Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vancomycin 1000 mg powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vancomycin 1000 mg, Powder for concentrate for solution for infusion
Each vial contains 1000 mg of vancomycin (as vancomycin hydrochloride), equivalent to 1,000,000 IU vancomycin.

One ml of reconstituted solution contains 50 mg of vancomycin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
Homogeneous solid, white to slightly brown.

After reconstitution a solution is obtained with a pH between 2.5 – 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 15 mg/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 - Necrotizing	7 to 14 days 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
The dose of vancomycin administered orally can be diluted in 30 ml of water and given to the patient, or administered by nasogastric tube.
For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

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.

Parental 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 authorized 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.

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, cisplatin and piperacillin/tazobactam may potentiate the nephrotoxicity and/or ototoxicity of vancomycin and consequently requires careful monitoring of the patient (see section 4.4).

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.

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.

Lactation

Vancomycin is excreted in human milk and should be therefore used in lactation period only if clearly necessary. 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).

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

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-Johnson syndrome, Linear IgA bullous dermatosis[5], Toxic epidermal necrolysis (TEN)
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
Reversible neutropenia usually starting one week or more after onset of intravenous therapy or after total dose of more than 25 g.

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.

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

Ototoxicity has primarily been reported in patients given high doses, or in those on concomitant treatment with other ototoxic medicinal products like aminoglycosides, 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
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

Toxicity due to overdose has been reported. 500 mg iv to a child, 2 year 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: 1.1.11 Anti-infectives. Antibacterials. Other antibacterials.
ATC Code: J01XA01 – Anti-infectives for systemic use – Antibacterials for systemic use – Other antibacterials – Glycopeptide antibacterials.

Mode of action
Vancomycin is a glycopeptide antibiotic. Vancomycin has a bactericidal effect on proliferating germs by inhibiting the biosynthesis of the cell wall. In addition, it impairs the permeability of the bacterial cell membrane and RNA synthesis.

Pharmacokinetics/Pharmacodynamics Relation
The degree of bactericidal activity of vancomycin depends on the ratio between the area under the curve (AUC) and the minimum inhibitory concentration (MIC).

Mechanism(s) of resistance
Acquired resistance to glycopeptides is based on acquisition of variousvangene complexesand alteration of the D-alanyl-D-alanine target to D-alanyl-D-lactate or D-alanyl-D-serine which bind vancomycin poorly. Cross-resistance with teicoplanin has been reported for some van genes.The reduced susceptibility or resistance to vancomycin in *Staphylococcus* is not well understood. Vangenes have rarely been found in*Staphylococcus aureus*, where changes in cell wall structure result in “intermediate” susceptibility, which is most commonly heterogeneous.

Susceptibility
Vancomycin is active against gram-positive bacteria. 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.

Breakpoints
EUCAST (European Committee on Antimicrobial Susceptibility testing) recommendations, version 6.0, valid from 01/01/2016

	Susceptible	Resistant
Staphylococcus spp.	≤ 2 mg/L	> 2 mg/L
Enterococcus spp.	≤ 4 mg/L	> 4 mg/L
Streptococcus spp.	≤ 2 mg/L	> 2 mg/L
Streptococcus pneumoniae	≤ 2 mg/L	> 2 mg/L
Gram positive anaerobes	≤ 2 mg/L	> 2 mg/L
Clostridium spp.	≤ 2 mg/L	> 2 mg/L
Non species related*	≤ 2 mg/L	> 4 mg/L

*Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

Vancomycin has a narrow spectrum of action:

Commonly susceptible species:
Enterococcus faecalis
Staphylococcus aureus
Staphylococcus coagulase negative
Streptococcus pneumoniae
Streptococcus spp.
Clostridium spp.

Species for which acquired resistance may be a problem:
Enterococcus faecium

Inherently resistant organisms
Gram-negative bacteria
Chlamydia spp.
Mycobacteria
Mycoplasma spp.
Rickettsia spp.

5.2 Pharmacokinetic properties

Distribution
Following intravenous administration, vancomycin is distributed to almost all tissues and diffuses in pleural, pericardial, ascitic and synovial fluid as well as in the cardiac muscle and in heart valves. Comparable high concentrations are achieved as in blood plasma. Data about the vancomycin concentrations in bone (spongiosa, compacta) vary widely. The apparent distribution volume in steady state is stated to be 0.43 (up to 0.9) L/kg. In non-inflamed meninges vancomycin passes the blood-brain barrier only to a low extent. Vancomycin is bound to plasma proteins at 30 to 55 % and even higher.

Elimination
Vancomycin is metabolized only to a low extent. After parenteral administration it is excreted almost completely as microbiologically active substance (approx. 75-90% within 24 hours) through glomerular filtration via the kidneys. Biliary excretion is insignificant (less than 5% of a dose).

In patients with normal renal function the half-life in serum is about 4-6 (5-11) hours, in children 2.2-3 hours. In impaired renal function, the half-life of vancomycin may be considerably prolonged (up to 7.5 days).

