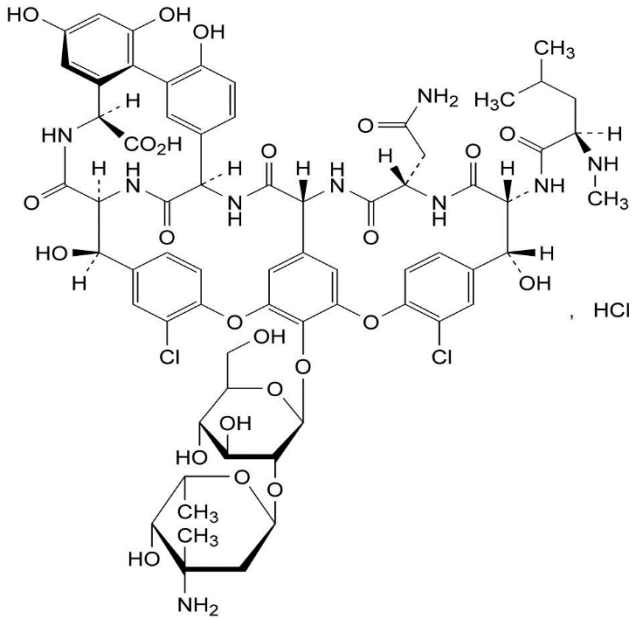
PRODUCT INFORMATION
VANCOMYCIN SANDOZ® 500mg & 1g POWDER FOR INJECTION

NAME OF THE MEDICINE

Active ingredient: Vancomycin hydrochloride

Inactive ingredient: Disodium edetate

Chemical structure:



Molecular formula: $C_{66}H_{75}Cl_2N_9O_{24}$•HCl

Molecular Weight: 1,485.7

CAS Number: 1404-93-9

DESCRIPTION

Vancomycin Sandoz is a chromatographically purified tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*) which is bactericidal against many gram-positive bacteria. It should be administered intravenously in dilute solution (see DOSAGE AND ADMINISTRATION).

Vancomycin hydrochloride is freely soluble in water and insoluble in alcohol. The structure of vancomycin hydrochloride has been confirmed by X-ray diffraction.

Vancomycin Sandoz is available as sterile vials containing vancomycin hydrochloride equivalent to 500,000 IU or 1,000,000 IU of vancomycin activity (approximately 500 mg and 1 g vancomycin) respectively. It is an off-white lyophilised plug. When reconstituted in water, it is a clear solution with a pH range of 2.5 to 4.5.

PHARMACOLOGY

Pharmacokinetics

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

In subjects with normal kidney function, multiple intravenous dosing of 1 g of vancomycin (15 mg/kg) infused over 60 minutes produces mean plasma concentrations of approximately 63 mg/L immediately at the completion of infusion, mean plasma concentrations of approximately 23 mg/L 2 hours after infusion, and mean plasma concentrations of approximately 8 mg/L 11 hours after the end of the infusion. Multiple dosing of 500 mg infused over 30 minutes produces mean plasma concentrations of about 49 mg/L at the completion of infusion, and mean plasma concentrations of about 19 mg/L 2 hours after infusion, and mean plasma concentrations of about 10 mg/L 6 hours after infusion. The plasma concentrations during multiple dosing are similar to those after a single dose.

Although commonly done, measurement of peak plasma levels has not been proven to correlate with either efficacy or toxicity. Monitoring of trough levels is useful in patients with abnormal volumes of distribution or abnormal renal function. Trough levels should be maintained between 10 to 20 mg/L, and sampled immediately before the next dose is administered. Peak levels, when measured, are usually in the range of 25 to 40 mg/L. Levels outside this range suggest abnormal volumes of distribution and dosage adjustments should be considered.

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 0.06 L/kg/hr, and mean renal clearance is about 0.05 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 0.69 L/kg. There is no apparent metabolism of the drug. About 60% of an intraperitoneal dose of vancomycin administered during peritoneal dialysis is absorbed systemically in 6 hours. Serum concentrations of about 10 mg/L are achieved by intraperitoneal injection of 30 mg/kg of vancomycin.

