

VANCOMYCIN HYDROCHLORIDE- vancomycin hydrochloride powder, for solution

ANI Pharmaceuticals, Inc.

Vancomycin Hydrochloride for Oral Solution USP

Rx only

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

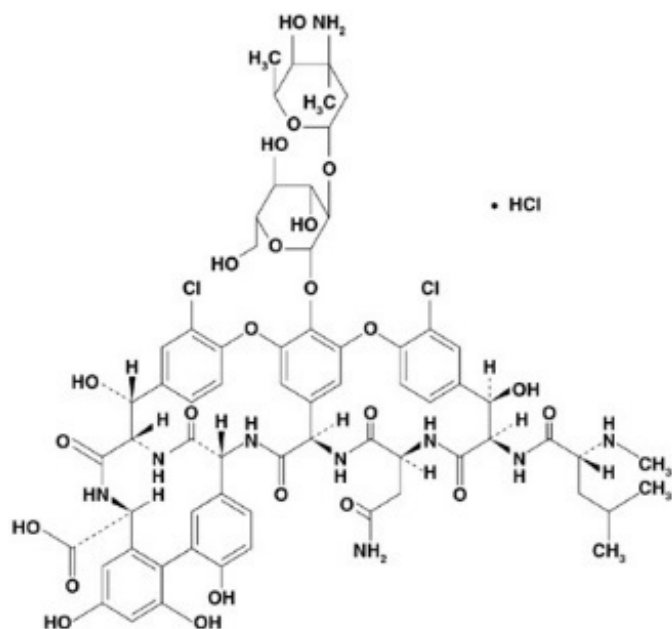
This preparation for the treatment of colitis is for oral use only and is not systemically absorbed. Vancomycin Hydrochloride for Oral Solution must be given orally for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile*. Orally administered Vancomycin Hydrochloride for Oral Solution is not effective for other types of infection.

Parenteral administration of vancomycin is not effective for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis caused by *C. difficile*. If parenteral vancomycin therapy is desired, use an intravenous preparation of vancomycin and consult the package insert accompanying that preparation.

DESCRIPTION

Vancomycin Hydrochloride for Oral Solution USP contains chromatographically purified vancomycin hydrochloride USP, a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*), which has the chemical formula $C_{66}H_{75}Cl_2N_9O_{24} \cdot HCl$. The molecular weight of vancomycin hydrochloride is 1,485.73; 500 mg of the base is equivalent to 0.34 mmol.

Vancomycin hydrochloride has the following structural formula:



Vancomycin Hydrochloride for Oral Solution USP is intended for reconstitution with water. Each 5 mL of reconstituted solution contains vancomycin hydrochloride equivalent to 250 mg (0.17 mmol) vancomycin.

Inactive ingredients: citric acid anhydrous, sodium benzoate, sucralose, and mixed berry flavor. Contains no ingredient made from a gluten-containing grain (wheat, barley or rye).

CLINICAL PHARMACOLOGY

Vancomycin is poorly absorbed after oral administration. During multiple dosing of 250 mg every 8 hours for 7 doses, fecal concentrations of vancomycin in volunteers exceeded 100 mg/kg in the majority of samples. No blood concentrations were detected and urinary recovery did not exceed 0.76%. In anephric patients with no inflammatory bowel disease, blood concentrations of vancomycin were barely measurable (0.66 mcg/mL) in 2 of 5 subjects who received 2 g of Vancomycin Hydrochloride for Oral Solution daily for 16 days. No measurable blood concentrations were attained in the other 3 subjects. With doses of 2 g daily, very high concentrations of drug can be found in the feces (>3,100 mg/kg) and very low concentrations (<1 mcg/mL) can be found in the serum of patients with normal renal function who have pseudomembranous colitis. Orally administered vancomycin does not usually enter the systemic circulation even when inflammatory lesions are present. After multiple-dose oral administration of vancomycin, measurable serum concentrations may infrequently occur in patients with active *C. difficile*-induced pseudomembranous colitis, and, in the presence of renal impairment, the possibility of accumulation exists.

Microbiology

The bactericidal action of vancomycin results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis.

NOTE: The oral form of vancomycin is effective only for the infections noted in the **INDICATIONS AND USAGE** section. The oral form is **not** effective for any other type of infection.

