

ADVERSE REACTIONS

Infusion-Related Events

During or soon after rapid infusion of vancomycin hydrochloride for injection, patients may develop anaphylactoid reactions, including hypotension (see ANIMAL PHARMACOLOGY), wheezing, dyspnea, urticaria, or pruritus. Rapid infusion may also cause flushing of the upper body ("red neck") or pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may persist for several hours. Such events are infrequent if vancomycin hydrochloride for injection is given by a slow infusion over 60 minutes. In studies of normal volunteers, infusion-related events did not occur when vancomycin hydrochloride for injection was administered at a rate of 10 mg/min or less.

Nephrotoxicity

Systemic vancomycin exposure may result in acute kidney injury (AKI). The risk of AKI increases as systemic exposure/serum levels increase. Additional risk factors for AKI in patients receiving vancomycin include receipt of concomitant drugs known to be nephrotoxic, in patients with pre-existing renal impairment or with co-morbidities that predispose to renal impairment. Interstitial nephritis has also been reported in patients receiving vancomycin.

Gastrointestinal

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS) (Appears prior to Ototoxicity in the NDA).

Ototoxicity

A few dozen cases of hearing loss associated with 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 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. Although a causal relationship has not been established, reversible agranulocytosis (granulocytes <500/mm³) has been reported rarely.

Phlebitis

Inflammation at the injection site has been reported.

Miscellaneous

Infrequently, patients have been reported to have had anaphylaxis, drug fever, nausea, chills, eosinophilia, rashes including exfoliative dermatitis, linear IgA bullous dermatosis, Stevens-Johnson syndrome, toxic epidermal necrolysis and vasculitis in association with the administration of vancomycin.

Chemical peritonitis has been reported following intraperitoneal administration (see PRECAUTIONS)

POST MARKETING REPORTS

The following adverse reactions have been identified during post-approval use of vancomycin. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

To report SUSPECTED ADVERSE REACTIONS, contact Xellia Pharmaceuticals USA, LLC at safety@xellia.com or 1-833-295-6953 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. The median lethal intravenous dose is 319 mg/kg in rats and 400 mg/kg in mice.

To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the Physicians' Desk Reference (PDR). In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

DOSAGE AND ADMINISTRATION

The intent of the pharmacy bulk package for this product is for preparation of solutions for IV infusion only.

Infusion-related events are related to both the concentration and the rate of administration of vancomycin. Concentrations of no more than 5 mg/mL and rates of no more than 10 mg/min, are recommended in adults (see also age-specific recommendations). In selected patients in need of fluid restriction, a concentration up to 10 mg/mL may be used; use of such higher concentrations may increase the risk of infusion-related events. An infusion rate of 10 mg/min or less is associated with fewer infusion-related events (see ADVERSE REACTIONS). Infusion-related events may occur, however, at any rate or concentration.

Patients With Normal Renal Function

Adults

The usual daily intravenous dose is 2 g divided either as 500 mg every 6 hours or 1 g every 12 hours. Each dose should be administered at no more than 10 mg/min or over a period of at least 60 minutes, whichever is longer. Other patient factors, such as age or obesity, may call for modification of the usual intravenous daily dose.

Pediatric patients

The usual intravenous dosage of vancomycin is 10 mg/kg per dose given every 6 hours. Each dose should be administered over a period of at least 60 minutes. Close monitoring of serum concentrations of vancomycin may be warranted in these patients.

Neonates

In pediatric patients up to the age of 1 month, the total daily intravenous dosage may be lower. In neonates, an initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours for neonates in the 1st week of life and every 8 hours thereafter up to the age of 1 month. Each dose should be administered over 60 minutes. In premature infants, vancomycin clearance decreases as postconceptional age decreases. Therefore, longer dosing intervals may be necessary in premature infants. Close monitoring of serum concentrations of vancomycin is recommended in these patients.

Patients With Impaired Renal Function and Elderly Patients

Dosage adjustment must be made in patients with impaired renal function. In premature infants and the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Measurement of vancomycin serum concentrations can be helpful in optimizing therapy, especially in seriously ill patients with changing renal function. Vancomycin serum concentrations can be determined by use of microbiologic assay, radioimmunoassay, fluorescence polarization immunoassay, fluorescence immunoassay, or high-pressure liquid chromatography. If creatinine clearance can be measured or estimated accurately, the dosage for most patients with renal impairment can be calculated using the following table. The dosage of vancomycin hydrochloride for injection per day in mg is about 15 times the glomerular filtration rate in mL/min (see following table).

DOSAGE TABLE FOR VANCOMYCIN IN PATIENTS WITH IMPAIRED RENAL FUNCTION

(Adapted from Moellering et al.)

DOSAGE TABLE FOR VANCOMYCIN IN PATIENTS WITH IMPAIRED RENAL FUNCTION (Adapted from Moellering et al')	
Creatinine Clearance mL/min	Vancomycin Dose mg/24 h
100	1,545
90	1,390
80	1,235
70	1,080
60	925
50	770
40	620
30	465
20	310
10	155

The initial dose should be no less than 15 mg/kg, even in patients with mild to moderate renal insufficiency. The table is not valid for functionally anephric patients. For such patients, an initial dose of 15 mg/kg of body weight should be given to achieve prompt therapeutic serum concentrations. The dose required to maintain stable concentrations is 1.9 mg/kg/24 hr. In patients with marked renal impairment, it may be more convenient to give maintenance doses of 250 to 1,000 mg once every several days rather than administering the drug on a daily basis. In anuria, a dose of 1,000 mg every 7 to 10 days has been recommended. When only serum creatinine is known, the following formula (based on sex, weight and age of the patient) may be used to calculate creatinine clearance. Calculated creatinine clearances (mL/min) are only estimates. The creatinine clearance should be measured promptly.

