ANNEX III

Amendments to relevant sections of the summary of product characteristics and the package leaflets

Note:

These amendments to the relevant sections of the Product Information are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

SUMMARY OF PRODUCT CHARACTERISTICS

Capsules

1. NAME OF THE MEDICINAL PRODUCT

[For all vancomycin 125 mg capsule]

<{(Invented) vancomycin 125mg capsule}>

[For all vancomycin 250 mg capsule]

<{(Invented) vancomycin 250mg capsule}>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[For all vancomycin 125 mg capsule]

[The following wording to be reflected in this section]

Each capsule contains 125mg vancomycin hydrochloride equivalent to 125,000IU vancomycin.

[For all vancomycin 250 mg capsule]

[The following wording to be reflected in this section]

Each capsule contains 250mg vancomycin hydrochloride equivalent to 250,000IU vancomycin.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[This section should read as follows:]

Vancomycin capsules are indicated in patients 12 years and older 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

[This section should read as follows:]

Posology

Adults and adolescents aged 12 to less than 18 years old

[This section should read as follows:]

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.

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 instituted.

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

Special populations

Renal impairment

Due to the very low systemic absorption, dose adjustment is unlikely, unless substantial oral absorption may occur in case of inflammatory intestinal disorders or *Clostridium difficile*-induced pseudomembranous colitis (see section 4.4).

Paediatric population

Vancomycin capsules are not appropriate for the treatment of children under the age of 12 years or for adolescents unable to swallow them. Below 12 years, age-appropriate formulation should be used.

Method of administration

For oral use.

The capsule should not be open and should be taken with plenty of water.

4.3 Contraindications

[This section should read as follows:]

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

4.4 Special warnings and precautions for use

[This section should read as follows:]

Oral Use Only

This preparation is for oral use only and is not systemically absorbed. Orally administered Vancomycin capsules are not effective for other types of infections.

Potential for Systemic Absorption

Absorption may be enhanced in patients with inflammatory disorders of the intestinal mucosa or *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

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.

4.8 Undesirable effects

[This section should read as follows:]

Summary of the Safety profile

The absorption of vancomycin from the gastrointestinal tract is negligible. However, in severe inflammation of the intestinal mucosa, especially in combination with renal insufficiency, side effects that occur when vancomycin is administered parenterally may appear. Therefore, the below mentioned adverse reactions and frequencies related to parenteral vancomycin administration are included.

When vancomycin is administered parenterally, 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, 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 (“red man syndrome”), exanthema and mucosal inflammation, pruritus, urticaria
Very rare	Exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome, 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 of more than 25 g.

Intravenous vancomycin should be infused slowly. 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. 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.

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 the national reporting system listed in Appendix V.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

[This section should read as follows:]

[the following paragraphs should be reflected in this section:]

(...)

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 bactericidal for dividing microorganisms. In addition, it impairs the permeability of the bacterial cell membrane and RNA synthesis. The drug is bactericidal for dividing microorganisms.

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.

Susceptibility testing breakpoints

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

	Susceptible	**Resistant**
Clostridium difficile[1]	≤ 2 mg/L	> 2 mg/L

[1] The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type isolates from those with reduced susceptibility.

5.2 Pharmacokinetic properties

[This section should read as follows:]

Absorption

Vancomycin is not usually absorbed into the blood after oral administration. However, absorption may be enhanced in patients with inflammatory disorders of the intestinal mucosa or with *Clostridium difficile*-induced pseudomembranous colitis. This may lead to vancomycin accumulation in patients with co-existing renal impairment.

Elimination

An oral dose is excreted almost exclusively in the faeces. During multiple dosing of 250 mg every 8 hours for 7 doses, faecal concentrations of vancomycin, in volunteers, exceeded 100 mg/kg in the majority of samples. No blood concentrations were detected and urinary recovery did not exceed 0.76%.

Powder for concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

[For all vancomycin 500 mg powder for concentrate for solution for infusion]

<{(Invented) vancomycin 500mg powder for concentrate for solution for infusion}>

[For all vancomycin 1000 mg powder for concentrate for solution for infusion]

<{(Invented) vancomycin 1000mg powder for concentrate for solution for infusion}>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[For all vancomycin 500 mg powder for concentrate for solution for infusion, the following wording to be reflected in this section]

Each vial contains 500 mg vancomycin hydrochloride equivalent to 500,000 IU vancomycin.

[For all vancomycin 1000 mg powder for concentrate for solution for infusion, the following wording to be reflected in this section]

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

(….)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[This section should read as follows:]

[For vancomycin powder for concentrate for solution for infusion for parenteral administration, the indications should be as follows:]

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

[For parenteral formulations authorised for the following indications:]

- acute bacterial meningitis

- 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.

