STERILE VANCOMYCIN HYDROCHLORIDE, USP

ADD-Vantage® Vials R_x only

This proposed draft package insert is derived from the currently approved package insert for ANDA 62-933, Sterile Vancomycin Hydrochloride, USP, ADD-Vantage® Vial. All proposed changes have been annotated for ease of review.

NOTE: An appropriate alternative proprietary or non-proprietary name will be substituted throughout to describe the "ADD-Vantage®" vial.

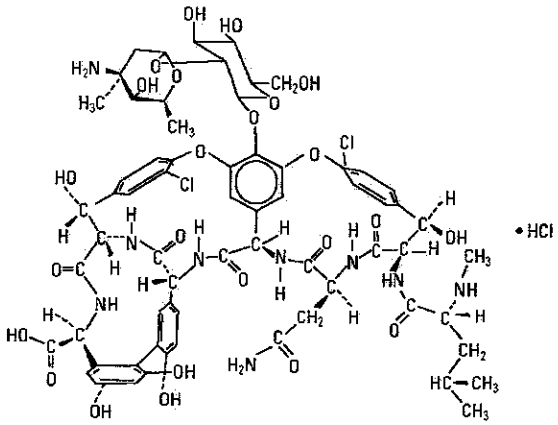
To reduce the development of drug-resistant bacteria and maintain the effectiveness of vancomycin and other antibacterial drugs, vancomycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Sterile Vancomycin Hydrochloride, USP, intravenous, is a chromatographically purified tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*) and has the molecular formula $C_{66}H_{75}Cl_2N_9O_{24}$ • HCl. The molecular weight is 1485.74; 500 mg of the base is equivalent to 0.34 mmol, 750 mg of the base is equivalent to 0.51 mmol and 1 g of the base is equivalent to 0.67 mmol.

mmol for 750 mg added

Vancomycin HCl has the following structural formula:



The vials contain sterile vancomycin hydrochloride equivalent to either 500 mg, 750 mg or 1 g vancomycin activity for reconstitution in the ADD-Vantage flexible diluent container containing 5% dextrose injection or 0.9% sodium chloride injection. Vancomycin Hydrochloride is an off-white lyophilized powder. May contain hydrochloric acid and/or sodium hydroxide for pH adjustment. When reconstituted in water, it forms a clear solution with a pH of 4.0 (2.5 to 4.5). This product is oxygen sensitive.

750 mg strength added

The solutions contain no bacteriostat, antimicrobial agent (except vancomycin) or buffer and are intended for

use only as a single-dose injection only with the ADD-Vantage Flexible Diluent Container.

CLINICAL PHARMACOLOGY

Vancomycin is poorly absorbed after oral administration; it is given intravenously for therapy of systemic infections. Intramuscular injection is painful.

In subjects with normal kidney function, multiple intravenous dosing of 1 g of vancomycin (15 mg/kg) infused over 60 minutes produces mean plasma concentrations of approximately 63 mcg/mL immediately after the completion of infusion, mean plasma concentrations of approximately 23 mcg/mL two hours after infusion, and mean plasma concentrations of approximately 8 mcg/mL eleven hours after the end of the infusion. Multiple dosing of 500 mg infused over 30 minutes produces mean plasma concentrations of about 49 mcg/mL at the completion of infusion, mean plasma concentrations of about 19 mcg/mL two hours after infusion, and mean plasma concentrations of about 10 mcg/mL six hours after infusion. The plasma concentrations during multiple dosing are similar to those after a single dose.

The mean elimination half-life of vancomycin from plasma is 4 to 6 hours in subjects with normal renal function. In the first 24 hours, about 75% of an administered dose of vancomycin is excreted in urine by glomerular filtration. Mean plasma clearance is about 0.058 L/kg/hr, and mean renal clearance is about 0.048 L/kg/hr. Renal dysfunction slows excretion of vancomycin. In anephric patients, the average half-life of elimination is 7.5 days. The distribution coefficient is from 0.3 to 0.43 L/kg. There is no apparent metabolism of the drug. About 60% of an intraperitoneal dose of vancomycin administered during peritoneal dialysis is absorbed systemically in six hours. Serum concentrations of about 10 mcg/mL are achieved by intraperitoneal injection of 30 mg/kg of vancomycin. Although vancomycin is not effectively removed by either hemodialysis or peritoneal dialysis, there have been reports of increased vancomycin clearance with hemoperfusion and hemofiltration.