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{\displaystyle \ {\frac {[Weight (kg) \times (140 - age in years)]}{72 \times serum creatinine concentration (mg/dL)}}}

Women: 0.85 x above value

The serum creatinine must represent a steady state of renal function. Otherwise, the estimated value for creatinine clearance is not valid. Such a calculated clearance is an overestimate of actual clearance in patients with conditions: (1) characterized by decreasing renal function, such as shock, severe heart failure, or oliguria; (2) in which a normal relationship between muscle mass and total body weight is not present, such as in obese patients or those with liver disease, edema, or ascites; and (3) accompanied by debilitation, malnutrition, or inactivity. The safety and efficacy of vancomycin administration by the intrathecal (intralubar or intraventricular) routes have not been established. Intermittent infusion is the recommended method of administration.

Compatibility with Other Drugs and IV Fluids

The following diluents are physically and chemically compatible (with 4 g/L vancomycin hydrochloride):

5% Dextrose Injection, USP

5% Dextrose Injection and 0.9% Sodium Chloride Injection, USP

Lactated Ringer’s Injection, USP

5% Dextrose and Lactated Ringer’s Injection

Normosol®-M and 5% Dextrose

0.9% Sodium Chloride Injection, USP

Isolyte® E

Good professional practice suggests that compounded admixtures should be administered as soon after preparation as is feasible.

Vancomycin solution has a low pH and may cause physical instability of other compounds.

Mixtures of solutions of vancomycin and beta-lactam antibiotics have been shown to be physically incompatible. The likelihood of precipitation increases with higher concentrations of vancomycin. It is recommended to adequately flush the intravenous lines between the administration of these antibiotics. It is also recommended to dilute solutions of vancomycin to 5 mg/mL or less.

Although intravitreal injection is not an approved route of administration for vancomycin, precipitation has been reported after intravitreal injection of vancomycin and ceftazidime for endophthalmitis using different syringes and needles. The precipitates dissolved gradually, with complete clearing of the vitreous cavity over two months and with improvement of visual acuity.

PREPARATION AND STABILITY

CAUTION: NOT TO BE DISPENSED AS A UNIT

DIRECTIONS FOR PROPER USE OF PHARMACY BULK PACKAGE

Not for direct infusion. The pharmacy bulk package is for use in the Pharmacy Admixture Service only in a suitable work area such as a laminar flow hood. Using aseptic technique, the closure may be penetrated only one time after reconstitution using a suitable sterile transfer device or dispensing set, which allows measured dispensing of the contents. Use of a syringe and needle is not recommended as it may cause leakage. After entry use entire contents of the Pharmacy Bulk Package bottle promptly. The entire contents of the Pharmacy Bulk Package bottle should be dispensed within **4 hours** after initial entry. A maximum time of **4 hours** from the initial entry may be allowed to complete fluid aliquoting/transferring operations. Discard the container no later than **4 hours** after initial closure puncture. This time limit should begin with the introduction of solvent or diluent into the Pharmacy Bulk Package bottle.

Preparation and Stability

10 g Pharmacy Bulk Package bottle

At the time of use, reconstitute by adding 95 mL of Sterile Water for Injection, USP to the 10 g bottle of dry, sterile vancomycin powder. The resultant solution will contain vancomycin equivalent to 500 mg/5 mL (1 g/10 mL). AFTER RECONSTITUTION, FURTHER DILUTION IS REQUIRED.

Reconstituted solutions of vancomycin (500 mg/5 mL) must be further diluted in at least 100 mL of a suitable infusion solution. For doses of 1 gram (10 mL), at least 200 mL of solution must be used. The desired dose diluted in this manner should be administered by intermittent IV infusion over a period of at least 60 minutes.

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration, whenever solution and container permit.

For Oral Administration

Oral vancomycin is used in treating antibiotic-associated pseudomembranous colitis caused by *C. difficile* and for staphylococcal enterocolitis. Vancomycin is not effective by the oral route for other types of infections. The usual adult total daily dosage is 500 mg to 2 g given in 3 or 4 divided doses for 7 to 10 days. The total daily dose in children is 40 mg/kg of body weight in 3 or 4 divided doses for 7 to 10 days. The total daily dosage should not exceed 2 g. The appropriate dose may be diluted in 1 oz of water and given to the patients to drink. Common flavoring syrups may be added to the solution to improve the taste for oral administration. The diluted solution may be administered via a nasogastric tube.

HOW SUPPLIED

NDC No.

70594-048-01 Vancomycin Hydrochloride for Injection, USP equivalent to 10 g vancomycin in a Pharmacy Bulk Package Bottle, packaged individually

Store dry powder at 20° to 25°C (68° to 77°F)[see USP Controlled Room temperature] in original container.

Bottle stoppers do not contain natural rubber latex.

ANIMAL PHARMACOLOGY

In animal studies, hypotension and bradycardia occurred in dogs receiving an intravenous infusion of vancomycin, 25 mg/kg, at a concentration of 25 mg/mL and an infusion rate of 13.3 mL/min.

REFERENCES:

- Moellering RC, Krogstad DJ, Greenblatt DJ: Vancomycin therapy in patients with impaired renal function: A nomogram for dosage. Ann Inter Med 1981;94:343.

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PHARMACEUTICALS

