AUSTRALIAN PRODUCT INFORMATION

VANCOMYCIN VIATRIS

Vancomycin (as hydrochloride) powder for injection

1 NAME OF THE MEDICINE

Vancomycin hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VANCOMYCIN VIATRIS 500 mg: Each vial contains 500 mg (500,000 IU) of vancomycin (as hydrochloride).

VANCOMYCIN VIATRIS 1000 mg: Each vial contains 1000 mg (1,000,000 IU) of vancomycin (as hydrochloride).

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

3 PHARMACEUTICAL FORM

Powder for injection. Off white to light tan coloured lyophilized plug or powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

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.

Vancomycin is effective alone or in combination with an aminoglycoside for endocarditis caused by *Strep. viridans* or *Strep. bovis*. For endocarditis caused by Enterococci (eg *Enterococcus 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 *Staph. 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

This product is for single use in one patient only. Discard any residue.

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/minute are recommended in adults (see also age specific recommendations). In selected patients in need of fluid restriction, a concentration of up to 10mg/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.

Normal renal function - Adults

The usual intravenous dose is 500 milligrams every 6 hours or 1 g every 12 hours. A 500 milligram dose of vancomycin should be infused over a period of at least 60 minutes, whereas a 1 g 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**).

Each dose should be administered at no more than 10 mg/minute 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.

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).

Table 1: Vancomycin dosage in patients with impaired renal function

Creatinine clearance mL/minute	**Vancomycin dose milligram/24 hours**
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 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.

Oral administration

The usual adult total daily dosage for antibiotic associated pseudomembranous colitis produced by *C. difficile* and staphylococcal enterocolitis 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.

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. 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.

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 1g (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 1 g 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 1 g 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.

Compatibility with other medicines and intravenous fluids

Vancomycin solutions have a low pH and may cause chemical or physical instability when mixed with other compounds. All parenteral medicine 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 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.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Vancomycin Hydrochloride for Intravenous Infusion should be administered in a dilute solution over a period of not less than 60 minutes to avoid rapid-infusion-related reactions. Stopping the infusion usually results in a prompt cessation of these reactions (See **SECTION 4.2 DOSE AND METHOD OF ADMINISTRATION** and **SECTION 4.8 ADVERSE EFFECTS (UNDESIRABLE 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 **SECTION 4.2 DOSE AND METHOD OF ADMINISTRATION,** *Compatibility with other medicines 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 **SECTION 4.2 DOSE AND METHOD OF ADMINISTRATION,** *Compatibility with other drugs and intravenous fluids*).

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 medicine levels in the blood.

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 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* in patients who receive intravenous vancomycin.

Since vancomycin is irritating to tissue and causes 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 medicine is administered in a volume of at least 200 mL of glucose or saline solution and if the injection sites are rotated.

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.

The safety and efficacy of vancomycin administration by the intrathecal (intralumbar or intraventricular) route have not been assessed. Vancomycin should not be administered by these routes.

Use in Renal Impairment

Because of its ototoxicity and nephrotoxicity, vancomycin should be used with care in patients with renal insufficiency. The risk of toxicity is appreciably increased by high blood concentrations or prolonged therapy. If it is necessary to use vancomycin in such patients, blood levels should be monitored and appropriate dosage modifications made.

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. (Vancomycin serum levels may be determined by use of the modified Rammelkamp serial twofold dilution technique with streptococcus C203 as the indicator organism). All patients receiving the medicine should have periodic hematologic studies, urinalyses, and liver and renal function tests.

Reports have revealed that administration of sterile vancomycin HCl 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.

Use in the Elderly

See **SECTION 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.** The natural decrement of glomerular filtration with increasing age may lead to elevated vancomycin serum concentrations if dosage is not adjusted. Vancomycin dosage schedules should be adjusted in elderly patients (See **SECTION 4.2 DOSE AND METHOD OF ADMINISTRATION**).

Paediatric Use

See **SECTION 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR 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 and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic medicines, e.g. amphotericin B (amphotericin) , 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 (See **SECTION 4.2 DOSE AND METHOD OF ADMINISTRATION)**.

