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Vantin® Tablets and Oral Suspension

PHARMACIA

cefpodoxime proxetil tablets and cefpodoxime proxetil for oral suspension, USP

To reduce the development of drug-resistant bacteria and maintain the effectiveness of VANTIN and other antibacterial drugs, VANTIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

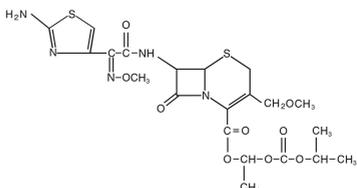
For Oral Use Only



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DESCRIPTION

Cefpodoxime proxetil is an orally administered, extended spectrum, semi-synthetic antibiotic of the cephalosporin class. The chemical name is (R)-1(isopropoxycarbonyloxy) ethyl (+)-(6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-(1Z)methoxyimino]acetamido]-3-methoxymethyl-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene- 2-carboxylate. Its empirical formula is C₂₁H₂₇N₅O₇S₂ 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.

VANTIN 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, hypromellose, lactose hydrous, magnesium 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 VANTIN 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 35% 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 cefpodoxime 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	Time after oral ingestion						
(Cefpodoxime equivalents)	1hr	2hr	3hr	4hr	6hr	8hr	12hr
100 mg	0.98	1.4	1.3	1.0	0.59	0.29	0.08
200mg	1.5	2.2	2.2	1.8	1.2	0.62	0.18
400mg	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	Time after oral ingestion						
(Cefpodoxime equivalents)	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 cefpodoxime exceeded the MIC₉₀ 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 MIC₉₀ for *S. pneumoniae* and *H. influenzae*. CSF:

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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.

Effect of Hepatic Impairment (cirrhosis):

Absorption was somewhat diminished and elimination unchanged in patients with cirrhosis. The mean cefpodoxime T_{max} 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 3.5 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 against a wide-spectrum of Gram-positive and Gram-negative bacteria. Cefpodoxime is stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillins and cephalosporins, due to their production of beta lactamase, may be susceptible to cefpodoxime. Cefpodoxime is inactivated by certain extended spectrum beta-lactamases. The bactericidal activity of cefpodoxime results from its inhibition of cell wall synthesis.

Cefpodoxime has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections, as described in the **INDICATIONS AND USAGE** section.

Aerobic Gram-positive microorganisms:

Staphylococcus aureus (including penicillinase-producing strains)

NOTE: Cefpodoxime is inactive against methicillin-resistant staphylococci.

Staphylococcus saprophyticus

Streptococcus pneumoniae (excluding penicillin-resistant strains)

Streptococcus pyogenes

Aerobic Gram-negative microorganisms:

Escherichia coli

Klebsiella pneumoniae

Proteus mirabilis

Haemophilus influenzae (including beta-lactamase producing strains)

Moraxella (Branhamella) catarrhalis

Neisseria gonorrhoeae (including penicillinase-producing strains)

The following *in vitro* data are available, but their clinical significance is unknown. Cefpodoxime exhibits *in vitro* minimum inhibitory concentrations (MICs) of ≤2.0 mcg/mL against most (≥90%) of isolates of the following microorganisms. However, the safety and efficacy of cefpodoxime in treating clinical infections due to these microorganisms have not been established in adequate and well controlled clinical trials.

Aerobic Gram-positive microorganisms:

Streptococcus agalactiae

Streptococcus spp. (Groups C, F, G)

NOTE: Cefpodoxime is inactive against enterococci.

Aerobic Gram-negative microorganisms:

Citrobacter diversus

Klebsiella oxytoca

Proteus vulgaris

Providencia rettgeri

Haemophilus parainfluenzae

NOTE: Cefpodoxime is inactive against most strains of *Pseudomonas* and *Enterobacter*.

Anaerobic Gram-positive microorganisms:

Peptostreptococcus magnus

SUSCEPTIBILITY TESTING

Dilution Techniques: Quantitative methods are used to determine antimicrobial inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of microorganisms to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution methods¹ (broth or agar) or equivalent using standardized inoculum concentrations, and standardized concentrations of cefpodoxime from a powder of known potency. The MIC values should be interpreted according to the following criteria:

For Susceptibility Testing of Enterobacteriaceae and Staphylococcus spp.

MIC (mcg/mL)	Interpretation
≤ 2.0	Susceptible (S)
4.0	Intermediate (I)
≥ 8.0	Resistant (R)

For Susceptibility Testing of Haemophilus spp.¹

MIC (mcg/mL)	Interpretation ²
≤ 2.0	Susceptible (S)

¹ The interpretive criteria for *Haemophilus spp.* is applicable only to broth microdilution susceptibility testing done with Haemophilus Test Medium (HTM) broth.²

² "Intermediate" and "Resistant" categories have not been determined.