[For parenteral formulations authorised for intraperitoneal use, the indication should be as follows:]

Intraperitoneal administration

Vancomycin is indicated in all age groups for the treatment of peritoneal dialysis–associated peritonitis (see sections 4.2, 4.4 and 5.1).

[For parenteral formulations authorised for oral use, the indication should be as follows:]

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).

[The below wording should be introduced in this section for all vancomycin containing products]

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

[This section should read as follows:]

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)].

[For parenteral formulations authorised for perioperative antibacterial prophylaxis, include the wording as follows:]

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***
Acute bacterial meningitis (*For parenteral formulations authorised for Acute bacterial meningitis)*	10 to 21 days

*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 hemodialysis. 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.

[For parenteral formulations authorised for intraperitoneal administration, include the wording as follows:]

Intraperitoneal administration

Peritoneal dialysis–associated peritonitis

Adults

Intermittent therapy: the recommended dose is 15-30 mg/kg in the long-dwell, every 5-7 days.

Continuous infusion: loading dose of 30 mg/kg followed by a maintenance dose of 1.5 mg/kg/bag in all exchanges.

Paediatric population

Intermittent therapy: initial dose of 30 mg/kg in the long-dwell, followed by 15 mg/kg every 3-5 days during the long-dwell (the second dose should be time-based on a blood level obtained 2–4 days after the initial dose, see section 4.4).

Continuous infusion: loading dose of 1000 mg/L per litter of dialysate followed by 25 mg/L (after 3-6 h of loading dose) in all exchanges.

Supplemental doses may be needed for patients on Automated Peritoneal Dialysis (APD) because rapid exchanges in APD may lead to inadequate time to achieve therapeutic levels when vancomycin is given via intraperitoneal intermittently.

[For parenteral formulations authorised for oral use, the following should be reflected in this section]

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.

[The below should be introduced in section 4.2 for all vancomycin products powder for concentrate]

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.

[For parenteral formulations authorised for intraperitoneal administration, include the wording as follows:]

Intraperitoneal administration

Intraperitoneal antibiotics should be added to the dialysate using sterile technique.

[For parenteral formulations authorised for oral administration, the following should be reflected in this section]

Oral administration

[This section must include instructions for preparation and administration of the oral solution. In addition, appropriate information should be given under Method of administration and in section 6.6.]

4.3 Contraindications

[This section should read as follows:]

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

[This section should read as follows:]

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 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.

[For parenteral formulations authorised for intraperitoneal administration, include the wording as follows:]

The administration of vancomycin by intraperitoneal injection during continuous ambulatory peritoneal dialysis has been associated with a syndrome of chemical peritonitis.

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.

[For parenteral formulations authorised for intraperitoneal administration, include the wording as follows:]

For the intraperitoneal treatment of peritoneal dialysis–associated peritonitis (PDP) in children with residual renal function, intermittent therapy should only be indicated provided that vancomycin serum levels can be monitored in a timely manner.

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.

[For parenteral formulations authorised for oral use, include the wording as follows:]

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.

4.8. Undesirable effects

[This section should read as follows:]

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.

[For parenteral formulations authorised for oral use, include the wording as follows:]

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.

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, 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 (“red man syndrome”), exanthema and mucosal inflammation, pruritus, urticaria
Very rare	Exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome, 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 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 the national reporting system listed in Appendix V.

5.1 Pharmacodynamic properties

[This section should read as follows:]

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 against some *Staphylococcus epidermidis* strains and in combination with rifampicin against some *Staphylococcus aureus* strains, preceding synergism testing is useful.

Specimens for bacterial cultures should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to vancomycin.

Susceptibility testing breakpoints

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

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent 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 staphylococci[1]	≤ 4 mg/L	> 4 mg/L
Enterococcus spp.	≤ 4 mg/L	> 4 mg/L
Streptococcus groups A, B, C and G	≤ 2 mg/L	> 2 mg/L
Streptococcus pneumoniae	≤ 2 mg/L	> 2 mg/L
Gram positive anaerobes	≤ 2 mg/L	> 2 mg/L

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

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

[This section should read as follows:]

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.

[For parenteral formulations authorised for intraperitoneal administration, include the wording as follows:]

If vancomycin is administered during a peritoneal dialysis intraperitoneally, approximately 30-65% reach the systemic cycle during the first 6 hours. After intraperitoneal administration of 30 mg/kg serum levels of approximately 10 mg/l are reached.

[For parenteral formulations authorised for oral use, include the wording as follows:]

Vancomycin is not usually absorbed into the blood after oral administration. However, absorption may occur after oral administration in patients with (pseudomembranous) colitis. This may lead to vancomycin accumulation in patients with co-existing renal impairment.

Distribution

The volume of distribution is about 60 L/1.73 m^2 body surface. At serum concentrations of vancomycin of 10 mg/l to 100 mg/l, the binding of the drug to plasma proteins is approximately 30-55%, measured by ultra-filtration.

