Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vancomycin Viatris 500 mg, powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg vancomycin (as hydrochloride), equivalent to 500,000 IU.
When reconstituted with 10 ml of water for injections, the solution contains 50 mg/ml vancomycin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.
White to almost white or slightly pink to yellow powder.

After reconstitution, the pH of the solution is between 2.8 and 4.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Intravenous administration
Vancomycin is indicated in all age groups for the treatment of the following infections (see sections 4.2, 4.4 and 5.1):

- complicated skin and soft tissue infections (cSSTI)
- bone and joint infections
- community acquired pneumonia (CAP)
- hospital acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP)
- infective endocarditis
- bacteraemia that occurs in association with, or is suspected to be associated with, any of the above.

Vancomycin is also indicated in all age groups for the perioperative antibacterial prophylaxis in patients that are at high risk of developing bacterial endocarditis when undergoing major surgical procedures.

Oral administration
Vancomycin is indicated in all age groups for the treatment of Clostridium difficile infection (CDI) (see sections 4.2, 4.4 and 5.1).
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology
Where appropriate, vancomycin should be administered in combination with other antibacterial agents.

Intravenous administration
The initial dose should be based on total body weight. Subsequent dose adjustments should be based on serum concentrations to achieve targeted therapeutic concentrations. Renal function must be taken into consideration for subsequent doses and interval of administration.

Patients aged 12 years and older:
The recommended dose is 15 to 20 mg/kg of body weight every 8 to 12 h (not to exceed 2 g per dose).
In seriously ill patients, a loading dose of 25–30 mg/kg of body weight can be used to facilitate rapid attainment of target trough serum vancomycin concentration.

Infants and children aged from one month to less than 12 years of age: The recommended dose is 10 to 15mg/kg body weight every 6 hours (see section 4.4).

Term neonates (from birth to 27 days of post-natal age) and preterm neonates (from birth to the expected date of delivery plus 27 days):
For establishing the dosing regimen for neonates, the advice of a physician experienced in the management of neonates should be sought. One possible way of dosing vancomycin in neonates is illustrated in the following table: (see section 4.4)

PMA (weeks)	Dose (mg/kg)	Interval of administration (h)
<29	15	24
29-35	15	12
>35	15	8

PMA: post-menstrual age [(time elapsed between the first day of the last menstrual period and birth (gestational age) plus the time elapsed after birth (post-natal age)].

Peri-operative prophylaxis of bacterial endocarditis in all age groups
The recommended dose is an initial dose of 15 mg/kg prior to induction of anaesthesia. Depending on the duration of surgery, a second vancomycin dose may be required.

Duration of treatment
Suggested treatment duration is shown in table below. In any case, the duration of treatment should be tailored to the type and severity of infection and the individual clinical response.

Indication	Treatment duration
Complicated skin and soft tissue infections	
-Non necrotizing	7 to 14 days
- Necrotizing	4 to 6 weeks*
Bone and joint infections	4 to 6 weeks**
Community-acquired pneumonia	7 to 14 days
Hospital-acquired pneumonia, including ventilator-associated pneumonia	7 to 14 days
Infective endocarditis	4 to 6 weeks***

*Continue until further debridement is not necessary, patient has clinically improved, and patient is afebrile for 48 to 72 hours
**Longer courses of oral suppression treatment with suitable antibiotics should be considered for prosthetic joint infections
***Duration and need for combination therapy is based on valve-type and organism

Special populations

Elderly:
Lower maintenance doses may be required due to the age–related reduction in renal function.

Renal impairment
In adult and paediatric patients with renal impairment, consideration should be given to an initial starting dose followed by serum vancomycin trough levels rather than to a scheduled dosing regimen, particularly in patients with severe renal impairment or those who undergo renal replacement therapy (RRT) due to the many varying factors that may affect vancomycin levels in them. In patients with mild or moderate renal failure, the starting dose must not be reduced. In patients with severe renal failure, it is preferable to prolong the interval of administration rather than administer lower daily doses. Appropriate consideration should be given to the concomitant administration of medicinal products that may reduce vancomycin clearance and/or potentiate its undesirable effects (see section 4.4). Vancomycin is poorly dialyzable by intermittent haemodialysis. However, use of high-flux membranes and continuous renal replacement therapy (CRRT) increases vancomycin clearance and generally requires replacement dosing (usually after the haemodialysis session in case of intermittent haemodialysis).

