



## 8.5 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 [see *Warnings and Precautions (5.3), Adverse Reactions (6.1) and Clinical Studies (14.1)*].

Patients over 65 years of age may take longer to respond to therapy compared to patients 65 years of age and younger [see *Clinical Studies (14.1)*]. 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.

## 10 OVERDOSAGE

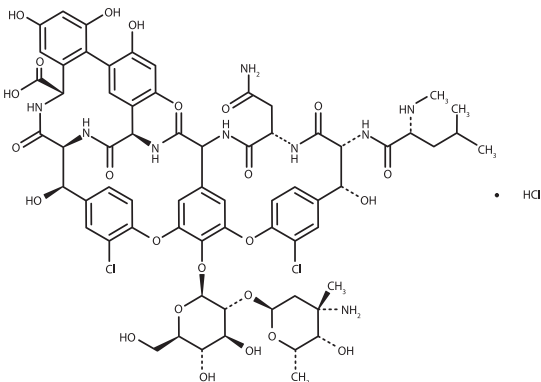
Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed by dialysis. Hemofiltration and hemoperfusion with polysulfone resin have been reported to result in increased vancomycin clearance.

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

## 11 DESCRIPTION

FIRVANQ for oral administration contains the hydrochloride salt of vancomycin, a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*), which has the chemical formula C<sub>66</sub>H<sub>75</sub>Cl<sub>2</sub>N<sub>6</sub>O<sub>24</sub>•HCl. The molecular weight of vancomycin hydrochloride is 1485.71 g/mol.

Vancomycin hydrochloride has the structural formula:



Each FIRVANQ kit contains a bottle of vancomycin hydrochloride USP, as white to almost white or tan to brown powder for oral solution, and a bottle of pre-measured Grape-Flavored Diluent, in the strengths and volumes listed in Table 3.

Vancomycin Strength per Bottle	Equivalent Amount of Vancomycin Hydrochloride per Bottle	Diluent Volume for FIRVANQ	Vancomycin Concentration after Reconstitution
3.75 g	3.84 g	147 mL	25 mg/mL
7.5 g	7.7 g	295 mL	
7.5 g	7.7 g	145 mL	50 mg/mL
15.0 g	15.4 g	289 mL	

The Grape-Flavored Diluent used to reconstitute the oral solution contains: artificial grape flavor, citric acid (anhydrous), D&C Yellow No. 10, FD&C Red No. 40, purified water, sodium benzoate and sucralose.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Vancomycin is an antibacterial drug [see *Microbiology (12.4)*].

### 12.3 Pharmacokinetics

Vancomycin is poorly absorbed after oral administration. During multiple dosing of vancomycin hydrochloride capsules at 250 mg every 8 hours for 7 doses, fecal concentrations of vancomycin in volunteers exceeded 100 mcg/g in the majority of samples. No blood concentrations were detected and urinary recovery did not exceed 0.76%. In anephric subjects with no inflammatory bowel disease who received vancomycin oral solution 2 g for 16 days, blood concentrations of vancomycin were ≤ 0.66 mcg/mL in 2 of 5 subjects. No measurable blood concentrations were attained in the other 3 subjects. Following doses of 2 g daily, concentrations of drug were > 3100 mcg/g in the feces and < 1 mcg/mL in the serum of subjects with normal renal function who had *C. difficile*-associated diarrhea. After multiple-dose oral administration of vancomycin, measurable serum concentrations may occur in patients with active *C. difficile*-associated diarrhea, and, in the presence of renal impairment, the possibility of accumulation exists. It should be noted that the total systemic and renal clearances of vancomycin are reduced in the elderly [see *Use in Specific Populations (8.5)*].

### 12.4 Microbiology

#### Mechanism of Action

The bactericidal action of vancomycin against the vegetative cells of *C. difficile* and *S. aureus* results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis.

#### Mechanism of Resistance

##### *C. difficile*

Isolates of *C. difficile* generally have vancomycin minimal inhibitory concentrations (MICs) of < 1 mcg/mL; however, vancomycin MICs ranging from 4 mcg/mL to 16 mcg/mL have been reported. The mechanism which mediates *C. difficile*'s decreased susceptibility to vancomycin has not been fully elucidated.

##### *S. aureus*

*S. aureus* isolates with vancomycin MICs as high as 1024 mcg/mL have been reported. The exact mechanism of this resistance is not clear but is believed to be due to cell wall thickening and potentially the transfer of genetic material.

Vancomycin has been shown to be active against susceptible isolates of the following bacteria in clinical infections [see *Indications and Usage (1)*].

##### Anaerobic gram-positive bacteria

*C. difficile* isolates associated with *C. difficile*-associated diarrhea.

##### Gram-positive bacteria

*S. aureus* (including methicillin-resistant isolates) associated with enterocolitis.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term carcinogenesis studies in animals have been conducted.

At concentrations up to 1000 mcg/mL, vancomycin had no mutagenic effect *in vitro* in the mouse lymphoma forward mutation assay or the primary rat hepatocyte unscheduled DNA synthesis assay. The concentrations tested *in vitro* were above the peak plasma vancomycin concentrations of 20 to 40 mcg/mL usually achieved in humans after slow infusion of the maximum recommended dose of 1 g. Vancomycin had no mutagenic effect *in vivo* in the Chinese hamster sister chromatid exchange assay (400 mg/kg IP) or the mouse micronucleus assay (800 mg/kg IP).

