Trials:

Film-coated Tablets (Multiple dose):
In clinical trials using multiple doses of cefpodoxime proxetil film-coated tablets, 3338 patients were treated with the recommended dosages of cefpodoxime (100 to 400 mg Q 12 hours). There were no deaths or permanent disabilities thought related to drug toxicity. Eighty-one (2.4%) patients discontinued medication due to adverse events thought possibly- or probably-related to drug toxicity. Sixty-six (66%) of the 100 patients who discontinued therapy (whether thought related to drug therapy or not) did so because of gastrointestinal disturbances, usually diarrhea. The percentage of cefpodoxime proxetil-treated patients who discontinued study drug because of adverse events was significantly greater at a dose of 800 mg daily than at a dose of 400 mg daily or at a dose of 200 mg daily.
Adverse events thought possibly- or probably-related to cefpodoxime in multiple dose clinical trials (N=3338 cefpodoxime-treated patients) were:

Incidence greater than 1%:

Diarrhea	7.2%

Diarrhea or loose stools were dose related: decreasing from 10.6% of patients receiving 800 mg per day to 5.9% for those receiving 200 mg per day. Of patients with diarrhea, 10% had *C. difficile* organism or toxin in the stool. (See WARNINGS.)

Nausea	3.8%
Vaginal Fungal Infections	3.1%
Abdominal Pain	1.6%
Rash	1.4%
Headache	1.1%
Vomiting	1.1%

Incidence less than 1%:
Cardiovascular: Chest pain, hypotension.
Dermatologic: Fungal skin infection, skin scaling/peeling.
Endocrine: Menstrual irregularity.
Genital: Pruritus.
Gastrointestinal: Flatulence, decreased salivation, candidiasis, pseudomembranous colitis.
Hypersensitivity: Anaphylactic shock.
Metabolic: Decreased appetite.
Miscellaneous: Malaise, fever.
Central Nervous System: Dizziness, fatigue, anxiety, insomnia, flushing, nightmares, weakness.
Respiratory: Cough, epistaxis.
Special Senses: Taste alteration, eye itching, tinnitus.

Granules for Oral Suspension (Multiple dose):

In clinical trials using multiple doses of cefpodoxime proxetil granules for oral suspension, 1586 pediatric patients (90% of whom were less than 12 years of age) were treated with the recommended dosages of cefpodoxime (10 mg/kg/day Q 24 hours or divided Q 12 hours to a maximum equivalent adult dose). There were no deaths or permanent disabilities in any of the patients in these studies. Twenty-three patients (1.5%) discontinued medication due to adverse events thought possibly- or probably-related to study drug. Primarily, these discontinuations were for gastrointestinal disturbances, usually diarrhea, vomiting, or diaper area rashes.

Adverse events thought possibly- or probably-related to cefpodoxime proxetil for oral suspension in multiple dose clinical trials (N=1586 cefpodoxime-treated patients) were:

Incidence greater than 1%:

Diarrhea	5.7%

The incidence of diarrhea in infants and toddlers (age 6 months to 2 years) was 15.4%.

Diaper rash/Fungal Skin Rash	2.3%

The incidence of diaper rash in infants and toddlers was 12.1%.

Other skin rashes	1.8%
Vomiting	2.1%

Incidence less than 1%:
Central Nervous System: Headache, irritability.
Dermatologic: Exacerbation of acne, exfoliative dermatitis.
Genital: Pruritus or vaginitis.
Gastrointestinal: Nausea, abdominal pain, candidiasis, decreased salivation, psudomembranous colitis.
Metabolic: Decreased appetite.
Miscellaneous: Fever.
Psychiatric: Hyperactivity/nervousness
Respiratory: Epistaxis, rhinitis.

Film-coated tablets (Single dose):

In clinical trials using a single dose of cefpodoxime proxetil film-coated tablets, 509 patients were treated with the recommended dosage of cefpodoxime (200 mg). There were no deaths or permanent disabilities thought related to drug toxicity in these studies.

Adverse events thought possibly- or probably-related to cefpodoxime in single dose clinical trials conducted in the United States were:

Incidence greater than 1%:

Nausea	1.4%
Diarrhea	1.2%

Incidence less than 1%:

Central Nervous System: Dizziness, headache, syncope.

Dermatologic: Rash.

Genital: Vaginitis.

Gastrointestinal: Abdominal pain.

Psychiatric: Anxiety.

Laboratory Changes (Adult patients):

Significant laboratory changes that have been reported in adult patients in clinical trials of cefpodoxime proxetil, without regard to drug relationship, were:

Hepatic: Transient increases in AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, bilirubin, and LDH.

Hematologic: Eosinophilia, leukocytosis, lymphocytosis, granulocytosis, basophilia, monocytosis, thrombocytosis, decreased hemoglobin, leukopenia, neutropenia, lymphocytopenia, thrombocytopenia, positive Coombs' test, and prolonged PT, and PTT.

Serum Chemistry: Increases in glucose, decreases in glucose, decreases in serum albumin, decreases in serum total protein.

Renal: Increases in BUN and creatinine.

Most of these abnormalities were transient and not clinically significant.