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

Aerobic gram-positive microorganisms

Staphylococcus aureus (including methicillin-resistant strains) associated with enterocolitis

Aerobic gram-positive microorganisms

Clostridium difficile antibiotic-associated pseudomembranous colitis

INDICATIONS AND USAGE

Vancomycin Hydrochloride for Oral Solution is administered orally for treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains) and antibiotic-associated pseudomembranous colitis caused by *C. difficile*. Parenteral administration of vancomycin is not effective for the above indications; therefore, Vancomycin Hydrochloride for Oral Solution must be given orally for these infections. **Orally administered Vancomycin Hydrochloride for Oral Solution is not effective for other types of infection.**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Vancomycin Hydrochloride for Oral Solution and other antibacterial drugs, Vancomycin Hydrochloride for Oral Solution 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.

CONTRAINDICATIONS

Vancomycin Hydrochloride for Oral Solution is contraindicated in patients with known hypersensitivity to vancomycin.

WARNINGS

Nephrotoxicity

Nephrotoxicity (e.g., reports of renal failure, renal impairment, blood creatinine increased) has occurred following oral vancomycin hydrochloride therapy in randomized controlled clinical trials, and can occur either during or after completion of therapy. The risk of nephrotoxicity is increased in patients over 65 years of age.

In patients over 65 years of age, including those with normal renal function prior to treatment, renal function should be monitored during and following treatment with vancomycin oral solution to detect potential vancomycin induced nephrotoxicity.

Ototoxicity

Ototoxicity has occurred in patients receiving vancomycin. It may be transient or permanent. It has been reported mostly in patients who have been given excessive intravenous doses, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside. Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity.

Severe Dermatologic Reactions

Severe dermatologic reactions such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and linear IgA bullous dermatosis (LABD) have been reported in association with the use of vancomycin. Cutaneous signs or symptoms reported include skin rashes, mucosal lesions, and blisters.

Discontinue Vancomycin Hydrochloride for Oral Solution at the first appearance of signs and symptoms of TEN, SJS, DRESS, AGEP, or LABD.

***Clostridium Difficile* Associated Diarrhea (CDAD)**

Significant systemic absorption has been reported in some patients (e.g., patients with renal insufficiency and/or colitis) who have taken multiple oral doses of vancomycin hydrochloride for *C. difficile*-associated diarrhea. In these patients, serum vancomycin concentrations reached therapeutic levels for the treatment of systemic infections. Some patients with inflammatory disorders of the intestinal mucosa also may have significant systemic absorption of vancomycin. These patients may be at risk for the development of adverse reactions associated with higher doses of vancomycin oral solution; therefore, monitoring of serum concentrations of vancomycin may be appropriate in some instances, e.g., in patients with renal insufficiency and/or colitis or in those receiving concomitant therapy with an aminoglycoside antibacterial drug.

PRECAUTIONS

Use of vancomycin may result in the overgrowth of non-susceptible bacteria. If superinfection occurs during therapy, appropriate measures should be taken.

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

Hemorrhagic occlusive retinal vasculitis, including permanent loss of vision, occurred in patients receiving intracameral or intravitreal administration of vancomycin during or after cataract surgery. The safety and efficacy of vancomycin administered by the intracameral or intravitreal route have not been established by adequate and well-controlled studies. Vancomycin is not indicated for prophylaxis of endophthalmitis.

Pregnancy

Animal reproduction studies have not been conducted with vancomycin. It is not known whether vancomycin can affect reproduction capacity. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin on infants were evaluated

when the drug was administered intravenously to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancomycin was found in cord blood. No sensorineural hearing loss or nephrotoxicity attributable to vancomycin was noted. One infant whose mother received vancomycin in the third trimester experienced conductive hearing loss that was not attributed to the administration of vancomycin. Because the number of patients treated in this study was limited and vancomycin was administered only in the second and third trimesters, it is not known whether vancomycin causes fetal harm. Vancomycin Hydrochloride for Oral Solution should be given to a pregnant woman only if clearly needed.