Total systemic and renal clearance of vancomycin may be reduced in the elderly.

Vancomycin is approximately 55% serum protein bound as measured by ultrafiltration at vancomycin serum concentrations of 10 to 100 mcg/mL. After I.V. administration of vancomycin hydrochloride, inhibitory

concentrations are present in pleural, pericardial, ascitic, and synovial fluids; in urine; in peritoneal dialysis fluid; and in atrial appendage tissue. Vancomycin hydrochloride does not readily diffuse across normal meninges into the spinal fluid; but, when the meninges are inflamed, penetration into the spinal fluid occurs.

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. There is no cross-resistance between vancomycin and other antibiotics. Vancomycin is active against staphylococci, including *Staphylococcus aureus* and *Staphylococcus epidermidis* (including heterogeneous methicillin-resistant strains); streptococci, including *Streptococcus pyogenes*, *Streptococcus pneumoniae* (including penicillin-resistant strains), *Streptococcus agalactiae*, the viridans group, *Streptococcus bovis*, and enterococci (e.g., *Enterococcus faecalis* [formerly *Streptococcus faecalis*]); *Clostridium difficile* (e.g., toxigenic strains implicated in pseudomembranous enterocolitis); and diphtheroids. Other organisms that are susceptible to vancomycin *in vitro* include *Listeria monocytogenes*, *Lactobacillus* species, *Actinomyces* species, *Clostridium* species, and *Bacillus* species.

In vitro resistance to vancomycin has been reported among some enterococcal and staphylococcal isolates.

Vancomycin is not active *in vitro* against gram-negative bacilli, mycobacteria, or fungi.

Synergy:

The combination of vancomycin and an aminoglycoside acts synergistically *in vitro* against many strains of *S. aureus*, nonenterococcal group D streptococci, enterococci, and *Streptococcus* species (viridans group).

Disk Susceptibility Tests: The standardized disk method described by the National Committee for Clinical Laboratory Standards has been recommended to test susceptibility to vancomycin. Results of standard susceptibility tests with a 30 mcg vancomycin hydrochloride disk should be interpreted according to the following criteria: Susceptible organisms produce zones greater than or equal to 12 mm, indicating that the test organism is likely to respond to therapy. Organisms that produce zones of 10 or 11 mm are considered to be of intermediate susceptibility. Organisms in this category are likely to respond if the infection is confined to tissues or

fluids in which high antibiotic concentrations are attained. Resistant organisms produce zones of 9 mm or less, indicating that other therapy should be selected.

Using a standardized dilution method, a bacterial isolate may be considered susceptible if the MIC value for vancomycin is 4 mcg/mL or less. Organisms are considered resistant to vancomycin if the MIC is greater than or equal to 16 mcg/mL. Organisms having an MIC value of less than
16 mcg/mL but greater than 4 mcg/mL are considered to be of intermediate susceptibility.[1-2]

Standardized procedures require the use of laboratory control organisms. The 30 mcg vancomycin disk should give zone diameters between 15 and 19 mm for *S. aureus* ATCC 25923. As with the standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard vancomycin powder should give MIC values in the range of 0.5 mcg/mL to 2.0 mcg/mL for *S. aureus* ATCC 29213. For *E. faecalis* ATCC 29212, the MIC range should be 1.0 to 4.0 mcg/mL.

INDICATIONS AND USAGE

Vancomycin hydrochloride is indicated for the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (ß-lactam-resistant) staphylococci. It is indicated for penicillin-allergic patients, for patients who cannot receive or who have failed to respond to other drugs, including the penicillins or cephalosporins, and for infections caused by vancomycin-susceptible organisms that are resistant to other antimicrobial drugs. Vancomycin hydrochloride is indicated for initial therapy when methicillin-resistant staphylococci are suspected, but after susceptibility data are available, therapy should be adjusted accordingly.