Due to ototoxicity of vancomycin therapy-adjuvant monitoring of the plasma concentrations is indicated in such cases.

Mean plasma concentrations after i.v. infusion of 1000 mg vancomycin over 60 minutes were about 63 mg/L at the end of the infusion, about 23 mg/L after 2 hours and about 8 mg/L after 11 hours.

The clearance of vancomycin from plasma correlates nearly with the glomerular filtration rate.
The total systemic and renal clearance of vancomycin can be reduced in elderly patients.
As studies in anephric patients showed, the metabolic clearance seems to be very low.
No vancomycin metabolites have been identified so far in humans.
If vancomycin is given during a peritoneal dialysis via the intraperitoneal route, approx. 60% reaches the systemic circulation during 6 hours. After i.p. administration of 30 mg/kg BW, serum levels of approx. 10 mg/l are achieved.

In case of oral use, high-polar vancomycin is virtually not absorbed. It appears after oral administration in active form in the stool, and is therefore a suitable chemotherapeutic for pseudomembranous colitis and staphylococcal colitis.

Vancomycin diffuses readily across the placenta and is distributed into cord blood.

5.3 Preclinical safety data

No reproduction tests were performed with the drug, so its effect on reproduction is not known. A conventional teratology study performed in female rats revealed no teratogenic effects and the same occurred in a similar study in female rabbits. In these species, the target organ of toxicity was the kidney.

Vancomycin has been studied in a number of standard studies *in vitro* and *in vivo* to determine the mutagenic potential, involving scanning of non-specific DNA damage, incidental mutations, chromosomal damage and loss of chromosomes.

The medicinal product was not genotoxic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide and hydrochloric acid (for pH adjustment).

6.2 Incompatibilities

Vancomycin solutions have a low pH that may cause chemical or physical instability if mixed with other compounds. Mixing with alkaline solutions should be avoided. Therefore, each parental solution should be checked visually for precipitation and discolouration prior to use.

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

6.3 Shelf life

Powder:
2 years

Reconstituted Solution:
For intravenous use, the reconstituted solution should be diluted immediately after preparation.
For oral use, the reconstituted solution with purified water for oral administration is stable when stored at 2-8 °C for 48 hours.

Diluted solution:
Chemical and physical in- use stability has been demonstrated:

- for a period of 24 hours at 25 °C, after reconstitution and further dilution with sodium chloride 9 mg/ml (0.9%) or glucose solution 50 mg/ml (5%);
- for a period of 96 hours when stored at 2-8 °C, after reconstitution and further dilution with sodium chloride 9 mg/ml (0.9%) or glucose solution 50 mg/ml (5%), or Ringer's lactate solution or with sodium chloride 9 mg/ml (0.9%) + glucose 50 mg/ml (5%).

From a microbiological point of view the medicinal product should be used immediately.

6.4 Special precautions for storage

Powder as packed for sale
Store below 25 °C.
Keep the vial in the outer carton in order to protect from light

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

6.5 Nature and contents of container

Immediate packaging: colourless type I glass vial, with a rubber stopper and a white aluminium flip-off cap.

Secondary packaging: cartons containing 1, 5, 10 or 20 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstituted solutions containing 50 mg/ml of vancomycin should be further diluted depending on the method of administration.

Preparation of the reconstituted solution
Dissolve the powder in 20 ml of sterile Water for injection

One ml of reconstituted solution contains 50 mg of vancomycin.

Appearance of reconstituted solution
After reconstitution the solution is clear and colorless to slightly yellowish brown without visible particles.

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

Preparation of final diluted Solution for infusion
Reconstituted solutions containing 50 mg/ml of vancomycin should be further diluted.
Suitable diluents are:

- 5% Glucose Injection
- 0.9% Sodium Chloride Injection
- 5% Glucose Injection with 0.9% Sodium Chloride Injection
- Ringer's Lactate Injection

Intermittent infusion:
Reconstituted solution containing 1000 mg vancomycin (50 mg/ml) must be diluted further with at least 200 ml diluent (to 5 mg/ml)
The concentration of vancomycin in Solution for infusion should not exceed 5 mg/ml.
The desired dose should be administered slowly by intravenous use at a rate of no more than 10 mg/minute, for at least 60 minutes or even longer.

Continuous infusion:
This should be used only if treatment with an intermittent infusion is not possible. Dilute 1000 mg to 2000 mg of dissolved vancomycin in a sufficient amount of the above suitable diluent and administer it in the form of a drip infusion, so that the patient will receive the prescribed daily dose in 24 hours.

Oral Administration
The contents of vials for parenteral administration may be used.
The reconstituted solutions containing 500 mg and 1000 mg of vancomycin can be diluted in 30 ml of water and given to the patient or administered through a nasogastric tube.

Appearance of diluted solution
After dilution the solution is clear and colorless without visible particles.

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

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

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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10 DATE OF REVISION OF THE TEXT

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