NEW ZEALAND DATA SHEET

VANCOMYCIN

1. Product Name

Vancomycin 500 mg and 1000 mg powder for infusion.

2. Qualitative and Quantitative Composition

Each vial contains 500 mg or 1000 mg of vancomycin base.

3. Pharmaceutical Form

Vancomycin powder for infusion is a white to almost white or slightly pink or yellow freeze-dried powder which has been prepared in a sterile fashion.

When reconstituted in water, it is a clear solution with a pH of 2.8 – 4.5.

4. Clinical Particulars

4.1 Therapeutic indications

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

Vancomycin hydrochloride 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 hydrochloride 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 hydrochloride is effective only in combination with an aminoglycoside. Vancomycin hydrochloride is effective for the treatment of diptheroid endocarditis. Vancomycin hydrochloride 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 hydrochloride.

Vancomycin hydrochloride should be administered orally for the treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis (produced by *C. difficile*). Parenteral administration of vancomycin hydrochloride alone is inappropriate for this indication.

Vancomycin hydrochloride 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 pseudo-membranous colitis.

4.2 Dose and method of administration

Dose

Adults

The usual intravenous dose is 500 mg every 6 hours or 1g every 12 hours. A 500 mg dose of vancomycin hydrochloride 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 2 hours. Vancomycin must not be given by intramuscular injections (see section 4.4).

Loading dose

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

Special populations

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 polarization 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).

Dosage table for vancomycin in patients with impaired renal function

Creatinine clearance (ml/min)	Vancomycin dose (mg/24h)
100	1,545
90	1,390
80	1,235
70	1,080
60	925
50	770
40	620
30	465
20	310
10	155

Anephric patients

The table is not valid for functionally anephric patients. For such patients, an initial dose of 15 mg/kg bodyweight should be given in order to promptly achieve therapeutic serum concentrations. The dose required to maintain stable concentrations is 1.9 mg/kg/24hours. Since individual maintenance

doses of 250 (250,000 IU) – 1,000 (1000,000 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 1,000 mg every 7 to 10 days has been recommended.

The majority of patients with infections caused by organisms susceptible to the antibiotic show a therapeutic response by 48 - 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 bodyweight 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. 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

Oral administration

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

The contents of one 500 mg (500,000 IU) vial 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.

Reconstituted powder, diluted solution for oral use can be stored for 96 hours at 2°C to 8°C or 24 hours below 25°C.

Preparation of solution for injection

At the time of use, the 500 mg (500,000 IU) vial should be reconstituted with 10 ml of Water for Injections. The resulting solution contains vancomycin 50 mg/ml. The 1 g (1,000,000 IU) vial should be reconstituted with 20 ml of Water for Injections. The resulting solution contains vancomycin 50 mg/ml. The reconstituted solution containing 500 mg 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% to a concentration of not more than 5 mg/ml. The resulting solution should be infused over a period of at least 60 minutes when 500 mg 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.

Displacement volumes

500 mg vial: following reconstitution with 10 ml of Water for Injections, the average displacement volume is 0.254 ml.

1000 mg vial: following reconstitution with 20 ml of Water for Injections, the average displacement volume is 0.486 ml.

Stability of reconstituted solution

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

When diluted to a concentration of either 10 mg/ml or 1 mg/ml with Sodium Chloride Intravenous Infusion 0.9% or Glucose Intravenous Infusion 5%, vancomycin was chemically stable for 24 hours at 2°C 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°C to 8°C for not more than 24 hours.

4.3 Contraindications

Vancomycin hydrochloride is contraindicated in patients with known hypersensitivity to vancomycin, or any other excipients or in patients with previous anaphylaxis or major allergy with other glycopeptides (see section 4.4).

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 medication 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 and 4.8). In case of hypersensitivity reactions, treatment with vancomycin must be discontinued immediately and the adequate emergency measures must be initiated.

In patients receiving vancomycin over a longer-term period or concurrently with other medications which may cause neutropenia or agranulocytosis, the leukocyte count should be monitored at regular intervals.

Severe cutaneous adverse reactions (SCARs)

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), which can be life-threatening or fatal, have been reported in association with vancomycin treatment (see section 4.8). Most of these reactions occurred within a few days and up to eight weeks after commencing treatment with vancomycin. Patients should be advised to inform their doctor at the first appearance of rash or any other sign of hypersensitivity.

At the time of prescription, patient should be advised of the signs and symptoms and monitored closely for skin reactions. If a SCAR is suspected, the medication should be discontinued, and specialist dermatological assessment should be carried out. If the patient has developed a SCAR with the use of vancomycin, treatment with vancomycin must not be restarted at ay time.

Infusion-related reactions (IRRs)

Rapid bolus administration (i.e. over several minutes) may be associated with exaggerated hypotension (including shock, and, rarely, cardiac arrest), histamine like responses and maculopapular or erythematous rash (“red man’s syndrome” or “red neck syndrome”).