Laboratory Changes (Pediatric patients):

Significant laboratory changes that have been reported in pediatric patients in clinical trials of cefpodoxime proxetil, without regard to drug relationship, were:

Hematologic: eosinophilia, decreased hemoglobin, decreased hematocrit.

Hepatic: transiently increased ALT (SGPT).

Most of these abnormalities were transient and not clinically significant.

Post-marketing Experience:

The following serious adverse experiences have been reported: allergic reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and serum sickness-like reactions, pseumembranous colitis, bloody diarrhea with abdominal pain, ulcerative colitis, rectorrhagia with hypotension, anaphylactic shock, acute liver injury, *in utero* exposure with miscarriage, purpuric nephritis, pulmonary infiltrate with eosinophilia, and eyelid dermatitis.

One death was attributed to pseudomembranous colitis and disseminated intravascular coagulation.

Cephalosporin Class Labeling:

In addition to the adverse reactions listed above which have been observed in patients treated with cefpodoxime proxetil, the following adverse reactions and altered laboratory tests have been reported for cephalosporin class antibiotics:

Adverse reactions and Abnormal Laboratory Tests: Renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, serum sickness-like reaction, hemorrhage, agranulocytosis, and pancytopenia.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. (See DOSAGE AND ADMINISTRATION and OVERDOSAGE.) If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsants therapy can be given if clinically indicated.

OVERDOSAGE

In acute rodent toxicity studies, a single 5 g/kg oral dose produced no adverse effects. In the event of serious toxic reactions from overdosage, hemodialysis or peritoneal dialysis may aid in the removal of cefpodoxime from the body, particularly if renal function is compromised. The toxic symptoms following an overdose of ß-lactam antibiotics may include nausea, vomiting, epigastric distress, and diarrhea.

DOSAGE AND ADMINISTRATION

(See INDICATIONS AND USAGE for indicated pathogens.)

FILM-COATED TABLETS:

BANAN Tablets should be administrated with food to enhance absorption. (See CLNICAL PHARMACOLOGY.) The recommended dosages, durations of treatment, and applicable patient population are as described in the following chart:

Adults (age 13 years and older):

Type of infection	Total daily dose	Dose Frequency	Duration
Acute community-acquired pneumonia	400 mg	200 mg Q 12 hours	14 days
Acute bacterial exacerbations chronic bronchitis	400 mg	200 mg Q 12 hours	10 days
Uncomplicated gonorrhea (men and women) and rectal gonococcal infections (women)	200 mg	single dose	
Skin and skin structure	800 mg	400 mg Q 12 hours	7 to 14 days
Pharyngitis and/or tonsillitis	200 mg	100 mg Q 12 hours	5 to 10 days
Uncomplicated urinary tract infection	200 mg	100 mg Q 12 hours	7 days

GRANULES FOR ORAL SUSPENSION:

BANAN for Oral Suspension may be given without regard to food. The recommended dosages, durations of treatment, and applicable patient populations are as described in the following chart:

Adults (age 13 years and older):

Type of infection	Total daily dose	Dose frequency	Duration
Acute community-acquired pneumonia	400 mg	200 mg Q 12 hours	14 days
Uncomplicated gonorrhea (men and women) and rectal gonococcal infections (women)	200 mg	single dose	
Skin and skin structure	800 mg	400 mg Q 12 hours	7 to 14 days
Pharyngitis and/or tonsillitis	200 mg	100 mg Q 12 hours	5 to 10 days
Uncomplicated urinary tract infection	200 mg	100 mg Q 12 hours	7 days

Children (age 5 months through 12 years):

Type of infection	Total daily dose	Dose frequency	Duration
Acute otitis media	10 mg/kg/day (Max 400 mg/day)	10 mg/kg Q 24 h (Max 400 mg/dose) or 5 mg/kg Q12 h (Max 200 mg/dose)	10 days
Pharyngitis and/or tonsillitis	10 mg/kg/day (Max 200 mg/day)	5 mg/kg/dose Q 12 hrs (Max 100 mg/dose)	5 to 10 days

Patients with Renal Dysfunction:

For patients with severe renal impairment (<30 mL/min creatinine clearance), the dosing intervals should be increased to Q 24 hours. In patients maintained on hemodialysis, the dose frequency should be 3 times per week after hemodialysis.

When only the serum creatinine level is available, the following formula (based on sex, weight, and age of patient) may be use to estimate creatinine clearance (mL/min). For this estimate to be valid, the serum creatinine level should represent a steady state of renal function.

Males: (mL/min) $$\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

Females: (mL/min) 0.85 x above value

Patients with Cirrhosis:
Cefpodoxime pharmacokinetics in cirrhotic patients (with or without ascites) are similar to those in healthy subjects. Dose adjustment is not necessary in this population.