Vancomycin hydrochloride is effective in the treatment of staphylococcal endocarditis. Its effectiveness has been documented in other infections due to staphylococci, including septicemia, bone infections, lower respiratory tract infections, skin and skin-structure infections. When staphylococcal infections are localized and purulent, antibiotics are used as adjuncts to appropriate surgical measures.

Vancomycin hydrochloride has been reported to be effective alone or in combination with an aminoglycoside for endocarditis caused by *S. viridans* or *S. bovis*. For endocarditis caused by enterococci (e.g., *E. faecalis*),

vancomycin hydrochloride has been reported to be effective only in combination with an aminoglycoside.

Vancomycin hydrochloride has been reported to be effective for the treatment of diphtheroid endocarditis. Vancomycin hydrochloride has been used successfully in combination with either rifampin, an aminoglycoside, or both in early-onset prosthetic valve endocarditis caused by *S. epidermidis* or diphtheroids.

Specimens for bacteriologic cultures should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to vancomycin hydrochloride.

The parenteral form of vancomycin hydrochloride may be administered orally for treatment of antibiotic-associated pseudomembranous colitis produced by *C. difficile* and for staphylococcal enterocolitis. Parenteral administration of vancomycin hydrochloride alone is of unproven benefit for these indications. **Vancomycin hydrochloride is not effective by the oral route for other types of infection.**

Although no controlled clinical efficacy studies have been conducted, intravenous vancomycin has been suggested by the American Heart Association and the American Dental Association as prophylaxis against bacterial endocarditis in penicillin-allergic patients who have congenital heart disease or rheumatic or other acquired valvular heart disease when these patients undergo dental procedures or surgical procedures of the upper respiratory tract.

NOTE: When selecting antibiotics for the prevention of bacterial endocarditis, the physician or dentist should read the full joint statement of the American Heart Association and the American Dental Association.[3]

To reduce the development of drug-resistant bacteria and maintain the effectiveness of vancomycin and other antibacterial drugs, vancomycin 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.

CONTRAINDICATION

Sterile vancomycin hydrochloride, USP is contraindicated in patients with known hypersensitivity to this antibiotic.

WARNINGS

Rapid bolus administration (e.g., over several minutes) may be associated with exaggerated hypotension and, rarely, cardiac arrest.

Vancomycin hydrochloride should be administered in a dilute solution over a period of not less than 60 minutes to avoid rapid-infusion-related reactions. Stopping the infusion usually results in a prompt cessation of these reactions.

Ototoxicity has occurred in patients receiving vancomycin hydrochloride. It may be transient or permanent. It has been reported mostly in patients who have been given excessive doses, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside. Vancomycin should be used with caution in patients with renal insufficiency because the risk of toxicity is appreciably increased by high, prolonged blood concentrations.

Dosage of vancomycin hydrochloride must be adjusted for patients with renal dysfunction (see ***PRECAUTIONS*** and ***DOSAGE AND ADMINISTRATION***).

Pseudomembranous colitis has been reported with nearly all antibacterial agents including vancomycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug effective against *C. difficile* colitis.

PRECAUTIONS

General

Clinically significant serum concentrations have been reported in some patients who have taken multiple oral doses of vancomycin for active *C. difficile*-induced pseudomembranous colitis.

Prolonged use of vancomycin may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

In order to minimize the risk of nephrotoxicity when treating patients with underlying renal dysfunction or patients receiving concomitant therapy with an aminoglycoside, serial monitoring of renal function should be performed and particular care should be taken in following appropriate dosing schedules (see ***DOSAGE AND ADMINISTRATION***).

Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity.

Reversible neutropenia has been reported in patients receiving vancomycin hydrochloride (see ***ADVERSE REACTIONS***). Patients who will undergo prolonged therapy with vancomycin hydrochloride or those who are receiving concomitant drugs which may cause neutropenia should have periodic monitoring of the leukocyte count.