Vancomycin hydrochloride should be administered in a dilute solution at a rate not exceeding 500 mg/hour to avoid rapid-infusion-related reactions (IRRs), e.g. hypotension, flushing, erythema,

urticaria and pruritus. Stopping the infusion usually results in a prompt cessation of these reactions (see sections 4.2 and 4.8).

The frequency of IRRs (hypotension, flushing, erythema, urticaria and pruritus) increases with the concomitant administration of anaesthetic agents. This may be reduced by administering the vancomycin by infusion over at least 60 minutes, before anaesthetic induction.

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.

Administration site related reactions

Pain and thrombophlebitis may occur in many patients receiving vancomycin and are occasionally severe. The frequency and severity of thrombophlebitis can be minimised if the medication is administered in a volume of at least 200 ml of glucose or saline solution and if the injection sites are rotated. The efficacy and safety of vancomycin has not been established for intrathecal, intralumbar and intraventricular or by intraperitoneal routes of administration. Since vancomycin hydrochloride is irritating to tissue and causes drug fever, pain and possibly necrosis it should never be injected intramuscularly; it must be administered intravenously.

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) 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, which may be transitory or permanent has been reported in patients with prior deafness, who have received excessive intravenous doses, when serum levels exceeded 80 microgram/ml, or who received concomitant treatment with another ototoxic active substance such as an aminoglycoside. Deafness may be preceded by tinnitus and should be regarded as an indication to discontinue treatment. Experience with other antibiotics suggests that deafness may be progressive despite cessation of treatment. Serial test of auditory function may be helpful in order to minimise the risk of ototoxicity. The elderly are more susceptible to auditory damage. Monitoring of vestibular and auditory function in the elderly should be carried out during and after treatment.

Vancomycin hydrochloride 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 medication 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 medication 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 medication (see section 4.5).

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). Patients who will undergo prolonged therapy with vancomycin hydrochloride 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 hydrochloride 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 or with *C. difficile*-induced pseudomembranous colitis 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. The greater the renal impairment, the greater the risk of developing the adverse reactions associated with the parenteral administration of vancomycin. Monitoring of serum vancomycin concentrations of patients with inflammatory disorders of the intestinal mucosa should be performed. It should be noted that the total systemic and renal clearances of vancomycin are reduced in the elderly.

Intravenous administration of vancomycin is not effective for the treatment of *C. difficile* infection. Vancomycin should be administered orally for this indication.

Testing for *C. difficile* colonization or toxin is not recommended in children younger than 1 year due to high rate of asymptomatic colonisation unless severe diarrhoea is present in infants with risk factors for stasis such as Hirschsprung disease, operated anal atresia or other severe motility disorders. Alternative aetiologies should always be sought, and *C. difficile* enterocolitis be proven.

Patients taking oral vancomycin hydrochloride 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).

Superinfection

The use of vancomycin hydrochloride may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy with this product, appropriate measures should be taken including withdrawal of vancomycin hydrochloride.

Development of Drug-Resistant Bacteria

Oral vancomycin use increases the chance of vancomycin-resistant Enterococci populations in the gastrointestinal tract. As a consequence, prudent use of oral vancomycin is advised.

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*. Anti-diarrhoeic medicinal products must not be given.

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.

Nephrotoxicity

Vancomycin should be used with care in patients with renal insufficiency, including anuria, as the possibility of developing toxic effects is much higher in the presence of prolonged high blood concentrations. The risk of toxicity is increased by high blood concentrations or prolonged therapy.

Regular monitoring of the blood levels of vancomycin is indicated in high dose therapy and longer-term use, particularly in patients with renal dysfunction or impaired faculty of hearing as well as in concurrent administration of nephrotoxic or ototoxic substances, respectively.

Serial monitoring of renal function should be performed when treating patients with underlying renal dysfunction or patients receiving concomitant therapy with an aminoglycoside or other nephrotoxic medications. Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly ethacrynic acid, neuromuscular blocking agents, aminoglycoside antibiotics, polymyxin 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 intracameral or intravitreal use, including 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).

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).

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

Concurrent or sequential administration of vancomycin with other neurotoxic (e.g. ototoxic) and/or nephrotoxic medications (e.g. streptomycin, neomycin, gentamicin, kanamycin, amikacin, amphotericin B, bacitracin, tobramycin, polymyxin B, colistin and cisplatin or piperacillin/tazobactam), may potentiate the ototoxicity and/or nephrotoxicity of vancomycin and consequently requires careful monitoring (see section 4.4).

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).

Diuretics such as ethacrynic acid and furosemide 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.

Concomitant administration of vancomycin and anaesthetic agents has been associated with erythema and histamine-like flushing.

