EXHIBIT C

Copy of the Package Insert
for the Listed Drug:
American Pharmaceutical Partners' Sterile Vancomycin Hydrochloride, USP

Sterile Vancomycin Hyd[illegible]oride 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, and skin and skin-structure infections. When staphylococcal infections are localized and purulent, antibiotics are used as adjuncts to appropriate surgical measures.

Sterile 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. *S. faecalis*), Sterile Vancomycin Hydrochloride has been reported to be effective only in combination with an aminoglycoside.

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

The parenteral form of Sterile 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 is not effective by the oral route for other types of infection.**

Although no controlled clinical efficacy studies have been conducted, IV vancomycin has been suggested by the American Heart Association and the American Dental Association as prophylaxis against bacterial endocarditis in patients allergic to penicillin 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 statements of the American Heart Association and the American Dental Association.[3]

CONTRAINDICATIONS:
Sterile Vancomycin Hydrochloride 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.

Sterile Vancomycin Hydrochloride should be administered in a diluted 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 Sterile 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 Sterile 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 Sterile Vancomycin Hydrochloride, and may range in severity from mild to lifethreatening. 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*.

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centrations of about 10 mcg/mL are [illegible]ved by intraperitoneal injection of 30 mg/kg o[illegible]omycin. Vancomycin is not effectively remove[illegible] either hemodialysis or peritoneal dialysis; there have been no reports of vancomycin clearance with hemoperfusion.

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 Sterile Vancomycin Hydrochloride, inhibitory concentrations are present in pleural, pericardial, ascitic and synovial fluids; in urine; in peritoneal dialysis fluid; and in atrial appendage tissue. Sterile 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.

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

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).

Diffusion Techniques/Susceptibility Tests
Quantitative methods that require measurement of zone diameter give the most precise estimate of the susceptibility of bacteria to antimicrobial agents. One such standard procedure[1] which has been recommended for use with disks to test susceptibility of organisms to vancomycin uses the 30 mcg vancomycin hydrochloride disk. Interpretation involves the correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for vancomycin.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30 mcg vancomycin disk should be interpreted according to the following criteria:

Zone diameter (mm)	Interpretation
≥ 12	(S) Susceptible
10-11	(I) Intermediate
≤ 9	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antibiotic levels are attained. A report of "Resistant" indicates that achievable concentrations of the antimicrobial agent are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 30 mcg vancomycin disk should give the following zone diameters:

Organism	Zone diameter (mm)
Staphylococcus aureus ATCC 25923	15-19

Dilution techniques
Use a standardized dilution method[2] (broth, agar, microdilution) or equivalent with vancomycin powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤ 4	(S) Susceptible
> 4-< 16	(I) Intermediate
≥ 16	(R) Resistant

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard vancomycin powder should provide the following MIC values:

Organism	MIC (mcg/mL)
Staphylococcus aureus ATCC 29213	0.5-2
Enterococcus faecalis ATCC 29212	1-4

INDICATIONS AND USAGE:
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Sterile Vancomycin Hydrochloride, USP and other antibacterial drugs, Sterile Vancomycin Hydrochloride, USP 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.

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

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FAPP AMERICAN PHARMACEUTICAL PARTNERS, INC.

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458568/Revised: December 2003

STERILE VANCOMYCIN HYDROCHLORIDE, USP

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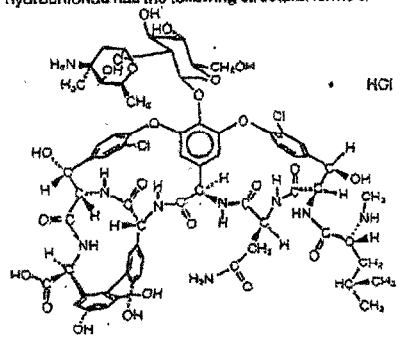
PHARMACY BULK PACKAGE—Not for Direct Infusion

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Sterile Vancomycin Hydrochloride, USP and other antibacterial drugs, Sterile Vancomycin Hydrochloride, USP 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 lyophilized powder, for preparing intravenous (IV) infusions, in vials containing the equivalent of 5 g or 10 g vancomycin base. 500 mg of the base are equivalent to 0.34 mmol. When reconstituted with Sterile Water for Injection to a concentration of 50 mg/mL for the 5 g vial and 100 mg/mL for the 10 g vial, the pH of the solution is between 2.5 and 4.5. Sterile Vancomycin Hydrochloride, USP should be administered intravenously in diluted solution (see **DOSAGE AND ADMINISTRATION**).