Adults
Dose adjustments in adult patients could be based on glomerular filtration rate estimated (eGFR) by the following formula:

Men: [Weight (kg) x [140 - age (years)]]/ [72 x serum creatinine (mg/dl)]

Women: 0.85 x value calculated by the above formula.

The usual starting dose for adult patients is 15 to 20 mg/kg that could be administered every 24 hours in patients with creatinine clearance between 20 to 49 ml/min. In patients with severe renal impairment (creatinine clearance below 20 ml/min) or those on renal replacement therapy, the appropriate timing and amount of subsequent doses largely depend on the modality of RRT and should be based on serum vancomycin trough levels and on residual renal function (see section 4.4). Depending on the clinical situation, consideration could be given to withhold the next dose while awaiting the results of vancomycin levels.

In the critically ill patient with renal insufficiency, the initial loading dose (25 to 30 mg/kg) should not be reduced.

Paediatric population
Dose adjustments in paediatric patients aged 1 year and older could be based on glomerular filtration rate estimated (eGFR) by the revised Schwartz formula:

eGFR (mL/min/1.73m^2) = (height cm x 0.413)/ serum creatinine (mg/dl)

eGFR (mL/min/1.73m^2) = (height cm x 36.2/serum creatinine (µmol/L)

For neonates and infants below 1 year of age, expert advice should be sought as the revised Schwartz formula is not applicable to them.

Orientative dosing recommendations for the paediatric population are shown in table below that follow the same principles as in adult patients.

GFR (mL/min/1.73 m^2)	**IV dose**	**Frequency**
50-30	15 mg/kg	12 hourly
29-10	15 mg/kg	24 hourly
< 10	10-15 mg/kg	Re-dose based on levels*
Intermittent haemodialysis		
Peritoneal dialysis		
Continuous renal replacement therapy	15 mg/kg	Re-dose based on levels*

*The appropriate timing and amount of subsequent doses largely depends on the modality of RRT and should be based on serum vancomycin levels obtained prior to dosing and on residual renal function. Depending on the clinical situation, consideration could be given to withhold the next dose while awaiting the results of vancomycin levels.

Hepatic impairment:
No dose adjustment is needed in patients with hepatic insufficiency.

Pregnancy
Significantly increased doses may be required to achieve therapeutic serum concentrations in pregnant women (see Section 4.6).

Obese patients:
In obese patients, the initial dose should be individually adapted according to total body weight as in non-obese patients.

Oral administration

Patients aged 12 years and older
Treatment of Clostridium difficile infection (CDI):
The recommended vancomycin dose is 125 mg every 6 hours for 10 days for the first episode of non-severe CDI. This dose can be increased to 500 mg every 6 hours for 10 days in case of severe or complicated disease. The maximum daily dose should not exceed 2 g.

In patients with multiple recurrences, consideration may be given to treat the current episode of CDI with vancomycin, 125 mg four times daily for 10 days followed by either tapering the dose, i.e., gradually decreasing it until 125 mg per day or a pulse regimen, i.e., 125–500 mg/day every 2–3 days for at least 3 weeks.

Neonates, infants and children less than 12 years old
The recommended vancomycin dose is 10 mg/kg orally every 6 hours for 10 days. The maximum daily dose should not exceed 2 g.

Treatment duration with vancomycin may need to be tailored to the clinical course of individual patients. Whenever possible the antibacterial suspected to have caused CDI should be discontinued. Adequate replacement of fluid and electrolytes should be ensured.

Monitoring of vancomycin serum concentrations
The frequency of therapeutic drug monitoring (TDM) needs to be individualized based on the clinical situation and response to treatment, ranging from daily sampling that may be required in some hemodynamically unstable patients to at least once weekly in stable patients showing a treatment response. In patients with normal renal function, the serum concentration of vancomycin should be monitored on the second day of treatment immediately prior to the next dose.

In patients on intermittent haemodialysis, vancomycin levels should be usually obtained before the start of the haemodialysis session.

After oral administration, monitoring vancomycin serum concentrations in patients with inflammatory intestinal disorders should be performed (see section 4.4).