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

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available

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 medicine 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 Hydrochloride for Intravenous Infusion should be given to a pregnant woman only if clearly needed.

Australian categorisation definition of Category B2:

Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

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)

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a serious, potentially life-threatening adverse drug reaction with distinct features. Prompt recognition along with drug withdrawal is essential for improved prognosis. DRESS is characterised by severe drug eruption accompanied by high fever, erythematous rash and inflammation of internal organs.

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 (epinephrine), 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 an appropriate 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.

Otoxicity

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.

Cardiovascular

Hypotension, palpitations, substernal pressure, tachycardia (See *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 medicine. Tissue irritation and necrosis occurs after intramuscular injection or extravasation from the intravenous site.

Gastrointestinal

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

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 grams. Neutropenia appears to be promptly reversible when vancomycin is discontinued. Thrombocytopenia has rarely been

reported. Eosinophilia has also been reported. Although a casual relationship has not been established, reversible agranulocytosis (granulocyte count less than 500/mm^3) has been reported rarely.

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 (See *Infusion related events*).

Nephrotoxicity

Rarely, renal failure, principally manifested by increased serum creatinine or urea concentrations, especially in patients given large doses of vancomycin, 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.

Liver Function

Elevation of liver transaminases.

General

The use of vancomycin may result in overgrowth of non-susceptible organisms. 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**).

Phlebitis

Inflammation at the injection site has been reported.

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. Haemoperfusion with Amberlite resin XAD-4 has been reported to be of limited benefit. Haemofiltration and heamoperfusion with polysulfone resin have been reported to result in increased vancomycin clearance.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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.

Microbiology

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*); *Clostridium difficile* (e.g. toxigenic strains implicated in pseudomembranous enterocolitis); diphtheroids (e.g. *JK corynebacterium*). The *in vitro* susceptibility data are listed in Table 2, 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.

Table 2: Vancomycin *in vitro* activity

Organism	Number of isolates	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Staphylococcus 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
Staphylococcus 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
Streptococcus pyogenes	110	0.5	0.5
Streptococcus pneumoniae	74	0.5	0.5
Streptococcus pneumoniae (penicillin resistant)	10	1	2
Streptococcus bovis	100	0.25	0.5
Streptococcus mutans (viridans group)	82	0.8	1.6
Enterococcus faecalis	347	1.6	1.6
Diphtheroids (JK strain)	98	0.8	0.8
Listeria sp.	26	0.8	1.6
Clostridium 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*, 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*.

Disc Susceptibility Tests: Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. The Bauer-Kirby-Sherris-Turck Method has been recommended for use with discs for testing susceptibility to vancomycin. Results of standard single-dose susceptibility tests with a 30 µg vancomycin hydrochloride disc should be interpreted according to the following criteria. Susceptible organisms produce zones greater than or equal to 12mm, indicating that the test organism is likely to respond to therapy. Organisms that produce zones of 10 or 11 mm are considered to be of intermediate susceptibility. Organisms in this category are likely to respond if the infection is confined to tissues or fluids in which high antibiotic concentrations are attained. Resistant organisms produce zones of 9 mm or less, indicating that other therapy should be selected. With a standardised dilution method, a bacterial isolate may be considered susceptible if the MIC value for vancomycin is 4 mg/L or less. Organisms are considered resistant to vancomycin if the MIC is greater than or equal to 16 mg/L. Organisms having an MIC value of less than 16 mg/L but greater than 4 mg/L are considered to be of intermediate susceptibility.

Standardised procedures require the use of laboratory control organisms. The 30 µg vancomycin disc should give zone diameters between 15 and 19 mm for S. aureus ATCC 25923. As with the standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard vancomycin powder should give MIC values in the range of 0.5 mg/L to 2.0 mg/L for S. aureus ATCC 29213. For E. faecalis ATCC 29212, the MIC range should be 1.0 to 4.0 mg/L.

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. 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.

About 60% of an intraperitoneal dose of vancomycin administered during peritoneal dialysis is absorbed systemically in 6 hours.

