

# Sterile Vancomycin Hydrochloride, USP

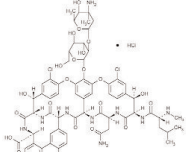
## FOR INTRAVENOUS USE ONLY Rx Only

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 is a white-to-off white lyophilized powder, for preparing intravenous (IV) infusions. Each vial contains the equivalent of 500 mg or 1 g vancomycin base, 500 mg of the base is equivalent to 0.34 mmol. When reconstituted with Sterile Water for Injection to a concentration of 50 mg/mL, a clear solution is obtained with a pH between 2.5 and 4.5. Sterile Vancomycin Hydrochloride, USP should be administered intravenously in diluted solution (see **DOSE AND ADMINISTRATION**). **AFTER RECONSTITUTION, FURTHER DILUTION IS REQUIRED BEFORE USE.**

Vancomycin is a cyclic glycopeptide antibiotic derived from *Amphotolactis orientalis* (formerly *Nocardia orientalis*). The molecular formula is  $C_{28}H_{42}Cl_2N_8O_{12}$  · HCl and the molecular weight is 1485.74. Vancomycin hydrochloride has the following structural formula:



### CLINICAL PHARMACOLOGY

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 2 hours after infusion, and mean plasma concentrations of approximately 8 mcg/mL 11 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/h, and mean renal clearance is about 0.048 L/kg/h. Renal dysfunction slows excretion of vancomycin. In anephric patients, the average half-life of elimination is 7.25 days. The distribution coefficient is from 0.2 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 6 hours. Serum concentrations of about 10 mcg/mL are achieved by intraperitoneal injection of 30 mg/kg of vancomycin. However, the safety and efficacy of the intraperitoneal use of vancomycin has not been established in adequate and well-controlled trials (see **PRECAUTIONS**).

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 IV administration of vancomycin, inhibitory concentrations are present in pleural, pericardial, ascitic, and synovial fluids; in urine; in peritoneal dialysis fluid; and in atrial appendage tissue. Vancomycin 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 DNA synthesis. There is no cross-resistance between vancomycin and other antibiotics. 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 *Staphylococcus aureus*, *Streptococcus bovis*, enterococci, and the viridans group streptococci.

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

### Aerobic gram-positive microorganisms

#### Diphtheroids

Enterococci (e.g., *Enterococcus faecalis*)

Staphylococci, including *Staphylococcus aureus* and *Staphylococcus epidermidis* (including heterogeneous methicillin-resistant strains)

*Streptococcus bovis*

Viridans group streptococci

The following *in vitro* data are available, but their clinical significance is unknown.

Vancomycin exhibits *in vitro* MICs of 1 mcg/mL or less against most (≥90%) strains of streptococci listed below and MICs of 4 mcg/mL or less against most (≥90%) strains of other listed microorganisms; however, the safety and effectiveness of vancomycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

### Aerobic gram-positive microorganisms

*Listeria monocytogenes*

*Streptococcus pyogenes*

*Streptococcus pneumoniae* (including penicillin-resistant strains)

*Streptococcus agalactiae*

### Anaerobic gram-positive microorganisms

*Actinomyces* species

*Lactobacillus* species

### Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

### Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method<sup>1,2</sup> (broth, agar or microdilution) or equivalent with standardized inoculum concentrations and standardized concentrations of vancomycin powder. The MIC values should be interpreted according to the criteria in Table 1.

### Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure<sup>3</sup> requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg of vancomycin to test the susceptibility of microorganisms to vancomycin. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for vancomycin. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 mcg vancomycin disk should be interpreted according to the following criteria in Table 1.