Therapeutic trough (minimum) vancomycin blood levels should normally be 10-20 mg/l, depending on the site of infection and susceptibility of the pathogen. Trough values of 15-20 mg/l are usually recommended by clinical laboratories to better cover susceptible-classified pathogens with MIC ≥1 mg/L (see sections 4.4 and 5.1).

Model-based methods may be useful in the prediction of individual dose requirements to reach an adequate AUC. The model-based approach can be used both in calculating the personalized starting dose and for dose adjustments based on TDM results (see section 5.1).

Method of administration

Intravenous administration
Intravenous vancomycin is usually administered as an intermittent infusion and the dosing recommendations presented in this section for the intravenous route correspond to this type of administration.

Vancomycin shall only be administered as slow intravenous infusion of at least one hour duration or at a maximum rate of 10 mg/min (whichever is longer) which is sufficiently diluted (at least 100 ml per 500 mg or at least 200 ml per 1000 mg) (see section 4.4).

Patients whose fluid intake must be limited can also receive a solution of 500 mg/50 ml or 1000 mg/100 ml, although the risk of infusion-related undesirable effects can be increased with these higher concentrations.

For information about the preparation of the solution, please see section 6.6.

Continuous vancomycin infusion may be considered, e.g., in patients with unstable vancomycin clearance.

Oral administration
After initial reconstitution of the solution in the vial, the quantity of solution to be administered is taken from the vial using a graduated syringe equipped with a needle, transferred to a glass or a baby bottle and diluted immediately prior to administration.

For information about the preparation of the solution, please refer to section 6.6 special precautions for disposal and other handling.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).

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

4.4 Special warnings and precautions for use

Hypersensitivity reactions
Serious and occasionally fatal hypersensitivity reactions are possible (see sections 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. All patients receiving vancomycin should have periodic haematologic studies, urine analysis, liver and renal function tests.

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

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.

Ototoxicity: Ototoxicity, which may be transitory or permanent (see section 4.8) has been reported in patients with prior deafness, who have received excessive intravenous doses, or who receive concomitant treatment with another ototoxic active substance such as an aminoglycoside. Vancomycin should also be avoided in patients with previous hearing loss. Deafness may be preceded by tinnitus. Experience with other antibiotics suggests that deafness may be progressive despite cessation of treatment. To reduce the risk of ototoxicity, blood levels should be determined periodically and periodic testing of auditory function is recommended.

The elderly are particularly susceptible to auditory damage. Monitoring of vestibular and auditory function in the elderly should be carried out during and after treatment. Concurrent or sequential use of other ototoxic substances should be avoided.

Infusion-related reactions
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 should be infused slowly in a dilute solution (2.5 to 5.0 mg/ml) at a rate no greater than 10 mg/min and over a period not less than 60 minutes to avoid rapid infusion-related reactions. Stopping the infusion usually results in a prompt cessation of these reactions.

The frequency of infusion-related reactions (hypotension, flushing, erythema, urticaria and pruritus) increases with the concomitant administration of anaesthetic agents (see section 4.5). This may be reduced by administering vancomycin by infusion over at least 60 minutes, before anaesthetic induction.

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 generalized 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.

At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, vancomycin should be withdrawn immediately and an alternative treatment considered. If the patient has developed a SCAR with the use of vancomycin, treatment with vancomycin must not be restarted at any time.

Administration site related reactions

Pain and thrombophlebitis may occur in many patients receiving intravenous vancomycin and are occasionally severe. The frequency and severity of thrombophlebitis can be minimized by administering the medicinal product slowly as a dilute solution (see section 4.2) and by changing the sites of infusion regularly.

The efficacy and safety of vancomycin has not been established for the intrathecal, intralumbar and intraventricular routes of administration.

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 (see sections 4.2 and 4.5).

Eye disorders
Vancomycin is not authorised for intracameral or intravitreal use, including prophylaxis of endophthalmitis.

Hemorrhagic occlusive retinal vasculitis (HORV), including permanent loss of vision, have been observed in individual cases following intracameral or intravitreal use of vancomycin during or after cataract surgery.

Paediatric population:
The current intravenous dosing recommendations for the paediatric population, in particular for children below 12 years of age, may lead to sub-therapeutic vancomycin levels in a substantial number of children. However, the safety of increased vancomycin dosing has not been properly assessed and higher doses than 60 mg/kg/day cannot be generally recommended.