Reversible neutropenia has been reported in patients receiving vancomycin hydrochloride (see section 4.8). Patients who are receiving concomitant medications 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 mg/hour prior to anaesthetic induction.

If vancomycin hydrochloride is administered during or immediately after surgery, effects of concomitantly administered muscle relaxants (e.g. succinylcholine), such as neuromuscular block, can be enhanced or prolonged.

4.6 Fertility, pregnancy and lactation

Pregnancy

(Category B2[1]).

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

[1]*Category B2: Medications 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. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.*

Breastfeeding

Vancomycin hydrochloride 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.

Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

4.7 Effects on ability to drive and use machines

Patients should refrain from driving a vehicle or operating machines since vancomycin hydrochloride is likely to produce severe adverse effects.

4.8 Undesirable effects

General disorders and administration site conditions

During or soon after infusion of vancomycin hydrochloride, 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 hydrochloride is given by a slow infusion at a rate not exceeding 500 mg/hr 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 medication. 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

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 g. Neutropenia appears to be promptly reversible when vancomycin is discontinued. Thrombocytopenia has rarely been reported. Eosinophilia and pancytopenia 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.

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), Acute Generalised Exanthematous Pustulosis (AGEP), exanthema and mucosal inflammation, pruritus, urticaria, and Toxic epidermal necrolysis (TEN) 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Toxicity due to overdose has been reported. In certain high-risk conditions (e.g. in case of severe renal impairment) high serum levels and oto- and nephrotoxic effects can occur.

Treatment of overdose includes symptomatic treatment while maintain renal function (i.e. 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 medication overdoses, interaction among medicines, and unusual medicine kinetics in your patient.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, ATC code: J01XA01

Mechanism of action

Vancomycin is a tricyclic glycopeptide antibiotic that inhibits the synthesis of the cell wall in sensitive bacteria by binding with high affinity to the D-alanyl-D-alanine terminus of cell wall precursor units. The medication is slowly bactericidal for dividing microorganisms. In addition, it impairs the permeability of the bacterial cell membrane and RNA synthesis.

Pharmacokinetic/Pharmacodynamic relationship

Vancomycin displays concentration-independent activity with the area under the concentration curve (AUC) divided by the minimum inhibitory concentration (MIC) of the target organism as the primary predictive parameter for efficacy. On basis of in vitro, animal and limited human data, an AUC/MIC ratio of 400 has been established as a PK/PD target to achieve clinical effectiveness with vancomycin. To achieve this target when MICs are ≥ 1.0 mg/l, dosing in the upper range and high trough serum concentrations (15-20 mg/l) are required.

Mechanism of resistance

Acquired resistance to glycopeptides is most common in enterococci and is based on acquisition of various van gene complexes which modifies the D-alanyl-D-alanine target to D-alanyl-D-lactate or D-alanyl-D-serine which bind vancomycin poorly. In some countries, increasing cases of resistance are observed particularly in enterococci; multi-resistant strains of Enterococcus faecium are especially alarming.

Van genes have rarely been found in Staphylococcus aureus, where changes in cell wall structure result in “intermediate” susceptibility, which is most commonly heterogeneous. Also, methicillin-resistant staphylococcus strains (MRSA) with reduced susceptibility for vancomycin were reported. The reduced susceptibility or resistance to vancomycin in Staphylococcus is not well understood. Several genetic elements and multiple mutations are required.

There is no cross-resistance between vancomycin and other classes of antibiotics. Cross-resistance with other glycopeptide antibiotics, such as teicoplanin, does occur. Secondary development of resistance during therapy is rare.

Synergism

The combination of vancomycin with an aminoglycoside antibiotic has a synergistic effect against many strains of Staphylococcus aureus, non-enterococcal group D-streptococci, enterococci and streptococci of the Viridians group. The combination of vancomycin with a cephalosporin has a synergistic effect against some oxacillin-resistant Staphylococcus epidermidis strains, and the combination of vancomycin with rifampicin has a synergistic effect against Staphylococcus epidermidis and a partial synergistic effect against some Staphylococcus aureus strains. As vancomycin in combination with a cephalosporin may also have an antagonistic effect against some Staphylococcus epidermidis strains and in combination with rifampicin against some Staphylococcus aureus strains, preceding synergism testing is useful. Specimens for bacterial cultures should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to vancomycin.

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 *Staphylococcus aureus* strains require 10 to 20 microgram/ml for inhibition.

Vancomycin is active against staphylococci, including *Staphyloccocus 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*). 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 hydrochloride 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 hydrochloride and a cephalosporin acts synergistically against some strains of *S. epidermidis* (methicillin-resistant). The combination of vancomycin hydrochloride 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 hydrochloride and a cephalosporin may act antagonistically against some strains of *S. epidermidis*, and the combination of vancomycin hydrochloride and rifampicin may act antagonistically against some strains of *S. aureus*.