Although vancomycin is not effectively removed by either haemodialysis or peritoneal dialysis; there have been reports of increased vancomycin clearance with haemoperfusion and haemofiltration.

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

Protein binding is approximately 55% as measured by ultrafiltration at vancomycin serum concentrations of 10 to 100 mg/L. Clinically effective concentrations of this antibiotic in the blood are usually achieved and maintained by its intravenous administration, moreover, inhibitory concentrations can be demonstrated in pleural, pericardial, ascitic and synovial fluids, in urine, in peritoneal dialysis fluid, and in atrial appendage tissue. This antibiotic does not readily diffuse across the meninges into the cerebrospinal fluid.

Measurable serum concentrations of vancomycin may occur in patients treated for active pseudomembranous colitis due to *Clostridium difficile.*

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. Cross resistance with teicoplanin has been reported. 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*]); *C. difficile* (e.g. toxigenic strains implicated in pseudomembranous enterocolitis); and diphtheroids. The following *in vitro* data are available, but their clinical significance is unknown. Other organisms that are susceptible to vancomycin *in vitro* include *Listeria monocytogenes*, Lactobacillus species, Actinomyces species, Clostridium species, and Bacillus species.

Organism (Number of Isolates)	**MIC_{50} (mg/L)**	**MIC_{90} (mg/L)**
S. aureus		
methicillin-susceptible (90)	1.6	3.1
methicillin-susceptible (22)	0.7	0.9
methicillin-resistant (22)	1.6	3.1
methicillin-resistant (26)	0.4	0.4
S. epidermidis		
methicillin-susceptible (50)	1.6	6.3
methicillin-resistant (27)	1.6	3.1
methicillin-resistant (20)	2	4
Coagulase-negative		
staphylococcus (200)	2	4
Strep. pyogenes (110)	0.5	0.5
Strep. pneumoniae (74)	0.5	0.5
Strep. pneumoniae (penicillin-resistant) (10)	1	2
Strep. bovis (100)	0.25	0.5
Strep. mutans (viridans) group (82)	0.8	1.6

E. faecalis (enterococcus) (347)	1.6	1.6
Diphtheroids (JK strain) (98)	0.8	0.8
Listeria sp. (26)	0.8	1.6
C. difficile (78)	1	2
Clostridium sp. (14)	0.8	3.1

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

Synergy

The combination of vancomycin and an aminoglycoside acts synergistically *in vitro* against many strains of *S. aureus*, nonenterococcal group D streptococci, enterococci, and Streptococcus sp. (viridans group). The combination of vancomycin and a cephalosporin acts synergistically against some strains of *S. epidermidis* (methicillin-resistant). The combination of vancomycin and rifampin acts with partial synergism against some strains of *S. aureus* and with synergism against *S. epidermidis.* Synergy testing is helpful because the combination of vancomycin and a cephalosporin may act antagonistically against some strains of *S. epidermidis*, and the combination of vancomycin and rifampicin may act antagonistically against some strains of *S. aureus.*

Disc Susceptibility Tests

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

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.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

INDICATIONS

Vancomycin Sandoz is indicated in potentially life-threatening infections which cannot be treated with another effective, less toxic antimicrobial drug, including the penicillins and cephalosporins.

Vancomycin Sandoz is useful in therapy of severe staphylococcal (including methicillin-resistant staphylococcal) infections in patients who cannot receive or who failed to respond to the penicillins and cephalosporins or who have infections with staphylococci that are resistant to other antibiotics. Once sensitivity data are available, therapy should be adjusted accordingly.

Vancomycin Sandoz is effective alone or in combination with an aminoglycoside for endocarditis caused by *S. viridans* or *S. bovis.* For endocarditis caused by enterococci (e.g. *E. faecalis*), vancomycin is effective only in combination with an aminoglycoside. Vancomycin is effective for the treatment of diphtheroid endocarditis. Vancomycin is used in combination with rifampicin, an aminoglycoside, or both in early-onset prosthetic valve endocarditis caused by *S. epidermidis* or diphtheroids.