Vancomycin hydrochloride is irritating to tissue and must be given by a secure intravenous route of administration. Pain, tenderness, and necrosis occur with intramuscular injection of vancomycin hydrochloride or with inadvertent extravasation. Thrombophlebitis may occur, the frequency and severity of which can be minimized by administering the drug slowly as a dilute solution (2.5 to 5 g/L) and by rotating the sites of infusion.

There have been reports that the frequency of infusion-related events (including hypotension, flushing, erythema, urticaria, and pruritus) increases with the concomitant administration of anesthetic agents. Infusion-related events may be minimized by the administration of vancomycin hydrochloride as a 60-minute infusion prior to anesthetic induction.

The safety and efficacy of vancomycin administration by the intrathecal (intralumbar or intraventricular) routes have not been assessed.

Reports have revealed that administration of sterile vancomycin HCl by the intraperitoneal route during continuous ambulatory peritoneal dialysis (CAPD) has resulted in a syndrome of chemical peritonitis. To date, this syndrome has ranged from a cloudy dialysate alone to a cloudy dialysate accompanied by variable degrees of abdominal pain and fever. This syndrome appears to be

short-lived after discontinuation of intraperitoneal vancomycin.

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

Drug Interactions

Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing (see **Pediatric Use**) and anaphylactoid reactions
(see ***ADVERSE REACTIONS***).

Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymyxin B, colistin, viomycin, or cisplatin, when indicated, requires careful monitoring.

Pregnancy: Teratogenic Effects, *Category C*—Animal reproduction studies have not been conducted with Vancomycin HCl. It is not known whether Vancomycin HCl can affect reproduction capacity. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of Vancomycin HCl on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancomycin HCl 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 should be given to a pregnant woman only if clearly needed.

Nursing Mothers

Vancomycin is excreted in human milk. Caution should be exercised when vancomycin is administered to a nursing woman. Because of the potential for adverse events, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

In premature neonates and young infants, it may be appropriate to confirm desired vancomycin serum

concentrations. Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing in pediatric patients (see *ADVERSE REACTIONS*).

Geriatrics

The natural decrement of glomerular filtration with increasing age may lead to elevated vancomycin serum concentrations if dosage is not adjusted. Vancomycin dosage schedules should be adjusted in elderly patients (see *DOSAGE AND ADMINISTRATION*).

Information for Patients

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

ADVERSE REACTIONS

Infusion-Related Events: During or soon after rapid infusion of vancomycin hydrochloride, 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 Man Syndrome") 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 is given by a slow infusion over 60 minutes. In studies of normal volunteers, infusion-related events did not occur when vancomycin HCl was administered at a rate of 10 mg/min or less.

Nephrotoxicity: Rarely, renal failure, principally manifested by increased serum creatinine or BUN concentrations, especially in patients given large doses of vancomycin, has been reported. Rare cases of interstitial nephritis have been reported. Most of these have occurred in patients who were given aminoglycosides concomitantly or who had preexisting kidney dysfunction. When vancomycin hydrochloride was discontinued, azotemia resolved in most patients.

Ototoxicity: A few dozen cases of hearing loss associated with vancomycin hydrochloride 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 one week or more after onset of therapy with vancomycin hydrochloride 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 hydrochloride is discontinued. Thrombocytopenia has rarely been reported.

Although a causal relationship has not been established, reversible agranulocytosis (granulocytes $< 500/mm^3$) has been reported rarely.

Phlebitis: Inflammation at the injection site has been reported.

Gastrointestinal: Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see ***WARNINGS***).

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 rare cases of vasculitis in association with the administration of vancomycin.

Chemical peritonitis has been reported following intraperitoneal administration of vancomycin (see ***PRECAUTIONS***).

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

Infusion-related events are related to both concentration and 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. Infusion-related events may occur, however, at any rate or concentration.