Sterile Vancomycin Hydrochloride is a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*). Vancomycin hydrochloride has the following structural formula:



$C_{66}H_{75}Cl_2N_9O_{24}\cdot HCl$ 1485.73

A *pharmacy bulk package* is a sterile dosage form containing many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for IV infusion.

FURTHER DILUTION IS REQUIRED BEFORE USE.

CLINICAL PHARMACOLOGY:
Vancomycin is poorly absorbed after oral administration.

In subjects with normal kidney function, multiple IV dosing of 1 g of vancomycin (15 mg/kg) infused over 60 minutes produces mean plasma concentrations of approximately 63 mcg/mL immediately at 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 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 four to six 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 [illegible]

PRECAUTIONS:

General

Prescribing Sterile Vancomycin Hydrochloride, USP 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.

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

Prolonged use of Sterile Vancomycin Hydrochloride 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 rare instances, there have been reports of pseudomembranous colitis due to *C. difficile* developing in patients who received IV 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 Sterile Vancomycin Hydrochloride (see **ADVERSE REACTIONS**). Patients who will undergo prolonged therapy with Sterile Vancomycin Hydrochloride or those who are receiving concomitant drugs which may cause neutropenia should have periodic monitoring of the leukocyte count.

Sterile Vancomycin Hydrochloride is irritating to tissue and must be given by a secure IV route of administration. Pain, tenderness and necrosis occur with intramuscular (IM) injection of Sterile 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 Sterile Vancomycin Hydrochloride as a 60-minute infusion prior to anesthetic induction.

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

Although the safety and efficacy of Sterile Vancomycin Hydrochloride by the intraperitoneal route have not been established, reports reveal that the product has been given by this route during peritoneal dialysis. Administration of Sterile Vancomycin Hydrochloride by the intraperitoneal route during continuous ambulatory peritoneal dialysis has resulted in over 50 reports of chemical peritonitis that developed in some patients within the 12-hour period after administration. To date, all have been self-limited and ranged from cloudy dialysate alone to severe abdominal pain and fever. Most cloudy dialysates were sterile and some contained increased numbers of white blood cells and polymorphonuclear cells. Fluids usually cleared promptly after discontinuation of the Sterile Vancomycin Hydrochloride.

Information for Patients

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

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, polymixin 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

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29561	63323-295-61	Sterile Vancomycin Hydrochloride, USP, equivalent to 5 g vancomycin in a 100 mL *pharmacy bulk package vial*, packaged individually.
314061	63323-314-61	Sterile Vancomycin Hydrochloride, USP equivalent to 10 g vancomycin in a 100 mL *pharmacy bulk package vial*, packaged individually.

Store at controlled room temperature 15°-30°C (59°-86°F).

ANIMAL PHARMACOLOGY:

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

REFERENCES:

1. National Committee for Clinical Laboratory Standards, *Performance Standards for Antimicrobial Disk Susceptibility Tests*—Fourth Edition: Approved Standard NCCLS Document M2-A4, Vol. 10, No. 7 NCCLS, Villanova, PA 1990.
2. National Committee for Clinical Laboratory Standards, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*—Second Edition, Approved Standard NCCLS Document M7-A2, Vol. 10, No. 8 NCCLS, Villanova, PA 1990.
3. Shulman, S.T., Amren, D.P., Bisno, A.L., *et al.*: Prevention of Bacterial Endocarditis, Circulation. 70:1123A, 1984.
4. Moellering, R.C., Krogstad, D.J., and Greenblatt, D.J.: *Vancomycin Therapy in Patients with Impaired Renal Function; A Nomogram for Dosage*, Ann. Intern. Med., 94:343, 1981.

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FAPP AMERICAN PHARMACEUTICAL PARTNERS, INC.

Schaumburg, IL 60173

456569

Revised: December 2003

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Isolyte® E

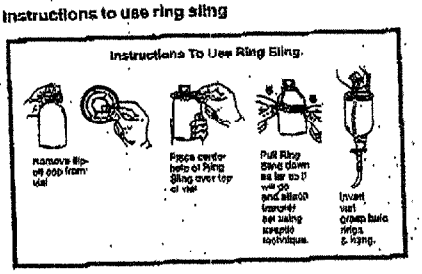
Good professional practice suggests that compounded admixtures should be administered as soon after preparation as is feasible.