The effectiveness of vancomycin has been documented in other infections due to staphylococci including osteomyelitis, pneumonia, septicaemia, and soft tissue infections. When staphylococcal infections are localised and purulent, antibiotics are used as adjuncts to appropriate surgical measures.

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

Note for clinicians: Vancomycin should be administered orally for the treatment of Staphylococcal enterocolitis and antibiotic associated pseudomembranous colitis produced by *C. difficile.* Parenteral administration of vancomycin alone is inappropriate for this indication. Vancomycin is not effective by the oral route for other types of infections. For oral administration the parenteral formulation may be used. Some systemic absorption may occur following oral administration in patients with pseudomembranous colitis.

CONTRAINDICATIONS

Vancomycin is contraindicated in patients with known hypersensitivity to this antibiotic.

PRECAUTIONS

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

Vancomycin should be administered in a dilute solution at a rate not exceeding 500 mg/hour to avoid rapid-infusion-related reactions e.g., hypotension, flushing, erythema, urticaria and pruritus. Stopping the infusion usually results in a prompt cessation of these reactions (see DOSAGE AND ADMINISTRATION and ADVERSE EFFECTS).

Complications of occasional severe hypotension, histamine-like responses and rash can be avoided by slow administration of the recommended dilute solutions over at least one hour for both adults and children.

Vancomycin should be administered with caution in patients allergic to teicoplanin, since allergic cross reactions between vancomycin and teicoplanin have been reported.

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 (see DOSAGE AND ADMINISTRATION, Compatibility with Other Drugs and Intravenous Fluids).

Although intravitreal injection is not an approved route of administration for vancomycin, precipitation has also been reported after intravitreal injection of vancomycin and ceftazidime for endophthalmitis using different syringes and needles (see DOSAGE AND ADMINISTRATION, Compatibility with Other Drugs and Intravenous Fluids).

When given intravenously, toxic serum levels can occur. Vancomycin is excreted fairly rapidly by the kidney and blood levels increase markedly with decreased renal clearance. During parenteral therapy, the risk of toxicity and nephrotoxicity appears appreciably increased by high blood concentrations or prolonged treatment.

Because of its ototoxicity and nephrotoxicity, vancomycin should be used with care in patients with renal insufficiency. If it is necessary to use vancomycin parenterally in patients with renal impairment, the dose and/or dose intervals should be adjusted carefully (see DOSAGE AND ADMINISTRATION) and blood levels monitored.

When patients receive concomitant therapy with an aminoglycoside, serial monitoring of renal function should be performed.

Vancomycin should be avoided in patients with previous hearing loss. If it is used in such patients, the dose of vancomycin should be regulated, if possible by periodic determination of the drug level in the blood. Ototoxicity has occurred when serum levels exceeded 80 μg/mL. It may be transient or permanent. Deafness may be preceded by tinnitus. The elderly are more susceptible to auditory damage. Experience with other antibiotics suggests that deafness may be progressive despite cessation of treatment.

Patients with borderline renal function and individuals over the age of 60 should be given serial tests of auditory function and of vancomycin blood levels. All patients receiving the drug should have periodic haematological studies, urinalyses and liver and renal function tests.

Some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption of oral vancomycin and, therefore, may be at risk for the development of adverse reactions associated with the parenteral administration of vancomycin. The risk is greater if renal impairment is present. It should be noted that the total systemic and renal clearances of vancomycin are reduced in the elderly.

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.

If parenteral and oral vancomycin are administered concomitantly an additive effect can occur. This should be taken into consideration when calculating the total dose. In this situation serum levels of the antibiotic should be monitored.

Prolonged use of vancomycin may result in the overgrowth of non-susceptible 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 intravenous vancomycin.

Vancomycin is irritating to tissue and causes necrosis when injected intramuscularly; it must be administered intravenously. Pain and thrombophlebitis occur in many patients receiving vancomycin and are occasionally severe. The frequency and severity of thrombophlebitis can be minimised if the drug is administered in a volume of at least 200 mL of glucose or saline solution and if the sites of injection are rotated.

