December 18, 2020

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

SUITABILITY PETITION

Dear Sir or Madam:

The undersigned submits this petition, on behalf of a client, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act ("FD&C Act"), and in accordance with 21 C.F.R. § 10.20 and 21 C.F.R. § 10.30 requesting the Commissioner of the Food and Drug Administration ("FDA") to declare that the proposed drug product, Vancomycin Hydrochloride for Oral Solution EQ 125 mg (base)/5 mL is suitable for consideration in an Abbreviated New Drug Application ("ANDA") based upon Vancomycin Hydrochloride for Oral Solution EQ 250 mg (base)/5 mL by ANI Pharmaceuticals Inc., approved under ANDA A061667, as Reference Listed Drug ("RLD")[1].

A. ACTION REQUESTED

The petitioner requests that the Commissioner of the FDA declare that the proposed drug product, Vancomycin Hydrochloride for Oral Solution EQ 125 mg (base)/5 mL is suitable for submission as an ANDA. The prospective RLD, upon which this petition is based, is Vancomycin

[1] The Petitioner is aware that Vancomycin Hydrochloride for Oral Solution EQ 250 mg (base)/5 mL by ANI Pharmaceuticals Inc., approved under ANDA A061667, is currently not designated as the RLD in the Orange Book.

The Petitioner is also aware of a Citizen Petition filed and pending with FDA (ID: FDA-2020-P-1626) that requests FDA to designate both Vancomycin HCl for Oral Solution, 250 mg (base)/5 mL and 500 mg (base)/6 mL, approved under ANDA 061667 as RLD for purposes of FDA evaluation of ANDAs for Vancomycin HCl for Oral Solution, 250 mg (base)/5 mL and 500 mg (base)/6 mL.

This Suitability Petition is submitted in anticipation of a favorable determination by the FDA on the RLD designations requested in the said Citizen Petition.

Hydrochloride, For Solution, Oral EQ 250 mg (base)/5 mL by ANI Pharmaceuticals Inc., approved under ANDA A061667, Product Number 002.

The petitioner, hereby, seeks suitability of Vancomycin Hydrochloride for Oral Solution EQ 125 mg (base)/5 mL as an additional strength for submission of an ANDA referencing the prospective ANI RLD.

B. STATEMENT OF GROUNDS

The FD&C Act § 505(j)(2)(A) provides for the submission of an ANDA for a drug product that differs in dosage strength from that of the listed drug provided the FDA has approved a petition that proposed filing such an application.

Furthermore, pursuant to Section 505(j) of the FD&C Act, the ANDA for a proposed drug product is not obligated to use the same container closure system as the one used by the applicant of the RLD. However, the ANDA is required to provide appropriate information to ensure that the proposed drug product has the same conditions of use and the same labeling as the RLD pursuant to Section 505(j)(2)(A)(v) of the FD&C Act.

- This petition is seeking a change in strength (drug concentration) and proposes a new strength of Vancomycin Hydrochloride for Oral Solution equivalent to 125 mg (base)/5 mL

A copy of the relevant excerpt from the current electronic Edition of the *Approved Drug Products with Therapeutic Equivalence Evaluations* is provided as **Attachment 1**. A copy of the current labeling for Vancomycin Hydrochloride, For Solution, Oral EQ 250 mg (base)/5 mL by ANI Pharmaceuticals Inc., approved under ANDA A061667, Product Number 002 is provided as **Attachment 2**.

In addition to the obvious changes in strength, there are no additional changes proposed in labeling, as sought in this petition. However, the active ingredient, dosage form and route of administration, as well as the uses, indications, warnings, and directions for use will remain the same as that of the RLD. The draft *Package Insert* incorporating the proposed additional strength, Vancomycin Hydrochloride for Oral Solution equivalent to 125 mg (base)/5 mL, is provided in **Attachment 3.**

The proposed changes in the strength[2] represent dosage strengths that are clearly contemplated in the labeling of the prospective RLD, Vancomycin Hydrochloride by ANI[3]. According to the Dosage and Administration in the current approved Package Insert for ANI's Vancomycin Hydrochloride, For Solution, Oral EQ 250 mg base/5 mL (*Source*: DailyMed):

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.

