Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vancomycin 500 mg powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

An off white to light beige coloured powder.
When reconstituted, it forms a clear solution.

The reconstituted solution has a pH value of 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

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 *Clostridioides 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 hours (not to exceed 2 g per dose).

In seriously ill patients, a loading dose of 25 – 30 mg/kg 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 of 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 must be tailored to the type and severity of the 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 the organism

Special populations

Elderly
Lower maintenance doses may be required due to 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, the 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 using the above formula.

The usual starting dose for adult patients is 15 to 20mg/kg that could be administered every 24 hours in patients with creatinine clearance between 20 and 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 vancomycin serum 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/1,73 m^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/1,73m^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 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 required 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 *Clostridioides difficile* infection(CDI):

The recommended vancomycin dose is 125 mg every 6 hours for 10 days at 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 electrolyte should be ensured.

Monitoring of vancomycin serum concentrations

The frequency of therapeutic drug monitoring (TDM) needs to be individualised 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 is 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 predicting individual dose requirements to achieve 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 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 may 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 infusion solution, see section 6.6.

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

Oral administration

The contents of vials for parenteral administration may be used.

The content of one Vancomycin 500 mg vial may be reconstituted in 30 ml of water, while the content of one Vancomycin 1000 mg vial may be reconstituted in 30 or 60 ml of water and given to the patient to drink (see also 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 transient 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 caried out during and after treatment. Concurrent or sequential use of other ototoxic substances should be avoided (see section 4.5).

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 ("vancomycin infusion reaction"). 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 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 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.
Haemorrhagic 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 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 carefully monitored 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.

Super infection
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 *Clostridioides difficile* infection. Vancomycin should be administered orally for this indication.

Testing for *Clostridioides difficile* colonisation 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 causes should always be sought and *Clostridioides difficile* enterocolitis be proven.

Potential for systemic absorption
Absorption may be enhanced in patients with inflammatory disorders of the intestinal mucosa or with *Clostridioides 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 minimize 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 systemic or topical use of other potentially ototoxic or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymixin B, colistin, viomycin, cisplatin, loop diuretics, piperacillin/tazobactam and NSAIDs may increase the toxicity of vancomycin and if they need to be given should be used with caution and appropriate monitoring (see section 4.4).

Anaesthetics
Concomitant administration of vancomycin and anaesthetic agents has been associated with erythema, histamine-like flushing and anaphylactoid reactions (see section 4.4).

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. When administered during anaesthesia, doses must be diluted to 5 mg/ml or less and

administered slowly with close cardiac monitoring. Position changes should be delayed until the infusion is completed to allow for postural adjustment (see section 4.4).

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.

Drugs that inhibit intestinal motility and proton pump inhibitors.
Oral administration: Consideration should be given to discontinuing proton pump inhibitors and anti-motility agents in line with local guidelines for *Clostridioides difficile* infection.

4.6 Fertility, pregnancy and lactation

Pregnancy
Teratology studies have been performed at 5 times the human dose in rats and 3 times the human dose in rabbits and have revealed no evidence of harm to the foetus due to vancomycin. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin hydrochloride on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancomycin hydrochloride was found in cord blood. No sensorineural hearing loss or nephrotoxicity attributable to vancomycin was noted. One infant, whose mother received vancomycin in the third trimester, experienced conductive hearing loss that was not attributable to vancomycin. Because vancomycin was administered only in the second and third trimesters, it is not known whether it causes foetal harm.

Vancomycin should be given in pregnancy only if clearly needed and blood levels should be monitored carefully to minimise the risk of foetal toxicity. It has been reported, however, that pregnant patients may require significantly increased doses of vancomycin to achieve therapeutic serum concentrations.

Breast-feeding
Vancomycin is excreted in human 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 alterations of gastrointestinal flora and diarrhoea in the infant. 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 ("vancomycin infusion reaction") 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 generalised 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 lymphatic system disorders:	
Rare	Reversible neutropenia, agranulocytosis, eosinophilia, thrombocytopenia, pancytopenia
Immune system disorders:	
Rare	Hypersensitivity reactions, anaphylactic reactions
Ear and labyrinth disorders:	
Uncommon	Transient or permanent loss of hearing
Rare	Vertigo, tinnitus, 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 ("vancomycin infusion reaction"), exanthema and mucosal inflammation, pruritus, urticaria
Very rare	Exfoliative dermatitis, Stevens-Johnson syndrome, 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

Reversible neutropenia usually starting one week or more after onset of intravenous therapy or after total dose greater 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 (see section 4.3).

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.

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

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: J01 XA01, for intravenous use.
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents, antibiotics, ATC code: A07 AA09, for oral use.