Vancomycin should be used with particular care in premature neonates and young infants, because of their renal immaturity and the possible increase in the serum concentration of vancomycin. The blood concentrations of vancomycin should therefore be monitored carefully in these children. Concomitant administration of vancomycin and anaesthetic agents has been associated with erythema and histamine-like flushing in children. 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 (see section 4.5) 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 (see section 4.2).

Drug interactions with anaesthetic agents
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 (see section 4.5).

Pseudomembranous enterocolitis
In case of severe persistent diarrhoea the possibility of pseudomembranous enterocolitis that might be life-threatening has to be taken into account (see section 4.8). Anti-diarrhoeic medicinal products must not be given.

Superinfection
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.

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

Testing for Clostridium 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 Clostridium difficile enterocolitis be proven.

Potential for Systemic Absorption
Absorption may be enhanced in patients with inflammatory disorders of the intestinal mucosa or with Clostridium difficile-induced pseudomembranous colitis. These patients may be at risk for the development of adverse reactions, especially if there is a concomitant renal impairment. 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.

Nephrotoxicity
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 drugs.

Ototoxicity
Serial tests of auditory function may be helpful in order to minimise the risk of ototoxicity in patients with an underlying hearing loss, or who are receiving concomitant therapy with an ototoxic agent such as an aminoglycoside.

Drug interactions with anti-motility agents and proton pump inhibitors
Anti-motility agents should be avoided and proton pump inhibitor use should be reconsidered.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Other potentially nephrotoxic or ototoxic medications
Concurrent or sequential administration of vancomycin with other potentially neurotoxic or/and nephrotoxic active substances particularly gentamycin, amphotericin B, streptomycin, neomycin, kanamycin, amikacin, tobramycin, viomycin, bacitracin, polymyxin B, colistin, piperacillin/tazobactam and cisplatin may potentiate the nephrotoxicity and/or ototoxicity of vancomycin and consequently requires careful monitoring of the patient (see section 4.4).

Because of synergic action (e.g. with gentamycin) in these cases the maximum dose of vancomycin has to be restricted to 500 mg every 8 hours.

Anaesthetics
Concurrent administration of vancomycin and anaesthetic agents has been associated with erythema, histamine like flushing and anaphylactoid reactions. This may be reduced if the vancomycin is administered over 60 minutes before anaesthetic induction. (see Section 4.4)

Muscle relaxants
If vancomycin is administered during or directly after surgery, the effect (neuromuscular blockade) of muscle relaxants (such as succinylcholine) concurrently used can be enhanced and prolonged.

4.6 Fertility, pregnancy and lactation

Pregnancy:
No sufficient safety experience is available regarding vancomycin during human pregnancy. Reproduction toxicological studies on animals do not suggest any effects on the development of the embryo, foetus or gestation period (see section 5.3).

However, vancomycin penetrates the placenta and a potential risk of embryonal and neonatal ototoxicity and nephrotoxicity cannot be excluded. Therefore, vancomycin should be given in pregnancy only if clearly needed and after a careful risk/benefit evaluation.

Breast-feeding:
Vancomycin is excreted into breast milk and is poorly absorbed orally, therefore systemic adverse reactions in breastfed infants are not expected. Vancomycin should be cautiously given to breast-feeding mothers because of potential alteration of gastrointestinal flora and diarrhoea and infants should be observed for possible diarrhoea.

Fertility
No fertility (male or female) study is available for vancomycin.

4.7 Effects on ability to drive and use machines

Vancomycin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the Safety profile
The most common adverse reactions are phlebitis, pseudo-allergic reactions and flushing of the upper body ("red-neck syndrome") in connection with too rapid intravenous infusion of vancomycin.

The absorption of vancomycin from the gastrointestinal tract is negligible. However, in severe inflammation of the intestinal mucosa, especially in combination with renal insufficiency, adverse reactions that occur when vancomycin is administered parenterally may appear.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) have been reported in association with vancomycin treatment (see section 4.4).

