AUSTRALIAN PRODUCT INFORMATION – DBL™ Vancomycin (Vancomycin hydrochloride)

1. NAME OF THE MEDICINE

Vancomycin hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of DBL Vancomycin contains 500 mg or 1000 mg of vancomycin (as the hydrochloride).

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Powder for injection is a white to light brown powder or plug.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

DBL Vancomycin is useful in therapy of severe staphylococcal (including methicillin-resistant staphylococcal) infections in patients who cannot receive or who have 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.

DBL Vancomycin 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., *S. faecalis*), vancomycin is effective only in combination with an aminoglycoside. Vancomycin is effective for the treatment of diphtheroid endocarditis. DBL 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, skin and skin structure infections. When staphylococcal infections are localised and purulent, antibiotics are used as adjuncts to appropriate surgical measures.

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

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.

4.2 Dose and method of administration

DBL Vancomycin is a lyophilized powder for reconstitution, which contains disodium edetate. When reconstituted in water, it is a clear solution with a pH of 2.5 to 4.5. Hydrochloric acid and sodium hydroxide are used to adjust the pH during the manufacture of DBL Vancomycin.

Dosage

Adults

The usual intravenous dose is 500 milligrams every 6 hours or 1000 mg every 12 hours. A 500 milligram dose of vancomycin should be infused over a period of at least 60 minutes, whereas a 1000 mg dose should be administered over a period of at least two hours. Vancomycin must not be given by intramuscular injections (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Oral administration

The usual adult total daily dosage for antibiotic associated pseudomembranous colitis produced by *C. difficile* is 500 milligrams to 2 g given in three or four divided doses for 7 to 10 days. The total daily dosage in children is 40 milligram/kg bodyweight in three or four divided doses. The total daily dosage should not exceed 2 g.

The contents of 1 vial (500 milligrams) (500,000 IU) 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.

Dosage adjustment

Adults with impaired renal function and the elderly

Dosage adjustment must be made in patients with impaired renal function to avoid toxic serum levels. 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 milligrams is about 15 times the glomerular filtration rate in mL/minute (see table below).

Vancomycin Dosage in patients with impaired renal function

Creatinine clearance mL/minute	**Vancomycin dose milligram/24 hours**
100	1545

Creatinine clearance mL/minute	Vancomycin dose milligram/24 hours
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 15 milligram/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 milligram/kg bodyweight should be given in order to promptly achieve therapeutic serum concentrations. The dose required to maintain stable concentrations is 1.9 milligram/kg/24 hours. Since individual maintenance doses of 250 (250,000 IU) to 1,000 (1,000,000 IU) milligrams 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 1,000 milligrams every seven to ten days has been recommended.

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 milligram/kg bodyweight every six hours after an initial loading dose of 15 milligram/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 milligram/kg is suggested, followed by 10 milligram/kg every twelve hours in the first week of life and every eight hours thereafter until one month of age. Close monitoring of serum vancomycin concentrations is mandatory in these patients. Each dose should be administered over a period of at least 60 minutes.

Method of administration

Preparation of solution for injection

At the time of use, the 500 milligram (500,000 IU) vial should be reconstituted with 10 mL of Water for Injections. The resulting solution contains vancomycin 50 milligram/mL. The 1000 mg (1,000,000 IU) vial should be reconstituted with 20 mL of Water for Injections. The resulting solution contains vancomycin 50 milligram/mL. The reconstituted solution containing 500 milligrams of vancomycin must be further diluted with at least 100 mL of Sodium Chloride Intravenous Infusion 0.9% or Glucose Intravenous Infusion 5%. The reconstituted solution containing 1000 mg of vancomycin must be further diluted with at least 200 mL of Sodium Chloride Intravenous Infusion 0.9% or Glucose Intravenous Infusion 5%. The resulting solution should be infused over a period of at least 60 minutes when 500 milligrams of vancomycin is to be administered, or at least 2 hours when 1000 mg of vancomycin is to be given. In selected patients in need of fluid restriction, a concentration of up to 10 mg/mL may be used; use of such higher concentration may increase the risk of infusion related events. Infusion related events may occur, however, at any rate of concentration.

Stability of reconstituted solution

Solutions of Vancomycin 50 milligram/mL (50,000 IU/mL) in Water for Injections do not show significant loss of potency when stored at 2 to 8°C for 96 hours.

When diluted to a concentration of either 10 milligram/mL or 1 milligram/mL with Sodium Chloride Intravenous Infusion 0.9% or Glucose Intravenous Infusion 5%, vancomycin was chemically stable for 24 hours at 25°C and 28 days at 2 to 8°C.