There is no cross-resistance between vancomycin hydrochloride 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 medications, the test should be repeated. This category implies possible clinical applicability in body sites where the medication is physiologically concentrated or in situations where high dosage of medication 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.

5.2 Pharmacokinetic properties

Absorption

Vancomycin is administered intravenously for the treatment of systemic infections. In the case of patients with normal renal function, intravenous infusion of multiple doses of 1 g vancomycin (15 mg/kg) for 60 minutes produces approximate average plasma concentrations of 50 - 60 mg/L, 20 - 25 mg/L and 5 - 10 mg/L, immediately, 2 hours and 11 hours after completing the infusion, respectively. The plasma levels obtained after multiple doses are similar to those achieved after a single dose.

Vancomycin is not usually absorbed into the blood after oral administration. However, absorption may occur after oral administration in patients with (pseudomembranous) colitis. This may lead to vancomycin accumulation in patients with co-existing renal impairment.

Distribution

The volume of distribution is about 60 L/1.73 m^2 body surface. At serum concentrations of vancomycin of 10 mg/l to 100 mg/l, the binding of the medication to plasma proteins is approximately 30 - 55%, measured by ultra-filtration.

Vancomycin diffuses readily across the placenta and is distributed into cord blood. In non-inflamed meninges, vancomycin passes the blood-brain barrier only to a low extent.

Biotransformation

There is very little metabolism of the medication. After parenteral administration it is excreted almost completely as microbiologically active substance (approx. 75 - 90% within 24 hours) through glomerular filtration via the kidneys.

Elimination

The elimination half-life of vancomycin is 4 to 6 hours in patients with normal renal function and 2.2 - 3 hours in children. Plasma clearance is about 0.058 L/kg/h and kidney clearance about 0.048 L/kg/h. In the first 24 hours, approximately 80 % of an administered dose of vancomycin is excreted in the urine through glomerular filtration.

Renal dysfunction delays the excretion of vancomycin. In anephric patients, the mean half-life is 7.5 days. Due to ototoxicity of vancomycin therapy-adjuvant monitoring of the plasma concentrations is indicated in such cases.

Biliary excretion is insignificant (less than 5% of a dose). Although the vancomycin is not eliminated efficiently by haemodialysis or peritoneal dialysis, there have been reports of an increase in vancomycin clearance with haemoperfusion and hemofiltration.

Linearity/non-linearity

Vancomycin concentration generally increases proportionally with increasing dose. Plasma concentrations during multiple dose administration are similar to those after the administration of a single dose.

Characteristics in specific groups

Renal impairment

Vancomycin is primarily cleared by glomerular filtration. In patients with impaired renal function the terminal elimination half- life of vancomycin is prolonged and the total body clearance is reduced.

Hepatic impairment

Vancomycin pharmacokinetics is not altered in patients with hepatic impairment.

Pregnant women

Significantly increased doses may be required to achieve therapeutic serum concentrations in pregnant women.

Overweight patients

Vancomycin distribution may be altered in overweight patients due to increases in volume of distribution, in renal clearance and possible changes in plasma protein binding. In these subpopulations vancomycin serum concentration were found higher than expected in male healthy adults.

Paediatric population

Vancomycin PK has shown wide inter-individual variability in preterm and term neonates. In neonates, after intravenous administration, vancomycin volume of distribution varies between 0.38

and 0.97 L/kg, similar to adult values, while clearance varies between 0.63 and 1.4 ml/kg/min. Half-life varies between 3.5 and 10 h and is longer than in adults, reflecting the usual lower values for clearance in the neonate. In infants and older children, the volume of distribution ranges between 0.26-1.05 L/kg while clearance varies between 0.33-1.87 ml/kg/min.

5.3 Preclinical safety data

Carcinogenicity and mutagenicity

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. Limited data on mutagenic effects are available, they show no indication of any hazard. Long-term studies in animals regarding a carcinogenic potential are not available. In teratogenicity studies, where rats and rabbits received doses approximately corresponding to the human dose based on body surface (mg/m^2), no direct or indirect teratogenic effects were observed.

Impairment of fertility

Animal studies of the use during the perinatal/postnatal period and regarding effects on fertility are not available.

6. Pharmaceutical Particulars

6.1 List of excipients

Vancomycin does not contain any excipients.

6.2 Incompatibilities

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

2 years.

For shelf life after reconstitution see section 4.2.

6.4 Special precautions for storage

Prior to reconstitution, store at or below 25°C.

For storage conditions after reconstitution of the medicine, see section 4.2

6.5 Nature and contents of container

Glass vial with a bromobutyl rubber stopper containing 500 mg or 1000 mg.

Not all strengths may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

9 Dec 1999

10. Date of Revision of the Text

30 July 2025

Summary table of changes

Section	Summary of new information
4.9	Editorial update to National Poisons Centre contact details.