The use of ADD-Vantage vials of vancomycin hydrochloride is indicated only when doses of 500 mg or 1 g are appropriate. Patient factors, such as renal function and age, are critical in calculating correct dosage regimens (see below). If doses of 500 mg or 1 g are determined to be inappropriate, conventional vials of vancomycin hydrochloride (500 mg, 10-mL size, or 1 g, 20-mL size) should be used. ADD-VANTAGE VIALS OF VANCOMYCIN HYDROCHLORIDE SHOULD NOT BE USED IN NEONATES, INFANTS, OR PEDIATRIC PATIENTS WHO REQUIRE DOSES OF LESS THAN 500 MG.

Patients with Normal Renal Function

Adults: The usual daily intravenous dose is 2 g divided either as 500 mg every six 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 daily dose.

Pediatric Patients: The usual intravenous dosage of vancomycin hydrochloride is 10 mg/kg per dose given every six hours. Each dose should be administered over a period of at least 60 minutes.

Infants and Neonates: In neonates and young infants, the total daily intravenous dosage may be lower. In both neonates and infants, an initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours for neonates in the first week of life and every eight hours thereafter up to the age of one month. Each dose should be administered over 60 minutes. Close monitoring of serum concentrations of vancomycin may be warranted 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 per day in mg is about 15 times the glomerular filtration rate in mL/min:

DOSAGE TABLE FOR VANCOMYCIN IN PATIENTS WITH IMPAIRED RENAL FUNCTION (Adapted from Moellering et al)[4]

Creatinine Clearance mL/min	Vancomycin Dose mg/24 h
100	1545
90	1390
80	1235
70	1080
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 h. In patients with marked renal impairment, it may be more convenient to give maintenance doses of 250 to 1000 mg once every several days rather than administering the drug on a daily basis. In anuria, a dose of 1000 mg every 7 to 10 days has been recommended.

When only serum creatinine concentration 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.

Men: $$\frac{\text{Weight (kg) x (140 — age in years)}}{\text{72 x serum creatinine concentration (mg/dL)}}$$

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 (intralumbar or intraventricular) route have not been assessed.

Intermittent infusion is the recommended method of administration.

PREPARATION AND STABILITY

Vancomycin Hydrochloride ADD-Vantage vials should be used only with approved diluents (5% dextrose injection or 0.9% sodium chloride injection). (see ***INSTRUCTIONS FOR USE***).

Chemical Stability: It has been shown that after reconstitution, the admixture solution prepared in either dextrose injection or sodium chloride injection may be stored for 24 hours at room temperature or in a refrigerator for 14 days without significant loss of potency. However, this information is not intended to suggest that it is acceptable practice to administer such an admixture well after the time of preparation. Admixtures should be prepared as close to the time of administration as is reasonable.

Intermittent infusion is the recommended method of administration.

The 500 mg ADD-Vantage vial should be joined with at least a 100 mL ADD-Vantage flexible diluent container, the 750 mg and the 1 g ADD-Vantage vial should be joined *only* to a 250 mL ADD-Vantage flexible diluent container. The desired dose diluted in this manner should be administered by intravenous infusion over a period of at least 60 minutes.

Dilution instructions for reconstituted solution for 750 mg added

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.

Prior to administration, parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution or container permits.

For Oral Administration

NOTE: For information only. ADD-Vantage Vials cannot be used to supply vancomycin for this purpose.

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 dosage in pediatric patients 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 patient to drink. Common flavoring syrups may be added to the solution to improve the taste for oral administration. The diluted material may be administered via nasogastric tube.

INSTRUCTIONS FOR USE

To Use Vial in ADD-Vantage Flexible Diluent Container

To Open:

Peel overwrap at corner and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

To Assemble Vial and Flexible Diluent Container:
(Use Aseptic Technique)

1. Remove the protective covers from the top of the vial and the vial port on the diluent container as follows:
   a. To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down far enough to start the opening (SEE FIGURE 1.), then pull straight up to remove the cap. (SEE FIGURE 2.) **NOTE:** Do not access vial with syringe.