Nursing Mothers

Vancomycin is excreted in human milk based on information obtained with the intravenous administration of vancomycin. However, systemic absorption of vancomycin is very low following oral administration of Vancomycin Hydrochloride for Oral Solution (see **CLINICAL PHARMACOLOGY**). It is not known whether oral vancomycin is excreted in human milk, as no studies of vancomycin concentration in human milk after oral administration have been done. Caution should be exercised when Vancomycin Hydrochloride for Oral Solution is administered to a nursing woman. Because of the potential for adverse events, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Geriatric Use

In clinical trials, 54% of vancomycin hydrochloride-treated subjects were > 65 years of age. Of these, 40% were between the ages of > 65 and 75, and 60% were > 75 years of age.

Clinical studies with vancomycin hydrochloride in *C. difficile*-associated diarrhea have demonstrated that geriatric subjects are at increased risk of developing nephrotoxicity following treatment with oral vancomycin hydrochloride, which may occur during or after completion of therapy. In patients over 65 years of age, including those with normal renal function prior to treatment, renal function should be monitored during and following treatment with vancomycin hydrochloride to detect potential vancomycin induced nephrotoxicity.

Patients over 65 years of age may take longer to respond to therapy compared to patients 65 years of age and younger. Clinicians should be aware of the importance of appropriate duration of vancomycin hydrochloride treatment in patients over 65 years of age and not discontinue or switch to alternative treatment prematurely.

Information for Patients

Severe Dermatologic Reactions

Advise patients about the signs and symptoms of serious skin manifestations. Instruct patients to stop taking Vancocin immediately and promptly seek medical attention at the first signs or symptoms of skin rash, mucosal lesions and blisters (see **WARNINGS**).

Patients should be counseled that antibacterial drugs including Vancomycin Hydrochloride for Oral Solution should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Vancomycin Hydrochloride for Oral Solution 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 Vancomycin Hydrochloride for Oral Solution or other antibacterial drugs in the future.

ADVERSE REACTIONS

Nephrotoxicity

Nephrotoxicity (e.g., reports of renal failure, renal impairment, blood creatinine increased) occurred in 5% of subjects treated with vancomycin hydrochloride. Nephrotoxicity following vancomycin hydrochloride typically first occurred within one week after completion of treatment (median day of onset was Day 16). Nephrotoxicity following vancomycin hydrochloride occurred in 6% of subjects over 65 years of age and 3% of subjects 65 years of age and younger. Nephrotoxicity can also occur during oral vancomycin administration.

The incidences of hypokalemia, urinary tract infection, peripheral edema, insomnia, constipation, anemia, depression, vomiting, and hypotension were higher among subjects over 65 years of age than in subjects 65 years of age and younger.

Discontinuation of study drug due to adverse events occurred in 7% of subjects treated with vancomycin hydrochloride. The most common adverse events leading to discontinuation of vancomycin hydrochloride were *C. difficile* colitis (< 1%), nausea (< 1%), and vomiting (< 1%).

Ototoxicity

Cases of hearing loss associated with intravenously administered vancomycin have been reported. Most of these patients had kidney dysfunction or a preexisting hearing loss or were receiving concomitant treatment with an ototoxic drug. Vertigo, dizziness, and tinnitus have been reported rarely.

Hematopoietic

Reversible neutropenia, usually starting 1 week or more after onset of intravenous therapy with vancomycin or after a total dosage of more than 25 g, has been reported for several dozen patients. Neutropenia appears to be promptly reversible when vancomycin is discontinued. Thrombocytopenia has rarely been reported.

Miscellaneous

Patients have been reported to have had anaphylaxis, drug fever, nausea, chills, eosinophilia, rashes including exfoliative dermatitis, Stevens-Johnson syndrome (see **WARNINGS, Severe Dermatologic Reactions**), and vasculitis in association with the administration of vancomycin.

A condition has been reported that is similar to the IV-induced syndrome with symptoms consistent with anaphylactoid reactions, including hypotension, wheezing, dyspnea, urticaria, pruritus, flushing of the upper body ("Red Man Syndrome"), pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may

persist for several hours.

Post Marketing Reports

Skin and Subcutaneous Tissue Disorders

Severe dermatologic reactions such as toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and linear IgA bullous dermatosis (LABD) (see **WARNINGS, Severe Dermatologic Reactions**).