For Susceptibility Testing of Neisseria gonorrhoeae.³

MIC (mcg/mL)	Interpretation ⁴
≤ 0.5	Susceptible (S)

³ The interpretive value for *N. gonorrhoeae* is applicable only to agar dilution susceptibility testing done with *Neisseria gonorrhoeae* susceptibility test medium.⁴

⁴ "Intermediate" and "Resistant" categories have not been determined.

For Susceptibility Testing of Streptococcus pneumoniae.

MIC (mcg/mL)	Interpretation ⁵
≤ 0.5	Susceptible (S)
1.0	Intermediate (I)
≥ 2.0	Resistant (R)

⁵ The interpretive value for *S. pneumoniae* is applicable only to broth microdilution susceptibility testing done with cation-adjusted Mueller-Hinton broth with lysed horse blood (LHB) (2-5% v/v).²

For Susceptibility Testing of Streptococcus spp. other than Streptococcus pneumoniae.¹

A streptococcal isolate that is susceptible to penicillin (MIC ≤0.12 mcg/mL) can be considered susceptible to cefpodoxime for approved indications, and need not be tested against cefpodoxime.

¹ The interpretive value for *Streptococcus spp.* is applicable only to broth microdilution susceptibility testing done with cation-adjusted Mueller-Hinton broth with lysed horse blood (LHB) (2-5% v/v).²

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the concentration of the antimicrobial compound in the blood reaches usually achievable levels. A report of "Intermediate" indicates that the results should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

A standardized susceptibility test procedure requires the use of laboratory control organisms to control the technical aspects of the laboratory procedures. Standard cefpodoxime powder should provide the following MIC values with the indicated quality control strains:

Microorganism (ATCC#)	MIC Range (mcg/mL)
<i>Escherichia coli</i> (25922)	0.25 - 1.0
<i>Staphylococcus aureus</i> (29213)	1.0 - 8.0
<i>Haemophilus influenzae</i> (49247)	0.25 - 1.0 ²
<i>Neisseria gonorrhoeae</i> (49226)	0.03 - 0.12 ²
<i>Streptococcus pneumoniae</i> (49619)	0.03 - 0.12 ²

² These quality control ranges are applicable to tests performed by a broth microdilution procedure using Haemophilus Test Medium (HTM).

³ These quality control ranges are applicable to tests performed by agar dilution only using GC agar base with 1% defined growth supplement.

⁴ These quality control ranges are applicable to tests performed by the broth microdilution method only using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.

⁵ When susceptibility testing *Streptococcus pneumoniae* or *Streptococcus spp.* this quality control strain should be tested.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure¹ requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 mcg cefpodoxime to test the susceptibility of microorganisms to cefpodoxime. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 10 mcg cefpodoxime disk should be interpreted according to the following criteria:

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For Susceptibility Testing of Enterobacteriaceae and Staphylococcus spp.

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

For Susceptibility Testing of Haemophilus spp.¹

Zone Diameter (mm)	Interpretation ²
≥ 21	Susceptible (S)

¹ The zone diameter for *Haemophilus spp.* is applicable only to tests performed on Haemophilus Test Medium (HTM) agar incubated under 5% CO₂.²

² "Intermediate" and "Resistant" criteria have not been determined.

For Susceptibility Testing of Neisseria gonorrhoeae.³

Zone Diameter (mm)	Interpretation ⁴
≥ 29	Susceptible (S)

³ The zone diameter for *N. gonorrhoeae* is applicable only to tests performed on GC agar base and 1% defined growth supplement incubated under 5% CO₂.²

⁴ "Intermediate" and "Resistant" categories have not been determined.

For Susceptibility Testing of Streptococcus pneumoniae.⁵

Isolates of pneumococci with oxacillin zone sizes of ≥20 mm are susceptible (MIC ≤0.06 mcg/mL) to penicillin and can be considered susceptible to cefpodoxime for approved indications, and cefpodoxime need not be tested.

⁵ The zone diameter for *S. pneumoniae* is applicable only to tests performed on Mueller-Hinton agar with 5% sheep blood incubated in 5% CO₂.²

For Susceptibility Testing of Streptococcus spp. other than Streptococcus pneumoniae.⁶ A streptococcal isolate that is susceptible to penicillin (zone diameter ≥28 mm) can be considered susceptible to cefpodoxime for approved indications, and cefpodoxime need not be tested.