To reduce microbiological hazard, the infusion should be commenced as soon as practicable after reconstitution/preparation. If storage is necessary, the solution should be held at 2 to 8°C for not more than 24 hours.

4.3 Contraindications

DBL Vancomycin is contraindicated in patients with known hypersensitivity to vancomycin or any of the excipients or other glycopeptides.

4.4 Special warnings and precautions for use

General

Patients with a creatinine clearance <60 mL/minute and all elderly individuals should be given serial tests of auditory function and of vancomycin blood levels. All patients receiving the drug should have periodic haematological studies, urine analysis, and renal function tests.

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions are possible (see section 4.3 CONTRAINDICATIONS and section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). In case of hypersensitivity reactions, treatment with vancomycin must be discontinued immediately and the adequate emergency measures must be initiated.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP) have been reported in association with vancomycin treatment (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Patients should be advised to inform their doctor at the first appearance of rash or any other sign of hypersensitivity.

If a SCAR is suspected, the drug should be discontinued and specialist dermatological assessment should be carried out.

Infusion reactions

Rapid bolus administration (e.g., over several minutes) may be associated with exaggerated hypotension, including shock, and, rarely, cardiac arrest, histamine like responses and maculopapular or erythematous rash ("red neck").

DBL Vancomycin should be administered in a dilute solution at a rate not exceeding 500 milligram/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 sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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.

Since vancomycin is irritating to tissue and causes drug fever, pain and possibly necrosis, it should **never** be 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 injection sites are rotated.

Use in renal impairment

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 section 4.2 DOSE AND METHOD OF ADMINISTRATION) and blood levels monitored. Serial monitoring of renal function should be performed.

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

Ototoxicity

Ototoxicity has occurred when serum levels exceeded 80 microgram/mL. It may be transient or permanent. Deafness may be preceded by tinnitus and should be regarded as an indication

to discontinue treatment. The elderly are more susceptible to auditory damage. Experience with other antibiotics suggests that deafness may be progressive despite cessation of treatment.

Vancomycin should be avoided (if possible) in patients with previous hearing loss. If it is used in such patients, the dose of vancomycin should be regulated by periodic determination of drug levels in the blood. Patients with renal insufficiency 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 hematologic studies, urinalyses, and liver and renal function tests.

Most of the patients who experienced hearing loss had kidney dysfunction, pre-existing hearing loss, or concomitant treatment with an ototoxic drug (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Cross-sensitivity reactions

Vancomycin should be used with caution in patients with allergic reactions to teicoplanin, since cross hypersensitivity, including fatal anaphylactic shock, may occur.

Blood disorders

Reversible neutropenia has been reported in patients receiving vancomycin hydrochloride (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Patients who will undergo prolonged therapy with vancomycin or those who are receiving concomitant medicines which may cause neutropenia should have periodic monitoring of the leukocyte count.

Other routes of administration

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

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.

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.

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 effects associated with the parenteral administration of vancomycin. The risk is greater if renal impairment is present.

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

Use during anaesthesia

In surgical patients, the administration of vancomycin should be carefully timed in relation to the induction of anaesthesia (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Superinfection

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 including withdrawal of vancomycin.

***Clostridioides difficile*-associated disease**

In rare instances there have been reports of pseudomembranous colitis due to *Clostridioides difficile* developing in patients who received intravenous vancomycin. *C. difficile* associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including vancomycin hydrochloride, and may range in severity from mild diarrhoea 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 diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Other

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly etacrynic acid, neuromuscular blocking agents, aminoglycoside antibiotics, polymixin B colistin, viomycin and cisplatin requires careful monitoring.

Haemorrhagic occlusive retinal vasculitis

Haemorrhagic occlusive retinal vasculitis, including permanent loss of vision, can occur in patients receiving intracameral or intravitreal administration of vancomycin during or after cataract surgery. The safety and efficacy of vancomycin administered by the intracameral or the intravitreal route have not been established by adequate and well-controlled trials and these are not approved routes of administration for vancomycin. Vancomycin is not indicated for prophylaxis of endophthalmitis.

Use in the elderly

It should be noted that the total systemic and renal clearances of vancomycin are reduced in the elderly. 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 section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Paediatric use

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 section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Concurrent administration with other neurotoxic (e.g. ototoxic) or nephrotoxic drugs, e.g., streptomycin, neomycin, gentamicin, kanamycin, amikacin, amphotericin B, bacitracin, tobramycin, polymyxin B, colistin, cisplatin or piperacillin/tazobactam, requires careful monitoring (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

In order to minimise the risk of nephrotoxicity 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 (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Diuretics such as etacrynic acid and furosemide (frusemide) may aggravate ototoxicity.

