Last Time Saved: 9/22/11 9:54 AM
Document Name: QEN-2890v3.qxp
PMS Black

EN-2890

EN-2890

Vancomycin Hydrochloride for Injection, USP

Fliptop Vial
For Intravenous Use
Rx only

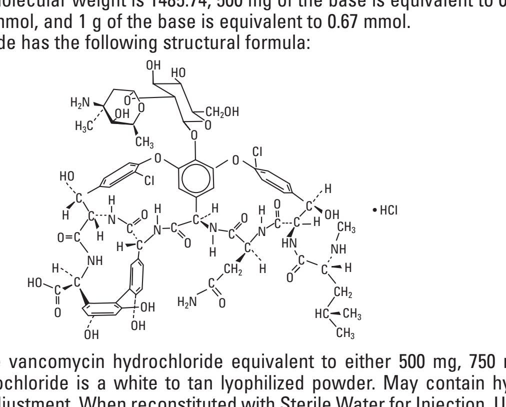
Vancomycin Hydrochloride for Injection, USP
Fliptop Vial
For Intravenous Use
Rx only

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

Vancomycin Hydrochloride for Injection, 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.

Vancomycin hydrochloride has the following structural formula:



The vials contain sterile vancomycin hydrochloride equivalent to either 500 mg, 750 mg, or 1 g vancomycin activity. Vancomycin hydrochloride is a white to tan lyophilized powder. May contain hydrochloric acid and/or sodium hydroxide for pH adjustment. When reconstituted with Sterile Water for Injection, USP, it forms a clear, light to dark tan solution with a pH of 4.0 (2.5 to 4.5). This product is oxygen sensitive.

Solutions of vancomycin hydrochloride reconstituted with Sterile Water for Injection, USP contain no bacteriostat and are intended for use only as a single-dose injection. When smaller doses are required, the unused portion should be discarded. When reconstituted with sterile water for injection, **FURTHER DILUTION IS REQUIRED BEFORE USE** (see ***DOSAGE AND ADMINISTRATION***).

Vancomycin hydrochloride is prepared as a solution and lyophilized in its final container.

CLINICAL PHARMACOLOGY

Vancomycin Hydrochloride for Injection, USP is administered intravenously for therapy of systemic infections.

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.

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 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 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.

Gram-positive bacteria
Diphtheroids
Enterococci (e.g., *Enterococcus faecalis*)
Staphylococci, including *Staphylococcus aureus* and *Staphylococcus epidermidis* (including heterogeneous methicillin-resistant strains) in adequate and well-controlled clinical trials.

Gram-positive bacteria
Listeria monocytogenes
Streptococcus pyogenes
Streptococcus pneumoniae (including penicillin-resistant strains)
Streptococcus agalactiae

Anaerobic Gram-positive bacteria
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 (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on dilution method[1,2] (broth, agar or microdilution) or equivalent using standardized inoculum and 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[2,3] 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

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

[a] A ß-lactamase test using an inoculum ≥ 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 ß-lactamase production.
[b] Plates should be held for a full 24 hours and examined using 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[1,2] (broth or agar) or equivalent.
[c] 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.
[d] Interpretative criteria applicable only to tests performed by broth microdilution method using cationadjusted Mueller-Hinton broth with 2 to 5% lysed horse blood[1,2].
[e] Interpretative criteria applicable only to tests performed by disk diffusion method using Mueller-Hinton agar with 5% defibrinated sheep blood and incubated in 5% CO_2[3].

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:

Table 2. *In Vitro* Susceptibility Test Quality Control Ranges for Vancomycin

Organism (ATTC #)	MIC range (mcg/mL)	Disk diffusion range (mm)
Enterococcus faecalis (29212)	1 – 4	Not applicable
Staphylococcus aureus (29213)	0.5 – 2	Not applicable
Staphylococcus aureus (25923)	Not applicable	17 – 21
Streptococcus pneumoniae (49619)[a]	0.12 – 0.5	20 – 27

[a] Interpretative criteria applicable only to tests performed using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood[1]. Disk diffusion interpretive criteria applicable only to tests performed using Mueller-Hinton agar with 5% defibrinated sheep blood and incubated in 5% CO_2.

INDICATIONS AND USAGE

Vancomycin hydrochloride is indicated for the treatment of serious 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 hydrochloride is effective in the treatment of staphylococcal endocarditis. It's 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 *Streptococcus 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.

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.

CONTRAINDICATIONS

Vancomycin Hydrochloride for Injection, 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, including shock, and, rarely, cardiac arrest.