In surgical patients the administration of vancomycin should be carefully timed in relation to the induction of anaesthesia (see PRECAUTIONS, Interactions with other medicines).

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

Neither the safety nor the efficacy of vancomycin administration by the intrathecal or intraventricular routes have been studied. Vancomycin should not be administered by these routes.

Reports have revealed that administration of sterile vancomycin hydrochloride 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 varying degrees of abdominal pain and fever. This syndrome appears to be short-lived after discontinuation of intraperitoneal vancomycin.

Patients taking oral vancomycin should be warned of its offensive taste.

<u>Effects on fertility</u>

No definitive fertility studies have been performed.

Use in pregnancy (Category B2)

Animal reproduction studies have not been conducted with vancomycin. It is also not known whether vancomycin can affect reproduction capacity. In a controlled clinical study, vancomycin was administered to pregnant women for serious staphylococcal infections complicating intravenous drug abuse to evaluate potential ototoxic and nephrotoxic effects on the infant. Vancomycin 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. As only 10 patients were treated with vancomycin in this study, and administration was only in the second and third trimesters, it is not known whether vancomycin causes foetal harm. Vancomycin should be given to a pregnant woman only if clearly needed.

Use in lactation

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

Paediatric use

(See PRECAUTIONS.) In premature neonates, infants and children, it is appropriate to confirm vancomycin serum concentrations. Concomitant administration of vancomycin and anaesthetic agents has been associated with erythema and histamine-like flushing in children (see ADVERSE EFFECTS).

Use in the elderly

(See PRECAUTIONS.) 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).

Carcinogenicity

No long-term carcinogenicity studies have been performed with vancomycin in animals.

Genotoxicity

There are no studies available demonstrating the mutagenic potential of vancomycin.

Effects on ability to drive and use machines

Vancomycin may have influence on the ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICINES

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

In animal studies designed to evaluate nephrotoxicity in the rat, renal impairment occurred with high serum concentrations of vancomycin alone and with lower concentrations when vancomycin was administered with an aminoglycoside. Combining vancomycin with a loop diuretic in the rat model did not potentiate the renal impairment that occurred with vancomycin alone.

When treating patients with underlying renal dysfunction or those 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 in order to minimise the risk of nephrotoxicity.

Diuretics such as ethacrynic acid and frusemide may aggravate ototoxicity.

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

Vancomycin may enhance neuromuscular blockade produced by drugs such as suxamethonium or vecuronium.

Cholestyramine has been shown to bind *in vitro.* Therefore, if oral vancomycin is used with cholestyramine, the two drugs should be administered several hours apart.

ADVERSE EFFECTS

Infusion-Related Events: During or soon after infusion of vancomycin, patients may develop anaphylactoid reactions including hypotension, palpitations, substernal pressure, tachycardia, wheezing, dyspnoea, urticaria, or pruritus. Severe anaphylactoid reactions require immediate treatment with adrenaline, corticosteroids and oxygen. Rapid infusion may 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. In animal studies, hypotension and bradycardia occurred in animals given large doses of vancomycin at high concentrations and rates. Such events are infrequent if

vancomycin is given by a slow infusion over 60 minutes and at a sufficient dilution. In a study using multiple infusion rates, infusion-related events were not reported by the 4 volunteers administered vancomycin hydrochloride at a rate of 10 mg/min or less.

Gastrointestinal: Oral doses of vancomycin are extremely unpalatable and have been associated with nausea, diarrhoea and occasional vomiting.

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

Transient elevations of urea and granular casts in the urine occasionally occur.

Ototoxicity: There have been reports of hearing loss associated with vancomycin. Most of these patients had kidney dysfunction, pre-existing hearing loss, or concomitant treatment with an ototoxic drug. Vertigo, dizziness, and tinnitus have also been reported rarely.