Preparation of Suspension:

Constitution Directions For Oral Suspension		
Bottle Size	Final Concentration	Directions
100 mL	50 mg per 5 mL	Suspend in a total of 58 mL of water. Method: First tap the bottle to loosen granules. Then add the water in two portions, shaking well after each aliquot of water.
75 mL	50 mg per 5 mL	Suspend in a total of 44 mL of water. Method: First tap the bottle to loosen granules. Then add the water in two portions, shaking well after each aliquot of water.
50 mL	50 mg per 5 mL	Suspend in a total of 29 mL of water. Method: First tap the bottle to loosen granules. Then add the water in two portions, shaking well after each aliquot of water.
100 mL	100 mg per 5 mL	Suspend in a total of 57 mL of water. Method: First tap the bottle to loosen granules. Then add the water in two portions, shaking well after each aliquot of water.
75 mL	100 mg per 5 mL	Suspend in a total of 43 mL of water. Method: First tap the bottle to loosen granules. Then add the water in two portions, shaking well after each aliquot of water.
50 mL	100 mg per 5 mL	Suspend in a total of 29 mL of water. Method: First tap the bottle to loosen granules. Then add the water in two portions, shaking well after each aliquot of water.

After mixing, the suspension should be stored in a refrigerator, 2° to 8°C (36° to 46°F). Shake well before using. Keep container tightly closed. The mixture may be used for 14 days. Discard unused portion after 14 days.

HOW SUPPLIED
BANAN Tablets are available in the following strengths (cefpodoxime equivalent), colors, and sizes:
100 mg (light orange, elliptical, debossed with xxxxx)
Bottles of 20 NDC xxxx-xxxx-xx
Bottles of 100 NDC xxxx-xxxx-xx
Unit dose packs of 100 NDC xxxx-xxxx-xx

200 mg (coral red, elliptical, debossed with xxxxx)
Bottles of 20 NDC xxxx-xxxx-xx
Bottles of 100 NDC xxxx-xxxx-xx
Unit dose packs of 100 NDC xxxx-xxxx-xx
Store tablets between 15° and 30°C (59° to 86°F). Replace caps securely after each opening. Protect unit dose packs from excessive moisture.

BANAN for Oral Suspension is available in the following strengths (cefpodoxime equivalents when constituted according to directions), flavor, and size:
50 mg/5 mL, lemon creme flavor in 100 mL bottles NDC xxxx-xxxx-xx
50 mg/5 mL, lemon creme flavor in 75 mL bottles NDC xxxx-xxxx-xx
50 mg/5 mL, lemon creme flavor in 50 mL bottles NDC xxxx-xxxx-xx

100 mg/5 mL, lemon creme flavor in 100 mL bottles	NDC xxxx-xxxx-xx
100 mg/5 mL, lemon creme flavor in 75 mL bottles	NDC xxxx-xxxx-xx
100 mg/5 mL, lemon creme flavor in 50 mL bottles	NDC xxxx-xxxx-xx

Store unsuspended granules between 15° and 30°C (59° to 86°F).

Directions for mixing are included on the label. After mixing, suspension should be stored in a refrigerator 2° to 8°C (36° to 46°F). Shake well before using. Keep container tightly closed. The mixture may be used for 14 days. Discard unused portions after 14 days.

REFERENCES

1. National Committee for Clinical Laboratory Standards, Approved Standard: Performance Standards for Antimicrobial Disk Susceptibility Tests, 4th Edition, Volume 10(7):M2-A4, Villanova, PA, April, 1990.
2. National Committee for Clinical Laboratory Standards, Approved Standard: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, 2nd Edition, Volume 10(8):M7-A2, Villanova, PA, April, 1990.

CLINICAL TRIALS:

CYSTITIS

In two double-blind, 2:1 randomized, comparative trials performed in adults in the United States, cefpodoxime proxetil was compared to other beta-lactam antibiotics. In these studies, the following bacterial eradication rates were obtained at 5 to 9 days after therapy:

Pathogen	Cefpodoxime	Comparators
E. coli	200/243 (82%)	99/123 (80%)
Other pathogens	34/42 (81%)	23/28 (82%)
K. pneumoniae		
P. mirabilis		
S. saprophyticus		
TOTAL	234/285 (82%)	122/151 (81%)

In these studies, clinical cure rates and bacterial eradication rates for cefpodoxime proxetil were comparable to the comparator agents; however, the clinical cure rates and bacteriologic eradication rates were lower than those observed with some other classes of approved agents for cystitis.

Acute Otitis Media Studies

In controlled studies of acute otitis media performed in the United States, where significant rates of B-lactamase-producing organisms were found, cefpodoxime proxetil was compared to other oral antibiotics. In these studies, using very strict evaluability criteria and microbiologic and clinical response criteria at the 15-to-28 day post-therapy follow-up, the following presumptive bacterial eradication/clinical cure outcomes (i.e., clinical success) were obtained.

Pathogen	Cefpodoxime proxetil 5 mg/kg Q 12h x 10 d	Comparator
H. influenzae	25/46 (54%)	18/36 (50%)
M. catarrhalis	20/42 (48%)	8/22 (36%)
S. pneumoniae	39/74 (53%)	19/37 (51%)

Pathogen	Cefpodoxime proxetil 10 mg/kg Q 24h x 10 d	Comparator
H. influenzae	36/56 (64%)	12/21 (57%)
M. catarrhalis	14/18 (78%)	8/12 (67%)
S. pneumoniae	56/89 (63%)	21/38 (55%)

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