Table 1: Susceptibility Test Interpretive Criteria for Vancomycin

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion Diameters (mm)		
	Susceptible (S)	Intermediate (I)	Resistant (R)	Susceptible (S)	Intermediate (I)	Resistant (R)
<i>Enterococci</i> <sup>a</sup>	≤ 4	8 - 16	≥ 32	≥ 17 <sup>b</sup>	15 - 16 <sup>b</sup>	≤ 14 <sup>b</sup>
<i>Staphylococcus aureus</i>	≤ 2	4 - 8	≥ 16	≥ 15 <sup>c</sup>	-	-
Coagulase-negative staphylococci	≤ 4	8 - 16	≥ 32	≥ 15 <sup>c</sup>	-	-
Streptococci other than S.	≤ 1 <sup>d</sup>	-	-	≥ 17 <sup>e</sup>	-	-

<sup>a</sup> A  $\beta$ -lactamase test using an inoculum  $\geq 10^7$  CFU/mL or direct colony growth and a nitrocefin-based substrate should be performed to detect either ampicillin or penicillin resistance due to  $\beta$ -lactamase production.

<sup>b</sup> Plates should be held for a full 24 hours and examined using a transmitted light. The presence of a haze or any growth within the zone of inhibition indicates resistance. Those enterococci with intermediate zones of inhibition should be tested by a standardized procedure based on a dilution method<sup>1,2</sup> (broth or agar) or equivalent.

<sup>c</sup> The current absence of resistant isolates precludes defining results other than "Susceptible". Isolates yielding results suggestive of "Nonsusceptible" should be submitted to a reference laboratory for further testing.

<sup>d</sup> Interpretive criteria applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood<sup>1,2</sup>.

<sup>e</sup> Interpretive criteria applicable only to tests performed by disk diffusion method using Mueller-Hinton agar with 5% defibrinated sheep blood and incubated in 5% CO<sub>2</sub>.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

### Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to monitor and ensure the accuracy and precision of the supplies and reagents used in the assay, and the techniques of the individuals performing the test. Standard vancomycin powder should provide MIC values provided below. For the diffusion technique, the 30 mcg vancomycin disk should provide the following zone diameters with the quality control strains:

Organism (ATCC)	MIC range (mcg/mL)	Disk diffusion range (mm)
<i>Enterococcus faecalis</i> (29212)	1 - 4	Not applicable
<i>Staphylococcus aureus</i> (29213)	0.5 - 2	Not applicable
<i>Staphylococcus aureus</i> (25923)	Not applicable	17 - 21
<i>Streptococcus pneumoniae</i> (49619) <sup>1</sup>	0.12 - 0.5	20 - 27

<sup>1</sup> Interpretive criteria applicable only to tests performed using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood. Disk diffusion interpretive criteria applicable only to tests performed using Mueller-Hinton agar with 5% defibrinated sheep blood and incubated in 5% CO<sub>2</sub>.

### INDICATIONS AND USAGE

Vancomycin is indicated for the treatment of moderate or severe infections caused by susceptible strains of methicillin-resistant (beta-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 is indicated for initial therapy when methicillin-resistant staphylococci are suspected, but after susceptibility data are available, therapy should be adjusted accordingly.

Vancomycin is effective in the treatment of staphylococcal endocarditis. Its effectiveness has been documented in other infections due to staphylococci, including septicemia, bone infections, low 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 has been reported to be effective alone or in combination with an aminoglycoside for endocarditis caused by *Streptococcus viridans* or S. bovis. For endocarditis caused by enterococci (e.g., E. faecalis), vancomycin has been reported to be effective only in combination with an aminoglycoside.

Vancomycin has been reported to be effective for the treatment of diphtheroid endocarditis. Vancomycin 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.

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 empirical selection of therapy.

### CONTRAINDICATIONS

Vancomycin 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, including shock, and, rarely, cardiac arrest. Vancomycin should be administered over a period of not less than 60 minutes to avoid rapid-onset reactions. Stopping the infusion usually results in prompt cessation of these reactions.

Otitotoxicity has occurred in patients receiving vancomycin. 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 appropriately increased by high, prolonged blood concentrations.

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

*Clostridium difficile* associated diarrhea (CDAD) has been reported in use of nearly all antibacterial agents, including sterile vancomycin hydrochloride, USP and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic therapy of C. difficile, and surgical evaluation should be instituted as clinically indicated.

### PRECAUTIONS

#### General

Prolonged use of vancomycin may result in the overgrowth of nonsusceptible microorganisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken. In rare instances, there have been reports of pseudomembranous colitis due to C. difficile developing in patients who received intravenous vancomycin.

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 **DOSE AND ADMINISTRATION**).

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