Haematological: Some patients have been reported to have developed reversible neutropenia, usually starting one week or more after onset of therapy with vancomycin or after a total dose of more than 25 g. Neutropenia appears to be promptly reversible when vancomycin is discontinued. Thrombocytopenia has rarely been reported. Eosinophilia has also been reported. Although a causal relationship has not been established, reversible agranulocytosis (granulocyte count less than 500 /mm^3) has been reported rarely.

Cardiovascular: Hypotension, palpitations, substernal pressure, tachycardia (see ADVERSE EFFECTS, Infusion-Related Events).

Dermatological: Pruritus at injection site, generalised flushing, erythematous macular rash with intense pruritus over face, neck and upper body have occurred after too rapid injection of the drug. Tissue irritation and necrosis occur after intramuscular injection or extravasation from the intravenous site.

Phlebitis: Inflammation at the injection site has been reported.

Immunological: Hypersensitivity reactions with chills, nausea, urticaria, rashes, including exfoliative dermatitis, linear IgA bullous dermatosis, Stevens-Johnson Syndrome, toxic epidermal necrolysis and rare cases of vasculitis, fever and rigors. Anaphylactoid reactions have been reported infrequently.

General: The use of vancomycin may result in overgrowth of non-susceptible organisms. If new infections due to bacteria or fungi appear during therapy with this product, appropriate measures should be taken.

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

The Therapeutic Guidelines Antibiotic, Version 12, 2003, categorised the frequency of incidence of some of the adverse reactions detailed above as follows:

Uncommon (incidence > 1 in 1000 and < 1 in 100): itch, fever, chills, eosinophilia, mild gastrointestinal tract disturbances (oral vancomycin), pain, erythema, thrombophlebitis, nephrotoxicity.

Rare (incidence < 1 in 1000): anaphylaxis, red man syndrome, superinfection, thrombocytopenia, leucopenia, neutropenia, tinnitus, dizziness, ototoxicity, toxic epidermal necrolysis.

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 intravenous dose is 500 mg (in sodium chloride 0.9% or glucose 5% in sterile water for injection) every six hours or 1g every twelve hours. Each dose should be administered at no more than 10 mg/min or over a period of at least 60 minutes, whichever is longer. Other patient factors, such as age or obesity, may call for modification of the usual daily dose.

The majority of patients with infections caused by organisms susceptible to the antibiotic show a therapeutic response by 48 to 72 hours. The total duration of therapy is determined by the type and severity of the infection and the clinical response of the patient. In staphylococcal endocarditis, therapy for three weeks or longer is recommended.

Children: The paediatric dosage of vancomycin is calculated on the basis of 10 mg/kg of body weight every six hours after an initial loading dose of 15 mg/kg. Each dose should be administered over a period of at least 60 minutes.

Infants and Neonates: In neonates and young infants, the total daily intravenous dosage may be lower. An initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours in the first week of life and every 8 hours thereafter until one month of age. Each dose should be administered over 60 minutes. Close monitoring of serum vancomycin

concentrations is mandatory in these patients. Each dose should be administered over a period of at least 60 minutes.

Patients with Impaired Renal Function and Elderly Patients

Dosage adjustment must be made in patients with impaired renal function. In premature infants and in the elderly, dosage reduction may be necessary to a greater extent than expected because of decreasing renal function. Measurement of vancomycin serum concentrations is required to optimise therapy, especially in seriously ill patients with changing renal function. Vancomycin serum concentrations may be determined by use of a microbiological assay, a radioimmunoassay, a fluorescence polarisation immunoassay, a fluorescence immunoassay, or high-pressure liquid chromatography.

For most patients with renal impairment or the elderly, the dosage calculations may be made by using the following table. The vancomycin dose per day in mg is about 15 times the glomerular filtration rate in mL/min (see table below).

DOSAGE TABLE FOR VANCOMYCIN IN ADULT PATIENTS WITH IMPAIRED RENAL FUNCTION	
Creatinine Clearance mL/min	**Vancomycin Dose mg/24h**
100	1545
90	1390
80	1235
70	1080
60	925
50	770
40	620
30	465
20	310
10	155

Loading dose: The initial dose should be no less than 15mg/kg even in patients with mild to moderate renal insufficiency.