Vancomycin hydochloride 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***).

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Vancomycin Hydrochloride for Injection, 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 treatment 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 ***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 that may cause neutropenia should have periodic monitoring of the leukocyte count.

Vancomycin is irritating to tissue and must be given by a secure intravenous route of administration. Pain, tenderness, and necrosis occur 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 as a 60-minute infusion prior to anesthetic induction.

The safety and efficacy of vancomycin administered by the intrathecal (intralumbar or intraventricular) route or by the intraperitoneal route have not been established by adequate and well-controlled trials.

Reports have revealed that administration of Vancomycin Hydrochloride for Injection, USP 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.

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, 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 or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions

Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing (see **Pediatric Use** under ***PRECAUTIONS***) 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of Vancomycin Hydrochloride for Injection, USP was found in standard laboratory tests. No definitive fertility studies have been performed.

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

Geriatric Use

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***).

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 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 is given by a slow infusion over 60 minutes. In studies of normal volunteers, infusion-related events did not occur when vancomycin was administered at a rate of 10 mg/min or less.

Nephrotoxicity: Renal failure, principally manifested by increased serum creatinine or BUN concentrations, especially in patients administered large doses of vancomycin, has been reported rarely. 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 was discontinued, azotemia resolved in most patients.

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

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 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.

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 administration of vancomycin.

Chemical peritonitis has been reported following intraperitoneal administration of vancomycin (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 the drug exposure.

Skin and Subcutaneous Tissue Disorders
Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

To report SUSPECTED ADVERSE EVENTS, contact FDA at 1-800-FDA-1088 or www.fda.gov.

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.

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 intravenous daily dose.

Pediatric Patients: The usual intravenous dosage of vancomycin is 10 mg/kg per dose given every six hours. Each dose should be administered over a period of at least 60 minutes. Close monitoring of serum concentrations of vancomycin is recommended 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 first week of life and every eight hours thereafter up to the age of one 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 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 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)[3]

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 the 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: $\dfrac{\text{Weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine concentration (mg/dL)}}$

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 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) routes have not been established.

Intermittent infusion is the recommended method of administration.

PREPARATION AND STABILITY

At the time of use, reconstitute the vial with Sterile Water for Injection by adding 10 mL of the diluting solution to the 500-mg vial, 15 mL of the diluting solution to the 750 mg vial, or 20 mL of the diluting solution to the 1-g vial of dry, vancomycin powder. FURTHER DILUTION IS REQUIRED.

After reconstitution with Sterile Water for Injection, the vials may be stored in a refrigerator for 14 days without significant loss of potency.

Reconstituted solutions containing 500 mg of vancomycin must be further diluted with at least 100 mL of diluent. Reconstituted solutions containing 750 mg must be further diluted with at least 150 mL of diluent. Reconstituted solutions containing 1 g must be further diluted with at least 200 mL of diluent. The desired dose, diluted in this manner, should be administered by intermittent intravenous infusion over a period of at least 60 minutes.

Compatibility with Other Drugs and Intravenous Fluids

Solutions that are diluted with 5% Dextrose Injection or 0.9% Sodium Chloride Injection may be refrigerated for 14 days without significant loss of potency. Solutions in the vial that are further diluted with the following infusion fluids may be stored in a refrigerator for 96 hours:

5% Dextrose Injection, USP
5% Dextrose and 0.9% Sodium Chloride Injection, USP
Lactated Ringer's Injection, USP
Lactated Ringer's and 5% Dextrose Injection, USP
Normosol®-M and 5% Dextrose
ISOLYTE® E

Vancomycin solution has a low pH and may cause chemical or physical instability when it is mixed with 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.

HOW SUPPLIED

Vancomycin Hydrochloride for Injection, USP is supplied as a sterile powder in single-dose fliptop vials that contain the vancomycin equivalent of either 500 mg, 750 mg, or 1 g.

NDC Number	Fill
0409-4332-01	500 mg
0409-6531-02	750 mg
0409-6533-01	1 g

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

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

1. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – 8th ed., CLSI document M07-A8. Clinical and Laboratory Standards Institute. Wayne, PA. January, 2009.
2. Performance Standards for Antimicrobial Susceptibility Testing; 21st Informational Supplement, CLSI document M100-S21. Clinical and Laboratory Standards Institute. Wayne, PA. January, 2011.
3. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard – 10th ed., CLSI document M02-A10. Clinical and Laboratory Standards Institute. Wayne, PA. January, 2009.
4. Moellering RC, Krogstad DJ, Greenblatt DJ: Vancomycin therapy in patients with impaired renal function: A nomogram for dosage. *Ann Inter Med* 1981;94:343.