⁶ The zone diameter for *Streptococcus spp.* is applicable only to tests performed on Mueller-Hinton agar with 5% sheep blood incubated in 5% CO₂.²

Quality Control

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 10 mcg cefpodoxime disk should provide the following zone diameters with the quality control strains listed below:

Microorganism (ATCC#)	Zone Diameter Range (mm)
<i>Escherichia coli</i> (25922)	23-28
<i>Staphylococcus aureus</i> (25923)	19-25
<i>Haemophilus influenzae</i> (49247)	25-31 ¹
<i>Neisseria gonorrhoeae</i> (49226)	35-43 ¹
<i>Streptococcus pneumoniae</i> (49619) ¹	28-34 ¹

¹ This zone diameter range is only applicable to tests performed on Haemophilus Test Medium (HTM) agar incubated in 5% CO₂.

² This zone diameter range is only applicable to tests performed on GC agar base and 1% defined growth supplement incubated in 5% CO₂.

³ This zone diameter range is only applicable to tests performed on Mueller-Hinton agar supplemented with 5% defibrinated sheep blood, incubated in 5% CO₂.

⁴ This organism is to be used for quality control testing for both *S. pneumoniae* and *Streptococcus spp.* ATCC[®] is a registered trademark of the American Type Culture Collection.

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, durations of therapy, and applicable patient populations vary among these infections. Please see DOSAGE AND ADMINISTRATION for specific recommendations. Acute otitis media caused by *Streptococcus pneumoniae*, (excluding penicillin-resistant strains), *Streptococcus pyogenes*, *Haemophilus influenzae* (including beta-lactamase-producing strains), *Streptococcus pneumoniae* (including beta-lactamase-producing strains), or *Moraxella (Branhamella) catarrhalis* (including beta-lactamase-producing strains).

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.

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*.

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

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

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

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**.)

Acute maxillary sinusitis caused by *Haemophilus influenzae* (including beta-lactamase-producing strains), *Streptococcus pneumoniae*, and *Moraxella catarrhalis*.

Uncomplicated urinary tract infections (cystitis) caused by *Escherichia coli*, *Klebsiella pneumoniae*, *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 other 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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of VANTIN and other antibacterial drugs, VANTIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

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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.

Prescribing VANTIN in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients:

Patients should be counseled that antibacterial drugs including VANTIN should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When VANTIN is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by VANTIN or other antibacterial drugs in the future.

Drug Interactions:

Antacids: Concomitant administration of high doses of antacids (sodium bicarbonate and aluminum hydroxide) or H₂ blockers reduces peak plasma levels by 24% to 42% and the extent of absorption by 27% to 32%, respectively. The rate of 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.

Carcinogenesis, 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/m²) 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/m²) or to rabbits at doses up to 30 mg/kg/day (1-2 times the human dose based on mg/m²).

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, this 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 2 months of age have not been established.

Geriatric Use:

Of the 3339 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, 4696 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. One-hundred twenty-nine (2.7%) patients discontinued medication due to adverse events thought possibly- or probably-related to drug toxicity. Ninety-three (52%) of the 178 patients who discontinued therapy (whether thought related to drug therapy or not) did so because of gastrointestinal disturbances, nausea, vomiting, or 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=4696 cefpodoxime-treated patients) were:

Incidence Greater Than 1%:

Diarrhea	7.0%
Diarrhea or loose stools were dose related; decreasing from 10.4% of patients receiving 800 mg per day to 5.7% for those receiving 200 mg per day. Of patients with diarrhea, 10% had <i>C. difficile</i> or ganism or toxin in the stool. (See WARNINGS .)	
Nausea	3.3%
Vaginal Fungal Infections	1.0%
Vulvovaginal Infections	1.3%
Abdominal Pain	1.2%
Headache	1.0%

Incidence Less Than 1%: By body system in decreasing order:

Clinical Studies

Adverse events thought possibly- or probably-related to cefpodoxime proxetil that occurred in less than 1% of patients (N=4696)

Body - fungal infections, abdominal distention, malaise, fatigue, asthenia, fever, chest pain, back pain, chills, generalized pain, abnormal microbiological tests, moniliasis, abscess, allergic reaction, facial edema, bacterial infections, parasitic infections, localized edema, localized pain.

Cardiovascular - congestive heart failure, migraine, palpitations, vasodilation, hematoma, hypertension, hypotension.