Tabulated List of Adverse reactions
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
The adverse reactions listed below are defined using the following MedDRA convention and system organ class database: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

System organ class	
Frequency	**Adverse reaction**
Blood and the lymphatic system disorders:	
Rare	Reversible neutropenia[1], agranulocytosis, eosinophilia, thrombocytopenia, pancytopenia.
Immune system disorders:	
Rare	Hypersensitivity reactions, anaphylactic reactions[2]
Ear and labyrinth disorders:	
Uncommon	Transient or permanent loss of hearing[4]
Rare	Vertigo, tinnitus[3], dizziness

Cardiac disorders	
Very rare	Cardiac arrest
Vascular disorders:	
Common	Decrease in blood pressure
Rare	Vasculitis
Respiratory, thoracic and mediastinal disorders:	
Common	Dyspnoea, stridor
Gastrointestinal disorders:	
Rare	Nausea
Very rare	Pseudomembranous enterocolitis
Not known	Vomiting, Diarrhoea
Skin and subcutaneous tissue disorders:	
Common	Flushing of the upper body ("red man syndrome"), exanthema and mucosal inflammation, pruritus, urticaria
Very rare	Exfoliative dermatitis, Stevens-Johnsonsyndrome, Toxic epidermal necrolysis (TEN), Linear IgA bullous dermatosis
Not known	Eosinophilia and systemic symptoms (DRESS syndrome), AGEP (Acute Generalized Exanthematous Pustulosis)
Renal and urinary disorders:	
Common	Renal insufficiency manifested primarily by increased serum creatinine and serum urea
Rare	Interstitial nephritis, acute renal failure.
Not known	Acute tubular necrosis
General disorders and administration site conditions:	
Common	Phlebitis, redness of the upper body and face.

Rare	Drug fever, shivering, Pain and muscle spasm of the chest and back muscles

Description of selected adverse drug reactions

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

[2]During or shortly after rapid infusion anaphylactic/anaphylactoid reactions including wheezing may occur. The reactions abate when administration is stopped, generally between 20 minutes and 2 hours. Vancomycin should be infused slowly (see sections 4.2 and 4.4). Necrosis may occur after intramuscular injection.

[3]Tinnitus, possibly preceding onset of deafness, should be regarded as an indication to discontinue treatment.

[4]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 pre-existing reduction in kidney function or hearing.

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 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 via HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

Toxicity due to overdose has been reported. 500 mg IV to a child, 2 years of age, resulted in lethal intoxication. Administration of a total of 56 g during 10 days to an adult resulted in renal insufficiency. In certain high-risk conditions (e. g. in case of severe renal impairment) high serum levels and oto- and nephrotoxic effects can occur.

Measures in case of overdose

- A specific antidote is not known.
- Symptomatic treatment while maintaining renal function is required.

Vancomycin is poorly removed from the blood by haemodialysis or peritoneal dialysis. Haemofiltration or haemoperfusion with polysulfone resins have been used to reduce serum concentrations of vancomycin.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antibacterials, glycopeptide antibacterials, ATC code: J01XA01.

Mechanism of action

Vancomycin is a glycopeptide antibioticthat 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 drug 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 (see section 4.2).

Mechanism(s) 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 glycopeptides 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 D-streptococci, enterococci and streptococci of the Viridans 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.

Susceptibility testing breakpoints
Vancomycin is active against gram-positive bacteria, such as staphylococci, streptococci, enterococci, pneumococci, and clostridia. Gram-negative bacteria are resistant.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent is at least some types of infections is questionable. This information only provides approximate guidance on the chance whether micro-organisms are susceptible to vancomycin.

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

	Susceptible	Resistant
Staphylococcusaureus[1]	≤ 2 mg/l	> 2 mg/l
Coagulase-negative staphylococci[1]	≤ 4 mg/l	> 4 mg/l
Enterococcus spp.	≤ 4 mg/l	> 4 mg/l
Streptococcus groups A, B, C and G	≤ 2 mg/l	> 2 mg/l
Streptococcus pneumoniae	≤ 2 mg/l	> 2 mg/l
Gram-positive anaerobes	≤ 2 mg/l	> 2 mg/l

[1]S. aureus with vancomycin MIC values of 2 mg/L are on the border of the wild type distribution and there may be an impaired clinical response.