It should further be noted that approving an additional strength of Vancomycin Hydrochloride, For Solution, Oral EQ 125 mg (base)/5 mL, based on ANI ANDA as prospective RLD, would not pose any concerns related to safety for the following reasons:

- The currently approved ANI product is available as Vancomycin Hydrochloride, For Solution, Oral EQ 250 mg (base)/5 mL as 80 mL bottle (4 g*), 150 mL bottle (7.5 g*) and 300 mL bottle (15 g*) (* Equivalent to vancomycin). The petitioner proposes the additional strength Vancomycin Hydrochloride for Oral Solution equivalent to 125 mg (base)/5 mL to be available in the following configurations: 150 mL bottle (3.75 g*) and 300 mL bottle (7.5 g*) (* Equivalent to vancomycin).

  Thus, as noted above, the proposed strength of Vancomycin Hydrochloride for Oral Solution EQ 125 mg (base)/5 mL to be available in the configuration of 150 mL bottle (containing 3.75 g of vancomycin) would have a total drug content which is slightly lower than the approved strength of ANI's Vancomycin Hydrochloride, For Solution, Oral EQ 250 mg (base)/5 mL, 80 mL bottle (containing 4 g of vancomycin). Also, the proposed strength of Vancomycin Hydrochloride for Oral Solution EQ 125 mg (base)/5 mL in the second configuration of 300 mL bottle (containing 7.5 g of vancomycin) would

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[2] Petitioner proposes Vancomycin Hydrochloride for Oral Solution USP equivalent to 125 mg per 5 mL vancomycin would be available in the following configurations: 150 mL bottle (3.75 g*) and 300 mL bottle (7.5 g*).
* Equivalent to vancomycin.

[3] Vancomycin Hydrochloride for Oral Solution USP equivalent to 250 mg per 5 mL vancomycin (by ANI) is available as: 80 mL bottle (4 g*), 150 mL bottle (7.5 g*) and 300 mL bottle (15 g*).
* Equivalent to vancomycin.

have a drug content which is equivalent to the approved strength of ANI's Vancomycin Hydrochloride, For Solution, Oral EQ 250 mg (base)/5 mL, 150 mL bottle (containing 7.5 g of vancomycin) and is half of the approved strength of ANI's Vancomycin Hydrochloride, For Solution, Oral EQ 250 mg base/5 mL, 300 mL bottle (containing 15 g of vancomycin). It can, thus, be determined that the proposed strength of Vancomycin Hydrochloride for Oral Solution EQ 125 mg (base)/5 mL would not pose any safety concerns.

- Furthermore, the proposed strength of Vancomycin Hydrochloride for Oral Solution EQ 125 mg (base)/5 mL (EQ 25 mg (base)/mL), based on ANI EQ 250 mg (base)/5 mL ANDA as prospective RLD, should not pose any concerns for approval, including safety concerns, since FDA has approved Vancomycin Hydrochloride for Oral Solution EQ 25 mg/mL under a different RLD (FIRVANQ KIT (vancomycin hydrochloride), For Oral Solution; EQ 25 mg (base)/mL; NDA # N208910, by Azurity Pharmaceuticals Inc.; approved on January 26, 2018), which, to the best of the petitioner's knowledge and information, is currently being sold in market (Source: IQVIA).

In view of the aforesaid, the petitioner's request for the Commissioner to find that a change in strength as proposed in the form of a new strength of Vancomycin Hydrochloride for Oral Solution EQ 125 mg (base)/5 mL, based on ANI's Vancomycin Hydrochloride for Oral Solution EQ 250 mg (base)/5 mL as RLD, should raise no questions of safety and effectiveness, and the Agency should approve the petition.

C. INAPPLICABILITY OF THE PEDIATRIC RESEARCH EQUITY ACT (PREA)

PREA, which is codified at FD&C Act§ 505B, does not apply to a new strength, such as the one proposed in this petition. As such, PREA should not serve as an impediment to the Agency's granting of this petition.

D. ENVIRONMENTAL IMPACT

The petitioner claims a categorical exclusion under 21 CFR 25.31.

E. ECONOMIC IMPACT

The petitioner does not believe that this is applicable in this case but will agree to provide such an analysis if requested by the Agency.

F. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned. This petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which is unfavorable to the petition.

Sincerely,

Michelle R. Ryder

Michelle R. Ryder
cn=Michelle R. Ryder, o=Lachman Consultant Services, Inc., ou, email=m.ryder@lachmanconsultants.com, c=US
2020.12.18 12:33:03 -07'00'

Michelle R. Ryder
Principal Consultant
Lachman Consulting Services, Inc.