Anephric patients

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 in order to promptly achieve therapeutic serum concentrations. The dose required to maintain stable concentrations is 1.9 mg/kg/24 hours. Since individual maintenance doses of 250 (250,000 IU) to 1000 (1,000,000 IU) mg are convenient in patients with marked renal impairment, a dose may be given every several days rather than on a daily basis. In anuria, a dose of 1000 mg every 7 to 10 days has been recommended.

Preparation of solution

At the time of use, add 10 mL of sterile water for injection to the vial of dry, sterile vancomycin 500 mg or 20 mL of sterile water for injection to the vial of vancomycin 1 g. Vials reconstituted in this manner will give a solution of 50 mg/mL.

Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

Further dilution is required, read instructions which follow:

1. Intermittent infusion is the preferred method of administration. The solution containing vancomycin 500 mg (500,000 IU) can be added to 100 to 200 mL of sodium chloride 0.9% injection or glucose 5% in sterile water for injection. The solution containing 1g vancomycin (1,000,000 IU) can be added to 200 to 400 mL of sodium chloride 0.9% injection or glucose 5% in sterile water for injection. The desired dose should be administered by intravenous infusion at a rate of not more than 10 mg/min.

2. Continuous infusion (should be used only when intermittent infusion is not feasible). 1 to 2 g (1,000,000 to 2,000,000 IU) vancomycin activity can be added to a sufficiently large volume of 0.9% sodium chloride injection or 5% glucose in sterile water for injection to permit the desired daily dose to be administered slowly by intravenous infusion over a 24 hour period.

Compatibility with Other Drugs and Intravenous Fluids

The following diluents are physically and chemically compatible (with 4 g/L vancomycin):
5% glucose solution
5% glucose and 0.9% sodium chloride solution
Hartmann's solution
Hartmann's and 5% glucose solution
0.9% sodium chloride solution
Normosol®-M in 5% glucose solution

To avoid microbiological hazards, the solutions should be used as soon as possible after preparation.

Vancomycin solution has a low pH that may cause chemical or physical instability when it is mixed with other compounds. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution or container permits.

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 also been reported after intravitreal injection of vancomycin and ceftazidime for endophthalmitis using different syringes and needles.

For Oral Administration

The usual adult total daily dosage for antibiotic-associated pseudomembranous colitis produced by *C. difficile* and Staphylococcal enterocolitis is 500 mg to 2 g given in 3 or 4 divided doses for 7 to 10 days. The total daily dosage in children is 40 mg/kg of body weight in 3 or 4 divided doses. The total daily dosage should not exceed 2 g.

After initial reconstitution of the vial the appropriate dose may be diluted in 30 mL of distilled or deionised water and given to the patient to drink, or the diluted material may be administered via nasogastric tube. Common flavouring syrups may be added to the solution to improve the taste for oral administration.

Stability of Prepared Solution

After reconstitution with water for injection, 5% glucose injection or 0.9% sodium chloride injection, the solution may be stored in a refrigerator for 24 hours without significant loss of potency. To reduce microbiological hazards, the solution should be used as soon as practicable after reconstitution.

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed by dialysis. Haemoperfusion with Amberlite resin XAD-4 has been reported to be of limited benefit. Haemofiltration and haemoperfusion with polysulfone resin have been reported to result in increased vancomycin clearance.

In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

PRESENTATION AND STORAGE CONDITIONS

Vancomycin Sandoz (vancomycin hydrochloride) equivalent to 500,000 IU vancomycin activity (approximately 500 mg vancomycin), 15 mL size, rubber-stoppered vials. Packs of 1, 5 or 10.

Vancomycin Sandoz (vancomycin hydrochloride) equivalent to 1,000,000 IU

vancomycin activity (approximately 1g vancomycin), 25 mL size, rubber-stoppered vials. Packs of 1, 5 or 10.

Not all presentations may be marketed in Australia

Store powder for injection below 25°C.
Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia
Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 04/11/2004

Date of most recent amendment: 10/02/2016