Revised: 09/2011

Printed in USA
Hospira, Inc., Lake Forest, IL 60045 USA
Hospira

Reference ID: 3051884

CODICE INTERNO GRAFIMED / *GRAFIMED Internal Code* :	**10/0129/11**
LABEL CHANGE REQUEST NR:	**LCR-030/11**
CLIENTE / *Customer* :	**HOSPIRA S.p.A. LISCATE (MI)**
BOZZA DEL / *Proof date* :	**10/10/2011**
PRODOTTO / *Product* :	**VANCOMICINA CLORIDRATO USP**
DESCRIZIONE MATERIALE / *Material description* :	**ISTRUZIONE**
DESTINAZIONE COMMERCIALE / *Presentation* :	**VENDITA**
MERCATO / *Market* :	**USA**
CODICE ITEM / *Code* :	**K163104B**
CODICE LAETUS / *Laetus code* :	**I I X (0)**
FORMATO POSA STESA / *Flat size* :	**180 mm x 610 mm**
FORMATO POSA PIEGATA / *Folded size* :	**180 mm x 44 mm (12 pieghe)**
NUMERO FACCIATE / *Sides number* :	**2**
CARTA / *Paper* :	**40 g/m²**
COLORI / *Colors* :	**NERO**
FONT - FONT SIZE / *Font - Font Size* :	**Univers cond 7,5 pt**
NOTE / *Notes* :	

grafimed
ARTWORK PROVIDER
Tel. + 39 0692708387 - Fax +39 0692504265
www.grafimed.it - info@grafimed.it

☐ 1st draft Date 06/10/2011 Operator Cirene ☐ 2nd draft Date 07/10/2011 Operator Cirene ☒ 3rd draft Date 10/10/2011 Operator Cirene ☐ 4th draft Date Operator ☐ 5th draft Date Operator ☐ 6th draft Date Operator ☐ 7th draft Date Operator

PAG 1 di 2

Vancomycin Hydrochloride for Injection, USP

℞ only

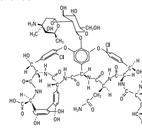
Fliptop Vial
For Intravenous Use

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

Vancomycin Hydrochloride for Injection, USP, intravenous, is a chromatographically purified tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*) and has the molecular formula $C_{66}H_{75}Cl_3N_9O_{24}$ • HCl. The molecular weight is 1485.74; 500 mg of the base is equivalent to 0.34 mmol and 1 g of the base is equivalent to 0.67 mmol.

Vancomycin hydrochloride has the following structural formula:



The vials contain sterile vancomycin hydrochloride equivalent to either 500 mg or 1 g vancomycin activity. Vancomycin hydrochloride is a white to tan lyophilized powder. May contain hydrochloric acid and/or sodium hydroxide for pH adjustment. When reconstituted with Sterile Water for Injection, USP, it forms a clear, light to dark tan solution with a pH of 4.0 (2.5 to 4.5). This product is oxygen sensitive.

Solutions of vancomycin hydrochloride reconstituted with Sterile Water for Injection, USP contain no bacteriostat and are intended for use only as a single-dose injection. When smaller doses are required, the unused portion should be discarded. When reconstituted with sterile water for injection, **FURTHER DILUTION IS REQUIRED BEFORE USE** (see ***DOSAGE AND ADMINISTRATION***).

Vancomycin hydrochloride is prepared as a solution and lyophilized in its final container.

CLINICAL PHARMACOLOGY

Vancomycin Hydrochloride for Injection, USP is administered intravenously for therapy of systemic infections.

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.

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 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 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.

Gram-positive bacteria

Diphtheroids

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

Staphylococci, including *Staphylococcus aureus* and *Staphylococcus epidermidis* (including heterogeneous methicillin-resistant strains) in adequate and well-controlled clinical trials.

Gram-positive bacteria

Listeria monocytogenes

Streptococcus pyogenes

Streptococcus pneumoniae (including penicillin-resistant strains)

Streptococcus agalactiae

Anaerobic Gram-positive bacteria

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 (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on dilution method[1,2] (broth, agar or microdilution) or equivalent using standardized inoculum and 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[2,3] 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

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

[a] A ß-lactamase test using an inoculum ≥ 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 ß-lactamase production.

[b] Plates should be held for a full 24 hours and examined using 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[1,2] (broth or agar) or equivalent.

