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

Each vial contains 1000 mg vancomycin hydrochloride equivalent to 1,000,000 IU vancomycin.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
A white to cream coloured porous cake.
After reconstitution a solution is obtained with a pH of approximately 3.

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

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.

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.

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.

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.

4.3 Contraindications

Hypersensitivity to the active substance (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 of 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 bullous reactions
Stevens-Johnson syndrome (SJS) has been reported with the use of vancomycin (see section 4.8). If symptoms or signs of SJS (e.g. progressive skin rash often with blisters or mucosal lesions) are present, vancomycin treatment should be discontinued immediately and specialised dermatological assessment be sought.

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 section 4.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Anaesthetic agents

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

There have been reports that the frequency of infusion-related events increases with the concomitant administration of anaesthetic agents. Infusion-related events may be minimised by the administration of vancomycin as a 60-minute infusion prior to anaesthetic induction.

Potentially nephro- or ototoxic medicinal products

Concurrent or sequential systemic or topical use of other potentially *ototoxic*, neurotoxic, or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymyxin B, colistin, viomycin or cisplatin, when indicated, requires careful monitoring as the risk for oto- or nephrotoxicity is increased.

Muscle relaxants

There is an increased potential of prolonged neuromuscular blockade with concomitant administration of vancomycin and neuromuscular blocking agents.

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.

BreastfeedingVancomycin 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 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.

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, Lyell's syndrome, Linear IgA bullous dermatosis[5]
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 product like aminoglycoside, or in those who had a pre-existing reduction in kidney function or hearing.

If a bullous disorder is suspected, the drug 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 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

Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed from the blood by haemodialysis or peritoneal dialysis. Haemoperfusion with Amberlite resin XAD-4 has been reported to be of limited benefit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use Glycopeptide Antibacterials, ATC code: J01X A01

Mechanism of action
Vancomycin is a tricyclic glycopeptide antibiotic that inhibits the synthesis of the cell wall in sensitive bacteria by binding with high affinity to the D-alanyl-D-alanine terminus of cell wall precursor units. The 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 the 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 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 oberved paarticularly in enterococci; multi-resistant strains of Enteroccous faecium are especially alarming.

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

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

Synergism
The combination of vancomycin with an aminoglycoside antibiotic has a synergistic effect against many strains of *Staphylococcus aureus*, non-enterococcal group D-streptococci, enterococci and streptococci of the *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, pnuemococci, 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 in 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
Staphylococcus aureus[1]	≤ 2 mg/L	> 2 mg/L
Coagulase-negative	≤ 4 mg/L	> 4 mg/L

staphylococci[1]		
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 teherfore 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.

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.

Linerarity/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 were 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

None.

6.2 Incompatibilities

Vancomycin solution has a low pH that may cause chemical or physical instability when it is mixed with other compounds. Mixing with alkaline solutions should be avoided. Each parenteral solution should be checked visually for precipitation and discolouration prior to use.

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

6.3 Shelf life

Powder as packaged for sale

2 years

Reconstituted concentrate

The reconstituted concentrate should be further diluted immediately after reconstitution.

Diluted product

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

6.4 Special precautions for storage

Powder as packaged for sale:

Store below 25°C.

Keep the vial in the outer carton in order to protect from light.

Reconstituted concentrate and diluted product:

For storage conditions after reconstitution and further dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless type 1, 20 ml glass vial, with a chlorobutyl type 1 silicone coated stopper and a green aluminium/polypropylene flip-off cap.

Pack sizes: 1 vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The product must be reconstituted and the resulting concentrate must then be diluted prior to use.

Preparation of the reconstituted concentrate
Dissolve the content of each 1000 mg vial in 20 ml of sterile water for injections.

Appearance of reconstituted concentrate
Clear and colourless to pale yellow solution, free from fibre and visible particulate matters.

One ml of reconstituted concentrate contains 50 mg of vancomycin.

For storage conditions of the reconstituted concentrate, see sections 6.3

Preparation of final diluted solution infusion
Reconstituted concentrate containing 50 mg/ml of vancomycin should be further diluted immediately after reconstitution.
Suitable diluents are:
Sodium Chloride 9 mg/ml (0.9%) Injection, Glucose 50 mg/ml (5%) Injection, Sodium Chloride 9 mg/ml (0.9 %) and Glucose 50 mg/ml (5%) Injection or Ringer acetate Injection.
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 fibre and visible particulate matter should be used.

Intermittent infusion
Reconstituted concentrate containing 1000 mg of vancomycin (50 mg/ml) must be diluted further with at least 200 ml diluent immediately after reconstitution.
The concentration of vancomycin in Solution for infusion should not exceed 5 mg/ml.

The desired dose should be administered slowly by intravenous infusion at a rate of no more than 10 mg/minute, for at least 60 minutes or even longer.

For storage conditions of the diluted medicinal product, see sections 6.3

Disposal
Vials are for single use only. Unused product must be discarded.

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

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/180/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th February 2015

10 DATE OF REVISION OF THE TEXT

December 2017