Digestive - vomiting, dyspepsia, dry mouth, flatulence, decreased appetite, constipation, oral moniliasis, anorexia, eructation, gastritis, mouth ulcers, gastrointestinal disorders, rectal disorders, tongue disorders, tooth disorders, increased thirst, oral lesions, tenesmus, dry throat, toothache.

Hemic and Lymphatic - anemia.

Metabolic and Nutritional - dehydration, gout, peripheral edema, weight increase.

Musculo-skeletal - myalgia.

Nervous - dizziness, insomnia, somnolence, anxiety, shakiness, nervousness, cerebral infarction, change in dreams, impaired concentration, confusion, nightmares, paresthesia, vertigo.

Respiratory - asthma, cough, epistaxis, rhinitis, wheezing, bronchitis, dyspnea, pleural effusion, pneumonia, sinusitis.

Skin - urticaria, rash, pruritus non-application site, diaphoresis, maculopapular rash, fungal dermatitis, desquamation, dry skin non-application site, hair loss, vesiculobullous rash, sunburn.

Special Senses - taste alterations, eye irritation, taste loss, tinnitus.

Urogenital - hematuria, urinary tract infections, metrorrhagia, dysuria, urinary frequency, nocturia, penile infection, proteinuria, vaginal pain.

Granules for Oral Suspension (Multiple dose):

In clinical trials using multiple doses of cefpodoxime proxetil granules for oral suspension, 2128 pediatric patients (93% 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-four patients (1.1%) 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 rashes.

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Adverse events thought possibly- or probably-related, or of unknown relationship to cefpodoxime proxetil for oral suspension in multiple dose clinical trials (N=2128 patients treated with cefpodoxime) were:

Incidence Greater Than 1%:

Diarrhea 6.0%
 The incidence of diarrhea in infants and toddlers (age 1 month to 2 years) was 12.8%.

Diaper rash/Fungal skin rash 2.0% (includes moniliasis)

The incidence of diaper rash in infants and toddlers was 8.5%.

Other skin rashes 1.8%

Vomiting 2.3%

Incidence Less Than 1%:

Body: Localized abdominal pain, abdominal cramp, headache, monilia, generalized abdominal pain, asthenia, fever, fungal infection.

Digestive: Nausea, monilia, anorexia, dry mouth, stomatitis, pseudomembranous colitis.

Hemic & Lymphatic: Thrombocytopenia, positive direct Coombs' test, eosinophilia, leukocytosis, leukopenia, prolonged partial thromboplastin time, thrombocytopenic purpura.

Metabolic & Nutritional: Increased SGPT.

Musculo-Skeletal: Myalgia.

Nervous: Hallucination, hyperkinesia, nervousness, somnolence.

Respiratory: Epistaxis, rhinitis.

Skin: Skin moniliasis, urticaria, fungal dermatitis, acne, exfoliative dermatitis, maculopapular rash.

Special Senses: Taste perversion.

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

Significant laboratory changes that have been reported in adult and pediatric 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, decreased hematocrit, leukopenia, neutropenia, lymphocytopenia, thrombocytopenia, thrombocytopenia, positive Coombs' test, and prolonged PT, and PTT.

Serum Chemistry: Hyperglycemia, hypoglycemia, hypoalbuminemia, hypoproteinemia, hyperkalemia, and hyponatremia.

Renal: increases in BUN and creatinine.

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, pseudomembranous 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. Anticonvulsant 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 reaction 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 beta-lactam antibiotics may include nausea, vomiting, epigastric distress, and diarrhea.

DOSAGE AND ADMINISTRATION

(See **INDICATIONS AND USAGE** for indicated pathogens.)

FILM-COATED TABLETS

VANTIN Tablets should be administered orally with food to enhance absorption. (See **CLINICAL PHARMACOLOGY**.)

The recommended dosages, durations of treatment, and applicable patient population are as described in the following chart:

Adults and Adolescents (age 12 years and older):

Type of Infection	Total Daily Dose	Dose Frequency	Duration
Pharyngitis and/or tonsillitis	200 mg	100 mg Q 12 hours	5 to 10 days
Acute community-acquired pneumonia	400 mg	200 mg Q 12 hours	14 days
Acute bacterial exacerbations of 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
Acute maxillary sinusitis	400 mg	200 mg Q 12 hours	10 days
Uncomplicated urinary tract infection	200 mg	100 mg Q 12 hours	7 days

GRANULES FOR ORAL SUSPENSION:

VANTIN 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 and Adolescents (age 12 years and older):