Distribution

The distribution coefficient is from 0.3 to 0.69 L/kg. Serum concentrations of about 10 mg/L are achieved by intraperitoneal injection of 30 mg/kg of vancomycin.

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 Clostridium difficile.

Metabolism

There is no apparent metabolism of the drug.

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.

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

No data available

Genotoxicity

No data available

Carcinogenicity

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Hydrochloric acid and sodium hydroxide for pH adjustment.

6.2 INCOMPATIBILITIES

Vancomycin solutions have a low pH and may cause chemical or physical instability when mixed with other compounds. All parenteral medicine 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 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.

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 in original container. Protect from light.

See also **SECTION 4.2 DOSE AND METHOD OF ADMINISTRATION,** *Stability of reconstituted solution.*

6.5 NATURE AND CONTENTS OF CONTAINER

The injections are packaged in clear Type I glass vials with a grey bromobutyl stopper – packs of 1 vial/carton.

Australian Register of Therapeutic Goods (ARTG)

AUST R 373670 – VANCOMYCIN VIATRIS 500 mg vancomycin (as hydrochloride) powder for injection vial

AUST R 373671 – VANCOMYCIN VIATRIS 1000 mg vancomycin (as hydrochloride) powder for injection vial

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

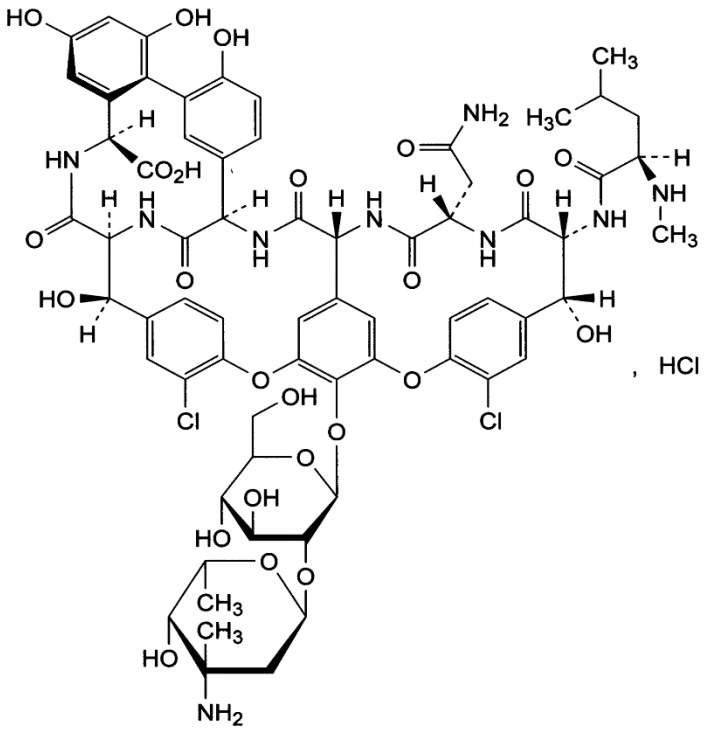
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Vancomycin is an amphoteric glycopeptide antimicrobial substance produced by the growth of certain strains of *Amycolatopsis orientalis* (formerly *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.

Vancomycin Hydrochloride for Intravenous Infusion is a lyophilized powder for reconstitution. When reconstituted in water, it is a clear solution with a pH of 2.8 to 4.5. It should be administered intravenously in dilute solution. See **SECTION 4.2 DOSE and METHOD of ADMINISTRATION**.

Chemical Structure



Molecular Formula: $C_{66}H_{75}Cl_2N_9O_{24}$,HCl
Molecular Weight: 1485.7

CAS Number

CAS No: 1404-93-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Alphapharm Pty Limited trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

15 March 2022

10 DATE OF REVISION

07/04/2022

Summary Table of Changes

Section Changed	Summary of New Information
3	Description of powder appearance updated.
6.1	Updated excipients.
6.5	Updated container type. Include AUST R numbers.
8	Sponsor details updated.

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