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## 1 PRODUCT NAME

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VANCOMYCIN SANDOZ 500 mg and 1000 mg Powder for Infusion

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## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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Vancomycin Sandoz 500 mg vial: Each vial contains vancomycin hydrochloride equivalent to 500 mg vancomycin base.

Vancomycin Sandoz 1000 mg vial: Each vial contains vancomycin hydrochloride equivalent to 1000 mg vancomycin base.

Excipient(s) with known effect: N/A

For the full list of excipients, see section 6.1 List of excipients.

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## 3 PHARMACEUTICAL FORM

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Powder for Infusion

Vancomycin Sandoz 500 mg vial: white to almost white lyophilised powder which has been prepared in a sterile fashion.

Vancomycin Sandoz 1000 mg vial: white to almost white lyophilised 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.

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## 4 CLINICAL PARTICULARS

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### 4.1 Therapeutic indications

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

Vancomycin Sandoz is useful in therapy of severe staphylococcal (including methicillin resistant staphylococcal) infections in patients who cannot receive or who 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 Sandoz is effective alone or in combination with an aminoglycoside for endocarditis caused by *Streptococcus viridans* or *S. bovis*. For endocarditis caused by enterococci (e.g. *Strep. faecalis*), vancomycin hydrochloride is effective only in combination with an aminoglycoside. Vancomycin hydrochloride is effective for the treatment of diptheroid endocarditis. Vancomycin Sandoz 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 hydrochloride.

Vancomycin Sandoz 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**

#### ***Recommended Dosage***

##### **Adults**

The usual intravenous dose is 500 mg every 6 hours or 1 g 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 two hours. Vancomycin must not be given by intramuscular injections (see section 4.4 Special warnings and precautions for use).

##### **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

**Loading dose**

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

**Anephric patients**

The table is not valid for functionally anephric patients. For such patients, an initial dose of 15 mg/kg 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 (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 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 milligrams/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 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.

### **Oral Administration**

The usual adult total daily dosage for antibiotic associated pseudomembranous colitis produced by *C. difficile* is 500 milligrams to 2g 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.

### **Method of administration**

#### **Preparation of solution for injection**

At the time of use, the 500 milligrams (500,000 IU) vial should be reconstituted with 10 mL of Water for Injections. The resulting solution contains vancomycin 50 milligram/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 milligrams/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% to a concentration of not more than 5 milligrams/mL. 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.

#### **Stability of reconstituted solution**

Solutions of vancomycin hydrochloride 50 milligrams/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 milligrams/mL or 1 milligram/mL with Sodium Chloride Intravenous Infusion 0.9% or Glucose Intravenous Infusion 5%, vancomycin was chemically stable for 14 days 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.

### **Compatibility with other Drugs and Intravenous Fluids**

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.

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

5% glucose solution

5% glucose and 0.9% sodium chloride solution

Hartmann's solution

Hartmann's and 5% glucose solution

0.9% sodium chloride solution

Normosol<sup>®</sup>-M in 5% glucose solution

### **4.3 Contraindications**

Vancomycin Sandoz is contraindicated in patients with known hypersensitivity to this drug.

Vancomycin Sandoz should not be administered intramuscularly due to the risk of necrosis at the site of administration.

### **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 Undesirable effects). In case of hypersensitivity reactions, treatment with vancomycin must be discontinued immediately and the adequate emergency measures must be initiated.

#### ***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.

#### ***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 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.

### *Spectrum of antibacterial activity*

Vancomycin has a spectrum of antibacterial activity limited to Gram-positive organisms. It is not suitable for use as a single agent for the treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a high suspicion that the most likely pathogen(s) would be suitable for treatment with vancomycin.

The rational use of vancomycin should take into account the bacterial spectrum of activity, the safety profile and the suitability of standard antibacterial therapy to treat the individual patient.

### *Infusion-related 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 man’s syndrome” or “red neck syndrome”). Vancomycin Sandoz should be administered in a dilute solution at a rate not exceeding 500 mg/hour to avoid rapid-infusion-related reactions, e.g. hypotension, flushing, erythema, urticaria and pruritus. Stopping the infusion usually results in a prompt cessation of these reactions (see sections 4.2 Dose and method of administration and 4.8 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.

### *Other*

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.

### ***Ototoxicity***

Ototoxicity has occurred when serum levels exceeded 80 micrograms/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.