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

DIRECTIONS FOR PROPER USE OF PHARMACY BULK PACKAGE:

Pharmacy bulk packages are for use in a pharmacy admixture service only in a suitable work area, such as a laminar flow hood. They should be hung by the integral hanger or inserted into the ring sling (plastic hanging device) provided and suspended as a unit in the laminar flow hood. The container closure should be penetrated only one time utilizing a suitable sterile dispensing set which allows measured distribution of the contents. Use of a syringe and needle is not recommended as it may cause leakage. Swab vial stopper with an antiseptic solution. Insert the dispensing set into the vial using aseptic technique. (See graphic illustration below.)

Instructions to use ring sling



Once the sterile dispensing set has been inserted into the container, withdrawal of the contents should be accomplished without delay. However, if this is not possible, a maximum time of 4 hours from the initial entry may be allowed to complete fluid aliquoting/transferring operations. Discard the container no later than 4 hours after initial closure puncture.

Preparation and Stability

5 g Vial

At the time of use, reconstitute by adding 100 mL of Sterile Water for Injection to the 5 g vial of dry, sterile vancomycin powder. The resultant solution will contain vancomycin equivalent to 500 mg/10 mL. FURTHER DILUTION IS REQUIRED.

Reconstituted solutions of vancomycin (500 mg/10 mL) must be further diluted in at least 100 mL of a suitable infusion solution. For doses of 1 gram (20 mL), at least 200 mL of solution must be used. The desired dose diluted in this manner should be administered by intermittent IV infusion over a period of at least 60 minutes.

10 g Vial

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

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

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

For Oral Administration

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

HOW SUPPLIED:

Product No.	NDC No.

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dosage, consider the possibility of multiple drug administrations, interaction among drugs and unusual kinetics in your patient.

DOSAGE AND ADMINISTRATION:

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

Patients with Normal Renal Function

Adults—The usual daily 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 patients factors, such as age or obesity, may call for modification of the usual intravenous daily dose.

Children—The usual intravenous dosage of vancomycin is 10 mg/kg per dose given every 6 hours. Each dose should be administered over a period of at least 60 minutes.

Infants and Neonates—In neonates and young infants, the total daily IV 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 Sterile Vancomycin Hydrochloride per day in mg is about 15 times the glomerular filtration rate in mL/min (see following table).

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

Creatinine Clearance mL/min	Vancomycin Dose mg/24 hr
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 hr. 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 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 or the estimated value for creatinine clearance will not be 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.

Compatibility with Other Drugs and IV Fluids

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

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

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mutagenic potential of Sterile Vancomycin Hydrochloride was found in standard laboratory tests. No definitive fertility studies have been performed.

Pregnancy

Teratogenic Effects: Pregnancy Category C— In a controlled clinical study, Sterile Vancomycin Hydrochloride was administered to pregnant women for serious staphylococcal infections that were complications of their IV drug abuse to evaluate potential ototoxic and nephrotoxic effects on the infant. Sterile Vancomycin Hydrochloride was found in cord blood. No sensorineural hearing loss or nephrotoxicity attributable to Sterile Vancomycin Hydrochloride was noted. One infant experienced conductive hearing loss that was not attributed to the administration of Sterile Vancomycin Hydrochloride. Because the number of patients treated in this study was limited and Sterile Vancomycin Hydrochloride was administered only in the second and third trimesters, it is not known whether Sterile Vancomycin Hydrochloride causes fetal harm.

Nursing Mothers

Sterile Vancomycin Hydrochloride is excreted in human milk. Caution should be exercised when Sterile Vancomycin Hydrochloride is administered to a nursing woman. Because of the potential for adverse events, a decision should be made whether to discontinue nursing or 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**).

ADVERSE REACTIONS:

Infusion-Related Events

During or soon after rapid infusion of Sterile 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 Sterile Vancomycin Hydrochloride is given by a slow infusion over 60 minutes. In studies of normal volunteers, infusion-related events did not occur when Sterile Vancomycin Hydrochloride 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 given large doses of Sterile Vancomycin Hydrochloride has been reported rarely. Cases of interstitial nephritis have been reported rarely. Some studies suggest that the incidence of nephrotoxicity is increased in patients given aminoglycosides concomitantly.

Ototoxicity

A few dozen cases of hearing loss associated with Sterile Vancomycin Hydrochloride have been reported. Most of these patients had kidney dysfunction or a pre-existing 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 Sterile 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 Sterile Vancomycin Hydrochloride is discontinued. Thrombocytopenia has rarely been reported.

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), Stevens-Johnson syndrome, toxic epidermal necrolysis and vasculitis in association with the administration of Sterile Vancomycin Hydrochloride. Chemical peritonitis has been reported following intraperitoneal administration (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 over-