OVERDOSAGE

Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed by dialysis. Hemofiltration and hemoperfusion with polysulfone resin have been reported to result in increased vancomycin clearance.

For current information on the management of overdose, contact the National Poison Control Center at 1-800-222-1222 or www.poisson.org.

DOSAGE AND ADMINISTRATION

Adults

Vancomycin Hydrochloride for Oral Solution is used in treating antibiotic-associated pseudomembranous colitis caused by *C. difficile* and staphylococcal enterocolitis. Vancomycin Hydrochloride for Oral Solution is not effective by the oral route for other types of infections. The usual adult total daily dosage is 500 mg to 2 g administered orally in 3 or 4 divided doses for 7 to 10 days.

Pediatric Patients

The usual daily dosage is 40 mg/kg in 3 or 4 divided doses for 7 to 10 days. The total daily dosage should not exceed 2 g.

PREPARATION AND STABILITY

Mix the contents of the bottle with water as directed below. When reconstituted, each 5 mL contains approximately 250 mg of vancomycin. These mixtures may be kept for two weeks in a refrigerator without significant loss of potency.

Directions for mixing Vancomycin Hydrochloride for Oral Solution USP:

80 mL – Slowly add 80 mL water and shake vigorously.

150 mL – Slowly add 150 mL water and shake vigorously.

300 mL – Slowly add 300 mL water and shake vigorously.

The appropriate oral solution dose may be diluted in 1 oz of water and given to the patient to drink. The diluted material may be administered via nasogastric tube.

HOW SUPPLIED

Vancomycin Hydrochloride for Oral Solution USP equivalent to 250 mg per 5 mL vancomycin is available as:

80 mL bottle (4 g*) NDC 62559-830-80
150 mL bottle (7.5 g*) NDC 62559-830-55
300 mL bottle (15 g*) NDC 62559-830-03
* Equivalent to vancomycin

Store at refrigerated conditions, 2° to 8°C (36° to 46°F).
After mixing, refrigerate and use within two weeks. Shake well before using. Keep tightly closed.

Manufactured by:
ANI Pharmaceuticals, Inc.
Baudette, MN 56623



10192 Rev 01/21

PRINCIPAL DISPLAY PANEL

NDC 62559-830-80
Vancomycin Hydrochloride for Oral Solution USP
250 mg per 5 mL*
FOR ORAL USE ONLY
Rx only
80 mL (when mixed)

NDC 62559-830-80

**Vancomycin
Hydrochloride
for Oral Solution USP**

250 mg per 5 mL*

FOR ORAL USE ONLY

Rx only
80 mL
(when mixed)



DYE FREE

Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).

Usual Dose: See accompanying prescribing information.

Not for Treatment of Systemic Infections.

Store at refrigerated conditions, 2° to 8°C (36° to 46°F).

DIRECTIONS FOR PREPARATION: Slowly add 80 mL of water and shake vigorously.

After mixing, refrigerate and use within two weeks.
Shake well before using. Keep tightly closed.

*When prepared as directed, each 5 mL contains vancomycin hydrochloride equivalent to approximately 250 mg of vancomycin in a mixed berry-flavored solution.

Bottle contains vancomycin hydrochloride equivalent to 4 g vancomycin.

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10189 Rev 03/19

GTIN: 00362559000000

EXP: MMM 0000

LOT: 123456

SN: A1234567890123



VANCOMYCIN HYDROCHLORIDE
vancomycin hydrochloride powder, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:62559-830
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
VANCOMYCIN HYDROCHLORIDE (UNII: 71WO621TJD) (VANCOMYCIN - UNII:6Q205EH1VU)	VANCOMYCIN	250 mg in 5 mL

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)	
SODIUM BENZOATE (UNII: OJ245FE5EU)	
SUCRALOSE (UNII: 96K6UQ3ZD4)	

Product Characteristics

Color	WHITE (light pink)	Score	
Shape		Size	
Flavor	BERRY	Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:62559-830-80	80 mL in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	09/09/2019	
2	NDC:62559-830-55	150 mL in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	09/09/2019	
3	NDC:62559-830-03	300 mL in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	09/09/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA061667	09/09/2019	

Labeler - ANI Pharmaceuticals, Inc. (145588013)