Attachments:

- ATTACHMENT 1: Copy of the relevant excerpt from the current electronic Edition of the *Approved Drug Products with Therapeutic Equivalence Evaluations*
- ATTACHMENT 2: Current labeling for Vancomycin Hydrochloride, For Solution, Oral EQ 250 mg (base)/5 mL by ANI Pharmaceuticals Inc., approved under ANDA A061667, Product Number 002, *Source*: DailyMed)
- ATTACHMENT 3: Draft Package Insert Proposed for Vancomycin Hydrochloride for Oral Solution incorporating the proposed additional strength of EQ 125 mg (base)/5 mL

ATTACHMENT 1

Search Results for Proprietary Name, Active Ingredient or Application Number: *vancomycin*

☑ RX ☑ OTC ☑ DISCN

Display records per page
Showing 1 to 6 of 6 entries (filtered from 110 total records)

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	VANCOMYCIN HYDROCHLORIDE	VANCOCIN HYDROCHLORIDE	A061667	FOR SOLUTION	ORAL	EQ 250MG BASE/5ML			RS	ANI PHARMACEUTICALS INC
RX	VANCOMYCIN HYDROCHLORIDE	FIRVANQ KIT	N208910	FOR SOLUTION	ORAL	EQ 25MG BASE/ML		RLD	RS	AZURITY PHARMACEUTICALS INC
RX	VANCOMYCIN HYDROCHLORIDE	FIRVANQ KIT	N208910	FOR SOLUTION	ORAL	EQ 50MG BASE/ML		RLD	RS	AZURITY PHARMACEUTICALS INC
DISCN	VANCOMYCIN HYDROCHLORIDE	VANCOCIN HYDROCHLORIDE	A061667	FOR SOLUTION	ORAL	EQ 500MG BASE/6ML				ANI PHARMACEUTICALS INC
DISCN	VANCOMYCIN HYDROCHLORIDE	VANCOLED	A063321	FOR SOLUTION	ORAL	EQ 250MG BASE/5ML				LEDERLE PARENTERALS INC
DISCN	VANCOMYCIN HYDROCHLORIDE	VANCOLED	A063321	FOR SOLUTION	ORAL	EQ 500MG BASE/6ML				LEDERLE PARENTERALS INC

Showing 1 to 6 of 6 entries (filtered from 110 total records)

ATTACHMENT 2

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.

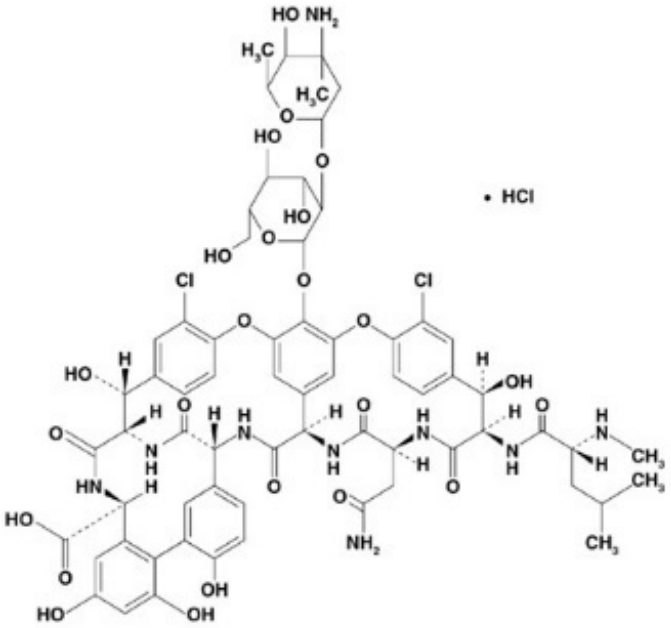
This preparation for the treatment of colitis is for oral use only and is not systemically absorbed. Vancomycin Hydrochloride for Oral Solution must be given orally for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile*. Orally 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 $C_{66}H_{75}Cl_2N_9O_{24}$•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.

PRECAUTIONS

General

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.

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 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.

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.

Information for Patients

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.

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.