Commonly susceptible species
Gram positive
Enterococcus faecalis.
Staphylococcus aureus
Methicillin-resistant *Staphylococcus aureus*
coagulase-negative Staphylococci
Streptococcus spp.
Streptococcus pneumoniae
Enteroccocus spp
Staphylococcus spp.
Anaerobic species
Clostridium spp. except *Clostridium innocuum*

Eubacterium spp. *Peptostreptococcus* spp.
Species for which acquired resistance may be a problem
Enterococcus faecium
Inherently resistant
All Gram negative bacteria
Gram positive aerobic species *Erysipelothrix rhusiopathiae,* Heterofermentative *Lactobacillus,* *Leuconostoc spp,* *Pediococcus spp.* **Anaerobic species** *Clostridium innocuum*
The emergence of resistance towards vancomycin differs from one hospital to another and a local microbiological laboratory should therefore be contacted for relevant local information.

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 1g 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 drug 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 drug. 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 haemofiltration.

After oral administration, only a fraction of the administered dose is recovered in the urine. In contrast, high concentrations of vancomycin are found in the faeces (>3100 mg/kg with doses of 2 g/day).

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. Subsequently, optimal dose should be calculated in line with dosing recommendations provided in section 4.2. Posology and method of administration.

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 (see Section 4.6).

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 was found higher than expected in male healthy adults (see section 4.2).

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

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 show negative results, 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.

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

Hydrochloric acid (pH adjustment)

6.2 Incompatibilities

Vancomycin solution has a low pH value. This may lead to chemical or physical instability if mixed with other substances. Therefore, each parenteral solution should be checked visually for precipitations and discolouration prior to use. Mixing with alkaline solutions should be avoided.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

Shelf life of the reconstituted solution:
When reconstituted in water for injections, the chemical and physical stability of the solution has been demonstrated for a storage period of 48 hours at 25°C or up to 96 hours between 2-8°C.

Shelf life of the diluted solution:
The chemical and physical stability of the ready-to-use solution (with 0.9% sodium chloride solution or 5% glucose solution) has been demonstrated for 48 hours at 25°C or up to 96 hours between 2-8°C.
From a microbiological point of view, the prepared solution for infusion should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user. Normally, a 24-hour storage period at 2-8°C may only be exceeded if the solution for infusion has been prepared under controlled and validated aseptic conditions.

Shelf life of the reconstituted solution for oral use: the reconstituted solution should be used immediately.

6.4 Special precautions for storage

Powder
This medicinal product does not require any special storage conditions.

Reconstituted and diluted product
For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

[For Vancomycin 500 mg:] 10 ml colourless glass vial, with a bromobutyl rubber stopper and a yellow aluminium/plastic flip-off cap.
[For Vancomycin 1000 mg:] 20 ml colourless glass vial, with bromobutyl rubber stopper and pink aluminium/plastic flip-off cap.

Pack sizes: 1 vial, 5 vials, 10 vials, 20 vials
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation of the solution for infusion
The product must be reconstituted and the resulting concentrate must then be diluted prior to use.
Dissolve the contents of one vial in 10 ml of water for injections.
The reconstituted solution should be a clear colourless to slightly yellowish solution, without visible particles.

One ml of reconstituted solution contains 50 mg of vancomycin.

For storage conditions of the reconstituted product see section 6.3.

Suitable diluents for further dilution are water for injections, 5% glucose solution or 0.9% sodium chloride solution.
Different dilution is required depending on method of administration.
- Intermittent infusion:
Reconstituted solutions containing 500 mg vancomycin must be diluted with at least 100 ml diluent. The desired dose should be administered by intravenous infusion at a rate of no more than 10 mg/min, over at least 60 minutes.

- Continuous infusion:
This should be used only if treatment with an intermittent infusion is not possible.
1 g or 2 g of vancomycin, corresponding to 2 to 4 vials of reconstituted solution, may be added to a sufficiently large volume of the above suitable diluent to permit the desired daily dose to be infused over twenty-four hours.

For storage conditions of the diluted product see section 6.3.

Before administration, the reconstituted and diluted solutions should be inspected visually for particulate matter and discoloration. Only clear and colourless to pale yellow solution free from particles should be used.

Preparation of the oral solution
After initial reconstitution of the vial, the selected dose may be diluted in 30 ml of water and given to the patient to drink or the diluted material may be administered by a nasogastric tube.

Disposal
Vials are for single use only. Unused medicinal products must be discarded.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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