[c] 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.

[d] Interpretative criteria applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood[1,2]

[e] Interpretative criteria applicable only to tests performed by disk diffusion method using Mueller-Hinton agar with 5% defibrinated sheep blood and incubated in 5% CO_2[3].

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:

Table 2. *In Vitro* Susceptibility Test Quality Control Ranges for Vancomycin

Organism (ATTC #)	MIC range (mcg/mL)	Disk diffusion range (mm)
Enterococcus faecalis (29212)	1 – 4	Not applicable
Staphylococcus aureus (29213)	0.5 – 2	Not applicable
Staphylococcus aureus (25923)	Not applicable	17 – 21
Streptococcus pneumoniae (49619)[a]	0.12 – 0.5	20 – 27

[a] Interpretative criteria applicable only to tests performed using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood[1]. Disk diffusion interpretive criteria applicable only to tests performed using Mueller-Hinton agar with 5% defibrinated sheep blood and incubated in 5% CO_2

INDICATIONS AND USAGE

Vancomycin hydrochloride is indicated for the treatment of serious 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 hydrochloride is effective in the treatment of staphylococcal endocarditis. It's 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 *Streptococcus 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.

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.

CONTRAINDICATIONS

Vancomycin Hydrochloride for Injection, 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, including shock, 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***).

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Vancomycin Hydrochloride for Injection, 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 treatment 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 ***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 that may cause neutropenia should have periodic monitoring of the leukocyte count.

Vancomycin is irritating to tissue and must be given by a secure intravenous route of administration. Pain, tenderness, and necrosis occur 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 as a 60-minute infusion prior to anesthetic induction.

CODICE INTERNO GRAFIMED / *GRAFIMED Internal Code* **:**	**10/0129/11**
LABEL CHANGE REQUEST NR:	**LCR-030/11**
CLIENTE / *Customer* **:**	**HOSPIRA S.p.A. LISCATE (MI)**
BOZZA DEL / *Proof date* **:**	**10/10/2011**
PRODOTTO / *Product* **:**	**VANCOMICINA CLORIDRATO USP**
DESCRIZIONE MATERIALE / *Material description* **:**	**ISTRUZIONE**
DESTINAZIONE COMMERCIALE / *Presentation* **:**	**VENDITA**
MERCATO / *Market* **:**	**USA**
CODICE ITEM / *Code* **:**	**K163104B**
CODICE LAETUS / *Laetus code* **:**	**I I X (0)**
FORMATO POSA STESA / *Flat size* **:**	**180 mm x 610 mm**
FORMATO POSA PIEGATA / *Folded size* **:**	**180 mm x 44 mm (12 pieghe)**
NUMERO FACCIATE / *Sides number* **:**	**2**
CARTA / *Paper* **:**	**40 g/m²**
COLORI / *Colors* **:**	**NERO**
FONT - FONT SIZE / *Font - Font Size* **:**	**Univers cond 7,5 pt**
NOTE / *Notes* **:**	

grafimed
ARTWORK PROVIDER
Tel. + 39 0692708387 - Fax +39 0692504265
www.grafimed.it - info@grafimed.it

☐ 1st draft Date 06/10/2011 Cirene — Operator
☐ 2nd draft Date 07/10/2011 Cirene — Operator
☒ 3rd draft Date 10/10/2011 Cirene — Operator
☐ 4th draft Date — Operator
☐ 5th draft Date — Operator
☐ 6th draft Date — Operator
☐ 7th draft Date — Operator

The safety and efficacy of vancomycin administered by the intrathecal (intralumbar or intraventricular) route or by the intraperitoneal route have not been established by adequate and well-controlled trials.

Reports have revealed that administration of Vancomycin Hydrochloride for Injection, USP 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.

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, 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 or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions

Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing (see **Pediatric Use** under ***PRECAUTIONS***) 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of Vancomycin Hydrochloride for Injection, USP was found in standard laboratory tests. No definitive fertility studies have been performed.

Pregnancy: Teratogenic Effects–*Category C*- Animal reproduction studies have not been conducted with vancomycin hydrochloride. It is not known whether vancomycin hydrochloride can affect reproduction capacity. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin hydrochloride on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancomycin hydrochloride 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 pediatric patients, 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***).

Geriatric Use

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***).

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 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 is given by a slow infusion over 60 minutes. In studies of normal volunteers, infusion-related events did not occur when vancomycin was administered at a rate of 10 mg/min or less.