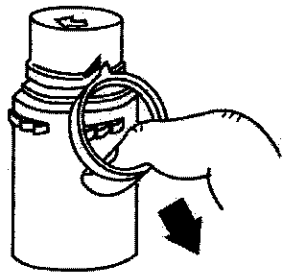


Fig. 1

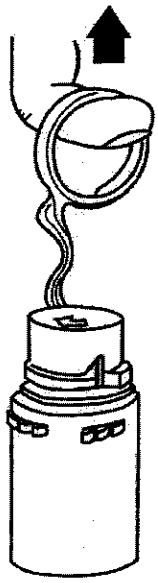


Fig. 2

   b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the tie membrane, then pull back to remove the cover. (SEE FIGURE 3.)
2. Screw the vial into the vial port until it will go no further. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. This occurs approximately 1/2 turn (180°) after the first audible click. (SEE FIGURE 4.) The clicking sound does not assure a seal; the vial must be turned as far as it will go.

NOTE: Once vial is seated, do not attempt to remove. (SEE FIGURE 4.)

3. Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.
4. Label appropriately.

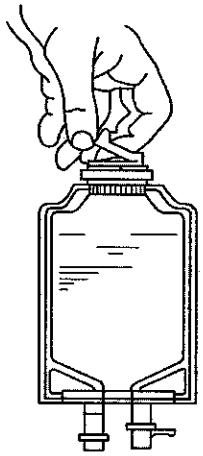


Fig. 3

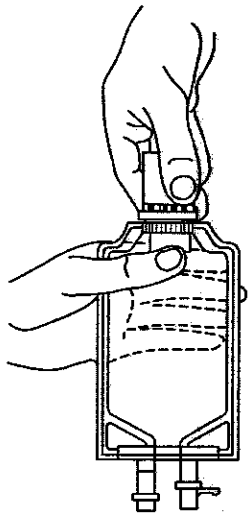


Fig. 4

To Reconstitute the Drug:

1. Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.
2. With the other hand, push the drug vial down into the container telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container. (SEE FIGURE 5.)
3. Pull the inner cap from the drug vial. (SEE FIGURE 6.) Verify that the rubber stopper has been pulled out, allowing the drug and diluent to mix.
4. Mix container contents thoroughly and use within the specified time.

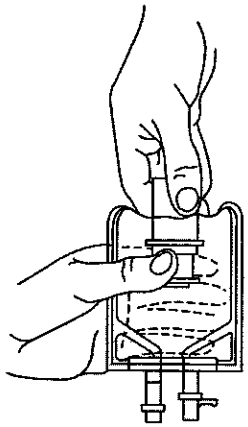


Fig. 5

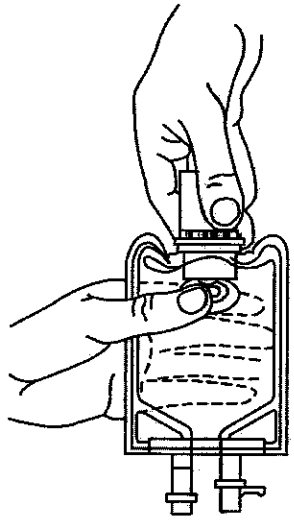


Fig. 6

Preparation for Administration:
(Use Aseptic Technique)

1. Confirm the activation and admixture of vial contents.
2. Check for leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.
3. Close flow control clamp of administration set.
4. Remove cover from outlet port at bottom of container.
5. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full directions on administration set carton.
6. Lift the free end of the hanger loop on the bottom of the vial, breaking the two tie strings. Bend the loop outward to lock it in the upright position, then suspend container from hanger.
7. Squeeze and release drip chamber to establish proper fluid level in chamber.
8. Open flow control clamp and clear air from set. Close clamp.
9. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
10. Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible containers in series connections.

HOW SUPPLIED

Sterile Vancomycin Hydrochloride, USP is supplied as a sterile powder in single-dose ADD-Vantage vials that contain either 500 mg (List No. 6534), 750 mg (List No. 6531) or 1 g (List No. 6535).

750 mg supply information added

Store at controlled room temperature 15° to 30°C (59° to 86°F). [See USP.]

The ADD-Vantage drug delivery system is covered by one or more of the following U.S. patent numbers: 4,614,267 and 4,614,515.

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.

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

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Manufacturer-specific information to be presented