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

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

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

Synergism
The combination of vancomycin with an aminoglycoside antibiotic has a synergistic effect against many strains of *Staphylococcus aureus*, non-enterococcal group D-streptococci, enterococci, and streptococci of the *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 on 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 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.

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for vancomycin and are listed here: www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Commonly susceptible species
Gram positive *Enterococcus faecalis* *Staphylococcus aureus* Methicillin-resistant *Staphylococcus aureus* coagulase-negative Staphylococci *Streptococcus* spp. *Streptococcus pneumoniae* *Enterococcus* 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 1000mg vancomycin (15 mg/kg) over 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 obtained 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 the 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 a 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 is approximately 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 the ototoxicity of vancomycin therapy-adjuvant monitoring of plasma concentrations is indicated in such cases.

Bile excretion is insignificant (less than 5% of a dose).

Although 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 vancomycin concentrations were 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 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.

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 concentrations 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 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 neonates.

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

Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of vancomycin was found in standard laboratory tests. No definitive fertility studies have been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Vancomycin solutions have a low pH (2.5 - 4.5) that may cause chemical or physical instability if mixed with other compounds. Mixing with alkaline solutions should be avoided.

Mixtures of vancomycin and beta-lactam antibiotics have been shown to be physically incompatible. The likelihood of precipitation increases with higher concentrations of vancomycin. It is recommended to adequately flush intravenous lines between administration of these antibiotics. It is also recommended to dilute solutions of vancomycin to 5 mg/ml or less.

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

6.3 Shelf life

2 years.

Intravenous administration

Reconstituted solution:
After reconstitution, chemical and physical stability of the concentrate has been demonstrated for up to 24 hours at 25 °C or for up to 96 hours in the refrigerator (2 °C to 8 °C).

Diluted solution:
After further dilution, chemical and physical stability of the solution has been demonstrated for up to 24 hours at 25 °C or 96 hours in the refrigerator at 2 – 8 °C, for the concentration range of 5 mg/ml to 10 mg/ml.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Oral administration
Reconstituted solutions for oral administration may be stored in the refrigerator (2 °C to 8 °C) for 96 hours.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container

Type I colourless glass vial with a bromobutyl stopper and aluminium closure with violet plastic flip off cap for 500 mg strength and green plastic flip off cap for 1000 mg strength.

Pack sizes: 1, 5, 10 vial(s)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation of the reconstituted solution

At the time of use, add 10 ml of water for injections to the 500 mg vial, or 20 ml water for injections to the 1 000 mg vial. Vials reconstituted in this manner will give a solution of 50 mg/ml. When reconstituted in water, it forms a clear solution.

FURTHER DILUTION IS REQUIRED. Read instructions below.

Preparation of the diluted solution for infusion

Reconstituted solutions containing 50 mg/ml of vancomycin should be further diluted depending on the method of administration. The following solutions are suitable diluents for the preparation of an infusion solution:

- Sodium Chloride 9 mg/ml (0,9 %) solution,
- Glucose 50 mg/ml (5 %) solution,
- Ringer's Lactate solution,
- Sodium Chloride 9 mg/ml (0,9 %) solution and Glucose 50 mg/ml (5 %) solution,
- Sodium Chloride 3 mg/ml (0,3 %) solution and Glucose 33 mg/ml (3,3 %) solution
- Ringers Lactate solution and Glucose 50 mg/ml (5 %) solution

Intermittent infusion is the preferred method of administration.
Reconstituted solutions containing 500 mg vancomycin must be diluted with at least 100 ml diluent.
Reconstituted solutions containing 1000 mg vancomycin must be diluted with at least 200 ml diluent.

The desired dose should be given by intravenous infusion over a period of at least 60 minutes. If administered over a shorter period of time or in higher concentrations, there is the possibility of inducing marked hypotension in addition to thrombophlebitis. Rapid administration may also produce flushing and a transient rash over the neck and shoulders.

Continuous infusion (should be used only when intermittent infusion is not feasible).
1 – 2 g can be added to a sufficiently large volume of the suitable above diluent to permit the desired daily dose to be administered slowly by intravenous drip over a 24-hour period.

Prior to administration, parenteral drug products should be inspected visually for particulate matter and discolouration whenever solution or container permits. Only clear and colourless solution free from particles should be used.

Preparation of the oral solution

The contents of vials for parenteral administration may be used.

The content of one Vancomycin 500 mg vial may be reconstituted in 30 ml of water, while the content of one Vancomycin 1000 mg vial may be reconstituted in 30 or 60 ml of water and given to the patient to drink.

7 MARKETING AUTHORISATION HOLDER

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