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

Reversible neutropenia has been reported in patients receiving vancomycin hydrochloride (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Patients who are receiving concomitant medicines which may cause neutropenia should have periodic monitoring of the leukocyte count.

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 at a rate not exceeding 500 milligram/hour prior to anaesthetic induction.

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

No definitive fertility studies have been performed.

Use in pregnancy – Category B2

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, 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 fetal harm. DBL Vancomycin should be given to a pregnant woman only if clearly needed and blood levels should be monitored carefully to minimise fetal toxicity.

Use in lactation

Vancomycin is excreted in breast milk but it is not known whether it is harmful to the newborn. Therefore, it is not recommended for nursing mothers unless the expected benefits outweigh any potential risk.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

General disorders and administration site conditions

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. Such events are infrequent if vancomycin is given by a slow infusion at a rate not exceeding 500 milligram/hour and at an appropriate dilution.

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 occurs after intramuscular injection or extravasation from the intravenous site.Hypotension, bradycardia, cardiogenic shock and cardiac arrest have been reported following rapid bolus injection.

Drug fever has also been reported.

Ear and labyrinth disorders

Sensorineural deafness which may be accompanied by tinnitus has occurred but the incidence is low. Permanent deafness is more likely to occur in patients with compromised auditory or renal function but reversible deafness has been reported in normal patients. Vertigo and dizziness have also been reported.

Gastrointestinal disorders

Nausea, vomiting, diarrhoea and pseudomembranous enterocolitis.

Oral doses are extremely unpalatable. In leukaemic patients, oral dosing regimens are associated with frequent nausea, diarrhoea and occasional vomiting.

Blood and lymphatic system disorders

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 grams. Neutropenia appears to be promptly reversible when vancomycin is discontinued. Thrombocytopenia has rarely been reported. Eosinophilia and pancytopenia have also been reported. Although a casual relationship has not been established, reversible agranulocytosis (granulocyte count less than $500/mm^3$) has been reported rarely.

Immune system disorders

Anaphylaxis and hypersensitivity reactions with chills, nausea, urticaria, macular rash, fever and rigors. Kounis syndrome has also been reported.

Skin and subcutaneous tissue disorders

The types of rashes that can occur include exfoliative dermatitis, Linear IgA bullous dermatosis, Stevens-Johnson syndrome, toxic epidermal necrolysis and rare cases of vasculitis. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and AGEP (Acute Generalised Exanthematous Pustulosis) have been reported. Anaphylactoid reactions have been reported infrequently (see General disorders and administration site conditions).

Renal and urinary disorders

Rarely, renal failure, principally manifested by increased serum creatinine or urea concentrations, especially in patients given large doses of vancomycin, has been reported. Acute tubular necrosis and 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, azotemia resolved in most patients. Transient elevations of urea and granular casts in the urine occasionally occur.

Vascular disorders

Phlebitis and vasculitis have been reported.

General

The use of vancomycin may result in overgrowth of non-susceptible organisms resulting in new bacterial or fungal infections. If the 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 section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is not effectively removed by either haemodialysis or peritoneal dialysis. Increased vancomycin clearance has been reported with highly permeable membranes (polysulfone resin) used in high-flux haemodialysis. At 4 to 6 hours following the onset of high-flux haemodialysis, steady state concentrations of vancomycin may be reduced by 10 to 15% of the predialysis concentrations. It has also been reported that haemoperfusion with XAD-4 Resin has been shown to be of benefit.

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Vancomycin is an amphoteric glycopeptide antimicrobial substance produced by the growth of certain strains of *Nocardia orientalis*. It is bactericidal against many gram-positive organisms. Vancomycin is not chemically related to any of the presently used antimicrobial agents. Vancomycin hydrochloride is freely soluble in water and insoluble in alcohol.

Microbiology

Vancomycin is active against many gram-positive organisms (see below). Gram-negative bacteria, mycobacteria and fungi are resistant. Many strains of gram-positive bacteria are sensitive *in vitro* to vancomycin concentrations of 0.5 to 5 microgram/mL, but a few *Staph. aureus* strains require 10 to 20 microgram/mL for inhibition.

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*); *Clostridioides difficile* (e.g., toxigenic strains implicated in pseudomembranous enterocolitis); diphtheroids (e.g., *JK corynebacterium*). Other organisms that are susceptible to vancomycin *in vitro* include *Listeria monocytogenes, Lactobacillus* species, *Actinomyces* species, *Clostridioides* species, and *Bacillus* species.

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

The combination of vancomycin and a cephalosporin acts synergistically against some strains of *S. epidermidis* (methicillin-resistant). The combination of vancomycin and rifampicin 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*.