No definitive fertility studies have been conducted.

## 14 CLINICAL STUDIES

### 14.1 Diarrhea Associated with *Clostridium difficile*

In two trials, vancomycin hydrochloride 125 mg orally four times daily for 10 days was evaluated in 266 adult subjects with *C. difficile*-associated diarrhea (CDAD). Enrolled subjects were 18 years of age or older and received no more than 48 hours of treatment with oral vancomycin hydrochloride or oral/intravenous metronidazole in the 5 days preceding enrollment. CDAD was defined as ≥ 3 loose or watery bowel movements within the 24 hours preceding enrollment, and the presence of either *C. difficile* toxin A or B, or pseudomembranes on endoscopy within the 72 hours preceding enrollment. Subjects with fulminant *C. difficile* disease, sepsis with hypotension, ileus, peritoneal signs, or severe hepatic disease were excluded.

Efficacy analyses were performed on the Full Analysis Set (FAS), which included randomized subjects who received at least one dose of vancomycin hydrochloride and had any post-dosing investigator evaluation data (N = 259; 134 in Trial 1 and 125 in Trial 2).

The demographic profile and baseline CDAD characteristics of enrolled subjects were similar in the two trials. Vancomycin hydrochloride-treated subjects had a median age of 67 years, were mainly white (93%), and male (52%). CDAD was classified as severe (defined as 10 or more unformed bowel movements per day or white blood cell count (WBC) ≥ 15000/mm<sup>3</sup>) in 25% of subjects, and 47% were previously treated for CDAD.

Efficacy was assessed by using clinical success, defined as diarrhea resolution and the absence of severe abdominal discomfort due to CDAD, on Day 10. An additional efficacy endpoint was the time to resolution of diarrhea, defined as the beginning of diarrhea resolution that was sustained through the end of the prescribed active treatment period.

The results for clinical success for vancomycin hydrochloride-treated subjects in both trials are shown in Table 4.

	Clinical Success Rate Vancomycin Hydrochloride % (N)	95% Confidence Interval
Trial 1	81.3 (134)	(74.4, 88.3)
Trial 2	80.8 (125)	(73.5, 88.1)

The median time to resolution of diarrhea was 5 days and 4 days in Trial 1 and Trial 2, respectively. For subjects older than 65 years of age, the median time to resolution was 6 days and 4 days in Trial 1 and Trial 2, respectively. In subjects with diarrhea resolution at end-of-treatment with vancomycin hydrochloride, recurrence of CDAD during the following four weeks occurred in 25 of 107 (23%) and 18 of 102 (18%) in Trial 1 and Trial 2, respectively.

Restriction Endonuclease Analysis (REA) was used to identify *C. difficile* baseline isolates in the BI group. In Trial 1, the vancomycin hydrochloride-treated subjects were classified at baseline as follows: 31 (23%) with BI strain, 69 (52%) with non-BI strain, and 34 (25%) with unknown strain. Clinical success rates were 87% for BI strain, 81% for non-BI strain, and 76% for unknown strain. In subjects with diarrhea resolution at end-of-treatment with vancomycin hydrochloride, recurrence of CDAD during the following four weeks occurred in 7 of 26 subjects with BI strain, 12 of 56 subjects with non-BI strain, and 6 of 25 subjects with unknown strain.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### How Supplied

Each FIRVANQ kit contains a bottle of vancomycin hydrochloride USP, as white to almost white or tan to brown powder for oral solution, and a bottle of pre-measured Grape-Flavored Diluent, in the strengths and volumes listed in Table 5.

Vancomycin Strength per Bottle	Diluent Volume for FIRVANQ	NDC Numbers
3.75 g	147 mL	65628-204-05
7.5 g	295 mL	65628-205-10
7.5 g	145 mL	65628-206-05
15.0 g	289 mL	65628-208-10

### Storage and Handling

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

Store reconstituted solutions of FIRVANQ at 2°C to 8°C [see *Dosage and Administration (2.4)*].

Do not freeze. Keep container tightly closed. Protect from light.

## 17 PATIENT COUNSELING INFORMATION

### Severe Dermatologic Reactions

Advise patients about the signs and symptoms of serious skin manifestations. Instruct patients to stop taking FIRVANQ immediately and promptly seek medical attention at the first signs or symptoms of skin rash, mucosal lesions or blisters, [see *Warnings and Precautions (5.5)*].

### Antibacterial Resistance

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

### Important Administration and Storage Instructions

Instruct the patient or caregiver to [see *Dosage and Administration (2.4)*]:

- Shake the reconstituted solutions of FIRVANQ well before each use and to use an oral dosing device that measures the appropriate volume of the oral solution in milliliters.
- Store the reconstituted solutions of FIRVANQ at refrigerated conditions, 2° C to 8° C (36° F to 46° F) when not in use.
- Discard reconstituted solutions of FIRVANQ after 14 days, or if it appears hazy or contains particulates.

Manufactured for:



Wilmington, MA 01887 USA

U. S. Patent 10,493,028

This product's label may have been updated. For current Full Prescribing Information, please visit [www.FIRVANQ.com](http://www.FIRVANQ.com)