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 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 Interaction with other medicines and other forms of interaction)

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

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

### ***Blood disorders***

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

### ***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 Interaction with other medicines and other forms of interaction).

Anaesthetic induced myocardial depression may be enhanced by vancomycin. During anaesthesia, doses must be well diluted and administered slowly with close cardiac

monitoring. Position changes should be delayed until the infusion is completed to allow for postural adjustment.

### ***Pseudomembranous enterocolitis***

In rare instances, there have been reports of pseudomembranous colitis due to *C. difficile* developing in patients who received intravenous vancomycin.

In case of severe persistent diarrhoea the possibility of pseudomembranous enterocolitis that might be life-threatening has to be taken into account. Anti-diarrhoeic medicinal products must not be given.

### ***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 (C.difficile)***

In rare instances, there have been reports of pseudomembranous colitis, due to *C. 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.

### ***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 children**

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 4.5 Interaction with other medicines and other forms of interaction). Similarly, concomitant use with nephrotoxic agents such as aminoglycoside antibiotics, NSAIDs (e.g., ibuprofen for closure of patent ductus arteriosus) or amphotericin B is associated with an increased risk of nephrotoxicity and therefore more frequent monitoring of vancomycin serum levels and renal function is indicated.

### **Use 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 Dosage and Administration).

### **4.5 Interaction with other medicines and other forms of interaction**

Concurrent administration with other neurotoxic (e.g. ototoxic) or nephrotoxic drugs, eg streptomycin, neomycin, gentamicin, kanamycin, amikacin, amphotericin B, bacitracin, tobramycin, polymyxin B, colistin and viomycin, cisplatin or piperacillin/tazobactam, requires careful monitoring (see section 4.4 Special warnings and precautions for use).

Diuretics such as ethacrynic 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 drugs should be administered several hours apart.

Reversible neutropenia has been reported in patients receiving Vancomycin Hydrochloride (see section 4.8 Undesirable effects). Patients who are receiving concomitant drugs 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, histamine-like 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 milligrams/hour prior to anaesthetic induction.

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

### **4.6 Fertility, pregnancy and lactation**

#### ***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 it was administered only in the second and third trimesters, it is not known whether vancomycin causes foetal harm. Vancomycin Sandoz should be given to a pregnant woman only if clearly needed.

### ***Use in lactation***

Vancomycin hydrochloride is excreted in breast milk and should be therefore used in lactation period only if other antibiotics have failed. Vancomycin should be cautiously given to breast-feeding mothers because of potential adverse reactions in the infant (disturbances in the intestinal flora with diarrhoea, colonisation with yeast-like fungi and possibly sensibilisation).

Therefore, it is not recommended for nursing mothers unless the expected benefits outweigh any potential risk. Considering the importance of this medicine for nursing mother, the decision to stop breastfeeding should be considered.

### **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, dyspnea, urticaria, phlebitis 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 500mg/hr and at an appropriate dilution.

Pruritus at injection site, generalised flushing, erythematous macular rash with intense pruritus and redness 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.

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.

#### ***Cardiovascular***

Hypotension, palpitations, substernal pressure, tachycardia and cardiac arrest (see Infusion related events) have 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. Pseudomembranous enterocolitis has been reported very rarely.

### ***Blood and lymphatic 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 has also been reported. Although a causal relationship has not been established, reversible agranulocytosis (granulocyte count less than 500/mm<sup>3</sup>) has been reported rarely.

### ***Immune system disorders***

Anaphylaxis and hypersensitivity reactions with chills, nausea, urticaria, macular rash, fever, exanthema and mucosal inflammation, and rigors.

### ***Skin and subcutaneous tissue disorders***

The types of rashes that can occur include exfoliative dermatitis, Linear IgA bullous dermatosis, Lyell's syndrome, Stevens-Johnson Syndrome, toxic epidermal necrolysis and rare cases of vasculitis. Anaphylactoid reactions have been reported infrequently (see General disorders and administration site conditions). Eosinophilia and systemic symptoms (DRESS syndrome) and AGEP (acute generalized exanthematous pustulosis) have been reported.

### ***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. 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. Acute tubular necrosis have also been reported

### ***Vascular disorders***

Phlebitis and vasculitis have been reported.

### ***Description of selected adverse drug reactions***

Reversible neutropenia usually starting one week or more after onset of intravenous therapy or after total dose of more than 25 g.