Vancomycin appears to act by inhibiting the production of bacterial cell wall mucopeptide. This effect occurs at a site different from that affected by penicillins and produces immediate inhibition of cell wall synthesis and secondary damage to the cytoplasmic membrane. There is also evidence that vancomycin alters the permeability of the cell membrane and selectively inhibits RNA synthesis.

There is no cross resistance between vancomycin and other antibiotics.

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.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Vancomycin is poorly absorbed by mouth. It is given intravenously for the treatment of systemic infections. In subjects with normal renal function participating in a multi-dose study,

1000 mg (1,000,000 IU) given over 60 minutes produced mean plasma levels of approximately 63 microgram/mL immediately after the completion of infusion, and mean plasma levels of approximately 23 microgram/mL and approximately 8 microgram/mL at 2 hours and 11 hours respectively, after completion of the infusion. Serum levels will be higher in patients with renal impairment, and toxicity may result.

Distribution

Protein binding is approximately 55% as measured by ultra filtration at vancomycin serum concentrations of 10 to 100 microgram/mL. 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. Vancomycin does not readily diffuse across the meninges into the cerebrospinal fluid.

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

Excretion

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 the urine by glomerular filtration. Mean plasma clearance is about 0.06 L/kg/hour, and mean renal clearance is about 0.05 L/kg/hour. 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.

Vancomycin is not effectively removed by either haemodialysis or peritoneal dialysis; there have been no reports of vancomycin clearance with haemoperfusion.

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

5.3 Preclinical safety data

Genotoxicity

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

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate

Hydrochloric acid

Sodium hydroxide

6.2 Incompatibilities

Vancomycin hydrochloride solutions have a low pH and may cause chemical or physical instability when mixed with other compounds. All parenteral drug products should be inspected visually for both 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 milligram/mL or less.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

DBL Vancomycin is available in a glass vial.

500 mg: 1 vial per pack, 10 vials per pack.

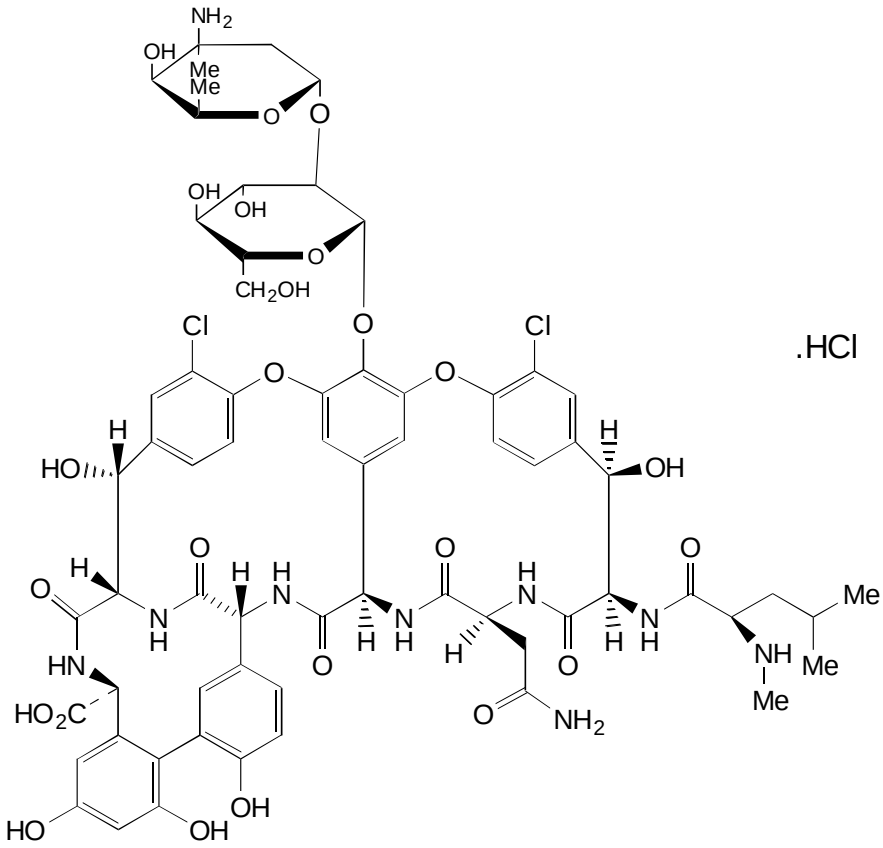
1000 mg: 1 vial per pack.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure



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

Molecular weight: 1485.7

CAS number

1404-93-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

26 March 1998

10. DATE OF REVISION

25 January 2023

Summary Table of Changes

Section changed	Summary of new information
4.8	Addition of ADR ‘Kounis syndrome’