

Vantin® Tablets and Oral Suspension

brand of cefpodoxime proxetil tablets and cefpodoxime proxetil for oral suspension, USP - For Oral Use Only

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 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, 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 gonorrhoea (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 gonorrhoea (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: (mL/min)	Weight (kg) x (140 - age)
Females: (mL/min)	72 x serum creatinine (mg/100 mL)
	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		
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

50-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

- 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.
- 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.
- 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, PA 19087-1898, 1997.

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	Comparator
<i>E. coli</i>	200/243 (82%)	99/123 (80%)
Other pathogens	34/42 (81%)	23/28 (82%)
<i>K. pneumoniae</i>		
<i>P. mirabilis</i>		
<i>S. saprophyticus</i>		

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 beta-lactamase-producing organisms were found, cefpodoxime proxetil was compared to cefixime. In these studies, using very strict evaluability criteria and microbiologic and clinical response criteria at the 4 to 21 day post-therapy follow-up, the following presumptive bacterial eradication/clinical success outcomes (cured and improved) were obtained.

Pathogen	Cefpodoxime Proxetil 5 mg/kg Q 12 h x 5 d	Cefixime
<i>S. pneumoniae</i>	88/122 (72%)	72/124 (58%)
<i>H. influenzae</i>	50/76 (66%)	61/81 (75%)
<i>M. catarrhalis</i>	22/39 (56%)	23/41 (56%)
<i>S. pyogenes</i>	20/25 (80%)	13/23 (57%)
Clinical success rate	171/254 (67%)	165/258 (64%)

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