Vancomycin diffuses readily across the placenta and is distributed into cord blood. In non-inflamed meninges, vancomycin passes the blood-brain barrier only to a low extent.

Biotransformation

There is very little metabolism of the drug. After parenteral administration it is excreted almost completely as microbiologically active substance (approx. 75-90% within 24 hours) through glomerular filtration via the kidneys.

Elimination

The elimination half-life of vancomycin is 4 to 6 hours in patients with normal renal function and 2.2-3 hours in children. Plasma clearance is about 0.058 L/kg/h and kidney clearance about 0.048 L/kg/h. In the first 24 hours, approximately 80 % of an administered dose of vancomycin is excreted in the urine through glomerular filtration. Renal dysfunction delays the excretion of vancomycin. In anephric patients, the mean half-life is 7.5 days. Due to ototoxicity of vancomycin therapy-adjuvant monitoring of the plasma concentrations is indicated in such cases.

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

Although the vancomycin is not eliminated efficiently by haemodialysis or peritoneal dialysis, there have been reports of an increase in vancomycin clearance with haemoperfusion and haemofiltration.

[For parenteral formulations authorised for oral use, include the wording as follows:]

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

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.

PACKAGE LEAFLET

Note: The existing package leaflet shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the wording below.

[For all vancomycin 125 mg capsule]

<{(Invented) vancomycin 125mg capsule}>

[For all vancomycin 250 mg capsule]

<{(Invented) vancomycin 250mg capsule}>

[to be completed nationally]

1. What Vancomycin is and what it is used for

Vancomycin is an antibiotic that belongs to a group of antibiotics called “glycopeptides”. Vancomycin works by eliminating certain bacteria that cause infections.

Vancomycin is used in adults and adolescents from 12 years of age for the treatment of infections of the mucosa of the small and the large intestines with damage to the mucosae (pseudomembranous colitis), caused by the *Clostridium difficile* bacterium.

2. What you need to know before you take [product name]

Do not take Vancomycin

If you are allergic to vancomycin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

If you have an inflammatory disorder of the digestive tract (you may be at risk of side effects, especially if you also have a kidney disorder).

Vancomycin capsules are not appropriate for children under 12 years or for adolescents unable to swallow them. Other forms of this medicine may be more suitable for children; ask your doctor or pharmacist.

3. How to take [product name]

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adults and adolescents (from 12 years and older)

The recommended dose is 125 mg every 6 hours. In some cases, your doctor may decide to give a higher daily dose of up to 500 mg every 6 hours. The maximum daily dose should not exceed 2 g.

If you suffered other episodes (infection of the mucosa) before you may need different dose and different duration of the therapy.

Method of administration

For oral use.

Swallow the capsules whole with water.

The usual duration of the therapy is 10 days but it may be different depending on the individual response to treatment for every patient.

4. Possible side effects

[This section should read as follows:]

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Vancomycin can cause allergic reactions, although serious allergic reactions (anaphylactic shock) are rare. Tell your doctor immediately if you get any sudden wheeziness, difficulty in breathing, redness on the upper part of the body, rash or itching.

Uptake of vancomycin from the gastrointestinal tract is negligible. Therefore adverse events following intake of capsules are unlikely.

However, if you have an inflammatory disorder of the digestive tract, especially if you also have a kidney disorder, similar side effects as those that occur when vancomycin is given by infusion may appear. Therefore, the side effects and frequencies which are reported for vancomycin given as infusion are included.

Common side effects (may affect up to 1 in 10 people):

- Fall in blood pressure
- Breathlessness, noisy breathing (a high pitched sound resulting from obstructed air flow in the upper airway)
- Rash and inflammation of the lining of the mouth, itching, itching rash, hives
- Kidney problems which may be detected primarily by blood tests
- Redness of upper body and face, inflammation of a vein

Uncommon side effects (may affect up to 1 in 100 people):

- Temporary or permanent loss of hearing

Rare side effects (may affect up to 1 in 1,000 people):

- Decrease in white blood cells, red blood cells and platelets (blood cells responsible for blood clotting)

  Increase in some of the white blood cells in the blood.
- Loss of balance, ringing in your ears, dizziness
- Blood vessel inflammation
- Nausea (feeling sick)
- Inflammation of the kidneys and kidney failure
- Pain in the chest and back muscles
- Fever, chills

Very rare side effects (may affect up to 1 in 10,000 people):

- Sudden onset of severe allergic skin reaction with skin flaking blistering or peeling skin. This may be associated with a high fever and joint pains
- Cardiac arrest
- Inflammation of the bowel which causes abdominal pain and diarrhea, which may contain blood

Not known (frequency cannot be estimated from the available data):

- Being sick (throwing up), diarrhoea
- Confusion, drowsiness, lack of energy, swelling, fluid retention, decreased urine
- Rash with swelling or pain behind the ears, in the neck, groin, under the chin and armpits (swollen lymph nodes), abnormal blood and liver function tests
- Rash with blisters and fever.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

6. Contents of the pack and other information

Other sources of information

Advice / medical education

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.