Type of Infection	Total Daily Dose	Dose Frequency	Duration
Pharyngitis and/or tonsillitis	200 mg	100 mg Q 12 hours	5 to 10 days
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
Acute maxillary sinusitis	400 mg	200 mg Q 12 hours	10 days
Uncomplicated urinary tract infection	200 mg	100 mg Q 12 hours	7 days

Infants and Pediatric Patients (age 2 months through 12 years):

Type of Infection	Total Daily Dose	Dose Frequency	Duration
Acute otitis media	10 mg/kg/day (Max 400 mg/day)	5 mg/kg Q 12 h (Max 200 mg/dose)	5 days
Pharyngitis and/or tonsillitis	10 mg/kg/day (Max 200 mg/day)	5 mg/kg/dose Q 12 h (Max 100 mg/dose)	5 to 10 days
Acute maxillary sinusitis	10 mg/kg/day (Max 400 mg/day)	5 mg/kg Q 12 hours (Max 200 mg/dose)	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/week after hemodialysis.

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

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Males: **Weight (kg) x (140 - age)**
 (mL/min) 72 x serum creatinine (mg/100 mL)

Females: 0.85 x above value
 (mL/min)

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		
Constituted Volume	Final Concentration	Directions
50 mL	50 mg per 5 mL	Suspend in a total of 29 mL of distilled water. Method: First, shake the bottle to loosen granules. Then add the water in two approximately equal portions, shaking vigorously after each aliquot of water.
75 mL	50 mg per 5 mL	Suspend in a total of 44 mL of distilled water. Method: First, shake the bottle to loosen granules. Then add the water in two approximately equal portions, shaking vigorously after each aliquot of water.
100 mL	50 mg per 5 mL	Suspend in a total of 58 mL of distilled water. Method: First, shake the bottle to loosen granules. Then add the water in two approximately equal portions, shaking vigorously after each aliquot of water.
50 mL	100 mg per 5 mL	Suspend in a total of 29 mL of distilled water. Method: First, shake the bottle to loosen granules. Then add the water in two approximately equal portions, shaking vigorously after each aliquot of water.
75 mL	100 mg per 5 mL	Suspend in a total of 43 mL of distilled water. Method: First, shake the bottle to loosen granules. Then add the water in two approximately equal portions, shaking vigorously after each aliquot of water.
100 mL	100 mg per 5 mL	Suspend in a total of 57 mL of distilled water. Method: First, shake the bottle to loosen granules. Then add the water in two approximately equal portions, shaking vigorously 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

VANTIN Tablets are available in the following strengths (cefpodoxime equivalent), colors, and sizes:

100 mg, (light orange, elliptical, debossed with U3617)

Bottles of 20 NDC 0009-3617-01

Bottles of 100 NDC 0009-3617-02

Unit dose packs of 100 NDC 0009-3617-03

200 mg, (coral red, elliptical, debossed with U3618)

Bottles of 20 NDC 0009-3618-01

Bottles of 100 NDC 0009-3618-02

Unit dose packs of 100 NDC 0009-3618-03

Store tablets at controlled room temperature 20° to 25°C (68° to 77°F) (see USP).

Replace cap securely after each opening. Protect unit dose packs from excessive moisture.

VANTIN Oral Suspension provides the equivalent of 50 mg or 100 mg cefpodoxime per 5 mL suspension (when constituted as directed) and is available in lemon creme flavor in the following sizes:

50 mg/5 mL

100-mL suspension NDC 0009-3531-01

75-mL suspension NDC 0009-3531-02

100-mL suspension NDC 0009-3531-03

100 mg/5 mL

100-mL suspension NDC 0009-3615-01

75-mL suspension NDC 0009-3615-02

50-mL suspension NDC 0009-3615-03

Store unsuspended granules at controlled room temperature 20° to 25°C (68° to 77°F) (see USP).

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 portion after 14 days.

REFERENCES

1. NCCLS. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically - fourth edition; Approved standard. NCCLS document M7-A4 (ISBN 1-56238-309-4). NCCLS, 940 West Valley Rd., Suite 1400, Wayne, PA 19087-1898, 1997.

2. NCCLS. Performance standards for antimicrobial susceptibility testing; Eighth informational supplement. NCCLS document M100-S8 (ISBN 1-56238-337-x). NCCLS, 940 West Valley Rd., Suite 1400, Wayne, PA 19087-1898, 1998.

3. NCCLS. Performance standards for antimicrobial disk susceptibility tests - sixth edition; Approved standard. NCCLS document M2-A6 (ISBN 1-56238-306-6). NCCLS, 940 West Valley Rd., Suite 1400, Wayne