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

Anaphylaxis, drug fever, chills, nausea, eosinophilia, rashes (including exfoliative dermatitis), Stevens-Johnson syndrome, toxic epidermal necrolysis, and rare cases of vasculitis have been reported 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.

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 overdosage, contact the National Poison Control Center at 1-800-222-1222 or www.poison.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 03/19

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.

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

10189 Rev 03/19

GTIN: 00362559000000
EXP: MMM 0000
LOT: 123456
SN: A1234567890123

N 62559 83080 5

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)

Registrant - ANI Pharmaceuticals, Inc. (145588013)

Revised: 9/2019 ANI Pharmaceuticals, Inc.

ATTACHMENT 3

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.

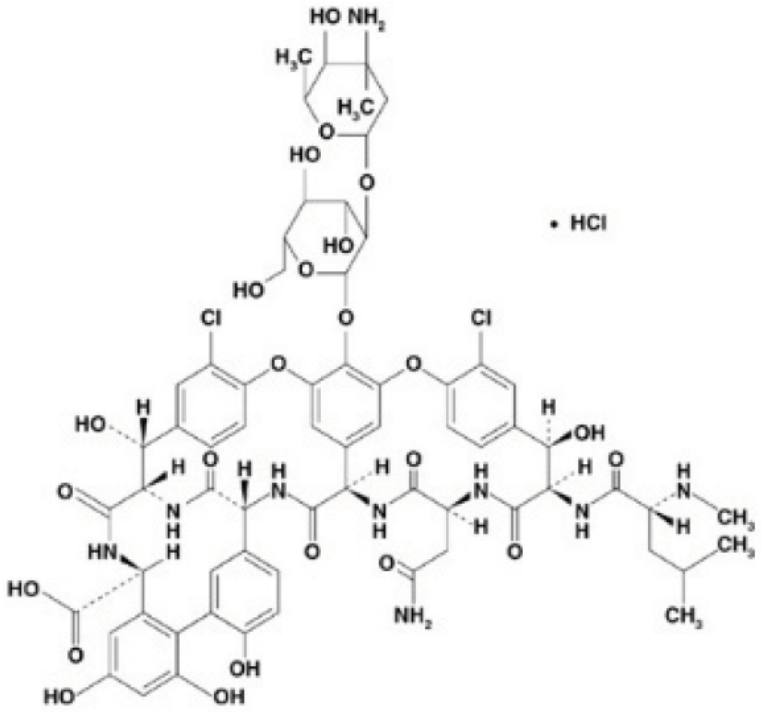
This preparation for the treatment of colitis is for oral use only and is not systemically absorbed. Vancomycin Hydrochloride for Oral Solution must be given orally for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile*. Orally 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 $C_{66}H_{75}Cl_2N_9O24$•HCl. The molecular weight of vancomycin hydrochloride, USP is 1,485.73; 500 mg of the base is equivalent to 0.34 mmol.

Vancomycin hydrochloride, USP 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, USP equivalent to either 125 mg or 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.

PRECAUTIONS

General

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.

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 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.

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.

Information for Patients

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.

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.

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

Anaphylaxis, drug fever, chills, nausea, eosinophilia, rashes (including exfoliative dermatitis), Stevens-Johnson syndrome, toxic epidermal necrolysis, and rare cases of vasculitis have been reported 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.

To report SUSPECTED ADVERSE REACTIONS, contact XXXXName at x-xxx-xxx-xxxx or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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 overdosage, contact the National Poison Control Center at 1-800-222-1222 or www.poison.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 125 mg and 250 mg of vancomycin, respectively. 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 either 125 mg or 250 mg per 5 mL vancomycin is available as:

Vancomycin, USP Strength, Diluent Volume and National Drug Code (NDC) Numbers

	Vancomycin, USP Strength per Bottle	**Diluent for Vancomycin Hydrochloride for Oral Solution, USP**	**NDC Numbers**
125 mg per 5 mL (150 mL bottle)	3.75 g*	147 mL	XXXXX-XXXX-X
125 mg per 5 mL (300 mL bottle)	7.5 g*	295 mL	XXXXX-XXXX-X
250 mg per 5 mL (150 mL bottle)	7.5 g*	145 mL	69238-2091-7
250 mg per 5 mL (300 mL bottle)	15 g*	289 mL	69238-2091-5

* 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.

Distributed by:
XXXXName
XXXXAddress

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