Nephrotoxicity: Renal failure, principally manifested by increased serum creatinine or BUN concentrations, especially in patients administered large doses of vancomycin, has been reported rarely. Rarely 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 was discontinued, azotemia resolved in most patients.

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

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 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/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 administration of vancomycin.

Chemical peritonitis has been reported following intraperitoneal administration of vancomycin (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 the drug exposure.

- Skin and Subcutaneous Tissue Disorders
- Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

To report SUSPECTED ADVERSE EVENTS, contact FDA at 1-800-FDA-1088 or www.fda.gov.

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.

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 intravenous daily dose.

Pediatric Patients: The usual intravenous dosage of vancomycin is 10 mg/kg per dose given every six 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 first week of life and every eight hours thereafter up to the age of one 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 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 per day in mg is about 15 times the glomerular filtration rate in mL/min:

DOSAGE TABLE FOR VANCOMYCIN
IN PATENTS WITH IMPAIRED RENAL FUNCTION
(Adapted from Moellering et al)[3]

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 the 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: $\frac{\text{Weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine concentration (mg/dL)}}$

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 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) routes have not been established.

Intermittent infusion is the recommended method of administration.

PREPARATION AND STABILITY

At the time of use, reconstitute the vial with Sterile Water for Injection, by adding 10 mL of the diluting solution to the 500-mg vial or 20 mL of the diluting solution to the 1-g vial of dry, vancomycin powder. FURTHER DILUTION IS REQUIRED.

After reconstitution with Sterile Water for Injection, the vials may be stored in a refrigerator for 14 days without significant loss of potency.

Reconstituted solutions containing 500 mg of vancomycin must be further diluted with at least 100 mL of diluent. Reconstituted solutions containing 1 g must be further diluted with at least 200 mL of diluent. The desired dose, diluted in this manner, should be administered by intermittent intravenous infusion over a period of at least 60 minutes.

Compatibility with Other Drugs and Intravenous Fluids

Solutions that are diluted with 5% Dextrose Injection or 0.9% Sodium Chloride Injection may be refrigerated for 14 days without significant loss of potency. Solutions in the vial that are further diluted with the following infusion fluids may be stored in a refrigerator for 96 hours:

- 5% Dextrose Injection, USP
- 5% Dextrose and 0.9% Sodium Chloride Injection, USP
- Lactated Ringer's Injection, USP
- Lactated Ringer's and 5% Dextrose Injection, USP
- Normosol®-M and 5% Dextrose
- ISOLYTE® E

Vancomycin solution has a low pH and may cause chemical or physical instability when it is mixed with 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.

HOW SUPPLIED

Vancomycin Hydrochloride for Injection, USP is supplied as a sterile powder in single-dose fliptop vials that contain the vancomycin equivalent of either 500 mg or 1 g.

NDC Number	**Fill**
0409-4332-01	500 mg
0409-6533-01	1 g

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

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

1. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – 8th ed., CLSI document M07-A8. Clinical and Laboratory Standards Institute. Wayne, PA. January, 2009.
2. Performance Standards for Antimicrobial Susceptibility Testing; 21st Informational Supplement, CLSI document M100-S21. Clinical and Laboratory Standards Institute. Wayne, PA. January, 2011.
3. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard – 10th ed., CLSI document M02-A10. Clinical and Laboratory Standards Institute. Wayne, PA. January, 2009.
4. Moellering RC, Krogstad DJ, Greenblatt DJ: Vancomycin therapy in patients with impaired renal function: A nomogram for dosage. *Ann Inter Med* 1981;94:343.

Revised: September, 2011

ISOLYTE® E is a registered trademark of B. Braun

Hospira, Inc., Lake Forest, IL 60045 USA
Product of Italy

Hospira

K163104B

Approved by:
The following item has been checked:

1 - TESTI / *Texts*
2 - IMPOSTAZIONE GRAFICA / *Graphic drawing up*
3 - FORMATO / *Size*
4 - INDICAZIONE DEI COLORI / *Color reference*
5 - SPECIFICHE TECNICHE / *Technical specification*

REG. AFFAIRS Item checked: 1 2 3 4 5		MARKETING Item checked: 1 2 3 4 5		MAINTENANCE/PRODUCTION Item checked: 1 2 3 4 5		APPROVED BY Q.A. FOR PRINTING FILM	
Firma *Resp. signature*	**Data** *Date*	**Firma** *Resp. signature*	**Data** *Date*	**Firma** *Resp. signature*	**Data** *Date*	**Firma** *Resp. signature*	**Data** *Date*
_____		_____		_____		_____	