Intravenous vancomycin should be infused slowly.

### ***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).

Ototoxicity has primarily been reported in patients given high doses, or in those on

concomitant treatment with other ototoxic medicinal product like aminoglycoside, or in those who had a preexisting reduction in kidney function or hearing.

If a bullous disorder is suspected, the medicinal product should be discontinued and specialised dermatological assessment should be carried out.

### ***Paediatric population***

The safety profile is generally consistent among children and adult patients. Nephrotoxicity has been described in children, usually in association with other nephrotoxic agents such as aminoglycosides.

### **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://nzphvc.otago.ac.nz/reporting/>.

### **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. Haemoperfusion with Amberlite resin XAD-4 has been reported to be of benefit.

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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## **5 PHARMACOLOGICAL PROPERTIES**

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### **5.1 Pharmacodynamic properties**

#### **Pharmacotherapeutic group:**

Glycopeptide Antibacterials

**ATC code:** J01X A01

#### **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**

## New Zealand Data sheet

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 micrograms/mL, but a few *Staph. aureus* strains require 10 to 20 micrograms/mL for inhibition. Using the Kirby-Bauer method of disc susceptibility testing, a 30 microgram vancomycin disc should produce a zone of more than 11mm when tested against a vancomycin sensitive strain (See Susceptibility tests for current NCCLS guidelines for testing details).

Vancomycin is active against staphylococci, including *Staphylococcus aureus* and *Staphylococcus epidermidis* (including heterogeneous methicillin-resistant strains); streptococci, including Streptococci, corynebacterium, *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, *Clostridium* species, and *Bacillus* species.

The combination of vancomycin hydrochloride and an aminoglycoside acts synergistically in vitro against many strains of *S. aureus*, nonenterococcal 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*.

Vancomycin hydrochloride 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 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 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.

### 5.2 Pharmacokinetic properties

#### Pharmacokinetics

##### *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 1g (1,000,000 IU) given over 60 minutes produced mean plasma levels of approximately 63 micrograms/mL immediately after the completion of infusion and mean plasma levels of approximately 23 micrograms/mL and approximately 8 micrograms/mL at 2 hour and 11 hour 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 micrograms/L. Clinically effective concentrations of this antibiotic in the blood are usually achieved and maintained by its intravenous administration, moreover, inhibitory concentrations can be demonstrated in pleural, pericardial, ascitic and synovial fluids, in urine, in peritoneal dialysis fluid, and in atrial appendage tissue. 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*.

##### *Metabolism*

There is no apparent metabolism of the drug.

##### *Elimination*

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.

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.

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### **6 PHARMACEUTICAL PARTICULARS**

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#### **6.1 List of excipients**

Nitrogen

#### **6.2 Incompatibilities**

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.

#### **6.3 Shelf life**

24 months from date of manufacture

96 hours reconstituted

#### **6.4 Special precautions for storage**

Store at or below 25°C, protect from light.

Reconstituted store at 2° to 8°C (Refrigerate, do not freeze) protect from light.

#### **6.5 Nature and contents of container**

Vial, glass, 1x10 mL, type 1 glass stoppered with a rubber stopper and closed with flipoff cap

Vial, glass, 5x10 mL, type 1 glass stoppered with a rubber stopper and closed with flipoff cap

Vial, glass, 10x10 mL, type 1 glass stoppered with a rubber stopper and closed with flipoff cap

Not all strengths / pack sizes may be marketed.

#### **6.6 Special precautions for handling, reconstitution and disposal**

No special requirements.

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### **7 MEDICINE SCHEDULE**

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Prescription Medicine.

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### **8 SPONSOR**

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**9 DATE OF FIRST APPROVAL**

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11/12/2014

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**10 DATE OF REVISION OF THE TEXT**

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17/08/2022

<b>Section</b>	<b>Summary of changes</b>
<b>Throughout</b>	Minor editorial changes
<b>4.4</b>	Additional warnings and precautions added under general, severe cutaneous adverse reactions, C.difficile associated disease, ototoxicity, haemorrhagic occlusive retinal vasculitis
<b>4.5</b>	Addition of piperacillin-tazobactam
<b>4.8</b>	Additional adverse effects under general, gastrointestinal and vascular disorders
<b>4.9</b>	Additional information on overdose
<b>5.1</b>	Additional information on mechanism of action