If your doctor has prescribed antibiotics, you need them precisely for your current illness.

Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.

Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:

- dosage

- schedules

- duration of treatment

Consequently, to preserve the efficacy of this drug:

1 - Use antibiotics only when prescribed.

2 - Strictly follow the prescription.

3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.

4 - Never give your antibiotic to another person; maybe it is not adapted to her/his illness.

5 - After completion of treatment, return all unused drugs to your chemist's shop to ensure they will be disposed of correctly.

[For all vancomycin 500 mg powder for concentrate for solution for infusion]

<{(Invented) vancomycin 500mg powder for concentrate for solution for infusion}>

[For all vancomycin 1000 mg powder for concentrate for solution for infusion]

<{(Invented) vancomycin 1000mg powder for concentrate for solution for infusion}>

[to be completed nationally]

1. What Vancomycin is and what it is used for

Vancomycin is an antibiotic that belongs to a group of antibiotics called “glycopeptides”. Vancomycin works by eliminating certain bacteria that cause infections.

Vancomycin powder is made into a <solution for infusion> <or> <oral solution>.

[for vancomycin powder for concentrate for infusion authorised for intravenous use]

Vancomycin is used in in all age groups by infusion for the treatment of the following serious infections:

- Infections of the skin and tissues below the skin.
- Infections of bone and joints.
- An infection of the lungs called "pneumonia".
- Infection of the inside lining of the heart (endocarditis) and to prevent endocarditis in patients at risk when undergoing major surgical procedures
- Infection in central nervous system.
- Infection in the blood linked to the infections listed above.

[For parenteral formulations authorised for intraperitoneal use:]

- In patients receiving peritoneal dialysis, vancomycin is used in adults and children for the treatment of infections related to peritoneal dialysis.

[for vancomycin powder for concentrate for infusion authorised for oral use]

Vancomycin can be given orally in adults and children for the treament of infection of the mucosa of the small and the large intestines with damage to the mucosae (pseudomembranous colitis), caused by the *Clostridium difficile* bacterium.

2. What you need to know before you use Vancomycin

Do not use Vancomycin

- If you are allergic to vancomycin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or hospital pharmacist or nurse before using Vancomycin if:

- You suffered a previous allergic reaction to teicoplanin because this could mean you are also allergic to vancomycin.
- You have a hearing disorder, especially if you are elderly (you may need hearing tests during treatment).
- You have kidney disorder (you will need to have your blood and kidneys tested during treatment).
- You are receiving vancomycin by infusion for the treatment of the diarrhoea associated to *Clostridium difficile* infection instead of orally.

Talk to your doctor or hospital pharmacist or nurse during treatment with Vancomycin if:

- You are receiving vancomycin for a long time (you may need to have your blood, hepatic and kidneys tested during treatment).
- You develop any skin reaction during the treatment.
- You develop severe or prolonged diarrhoea during or after using vancomycin, consult your doctor immediately. This may be a sign of bowel inflammation (pseudomembranous colitis) which can occur following treatment with antibiotics.

Children

Vancomycin will be used with particular care in premature infants and young infants, because their kidneys are not fully developed and they may accumulare vancomycin in the blood. This age group may need blood tests for controlling vancomycin levels in blood.

Concomitant administration of vancomycin and anaesthetic agents has been associated with skin redness (erythema) and allergic reactions in children. Similarly, concomitant use with other medicines such as aminoglycoside antibiotics, nonsteroidal anti-inflammatory agents (NSAIDs, e.g., ibuprofen) or amphotericin B (medicine for fungal infection) can increase the risk of kidney damage and therefore more frequent blood and renal test may be necessary.

3. How to use [product name]

You will be given Vancomycin by medical staff while you are in hospital. Your doctor will decide how much of this medicine you should receive each day and how long the treatment will last.

Dosage

The dose given to you will depend on:

- your age,
- your weight,
- the infection you have,
- how well your kidneys are working,

- your hearing ability,

- any other medicines you may be taking.

Intravenous administration

Adults and adolescents (from 12 years and older)

The dosage will be calculated according to your body weight. The usual infusion dose is 15 to 20 mg for each kg of body weight. It is usually given every 8 to 12 hours. In some cases, your doctor may decide to give an initial dose of up to 30 mg for each kg of body weight. The maximum daily dose should not exceed 2 g.

Use in children

Children aged from one month to less than 12 years of age

The dosage will be calculated according to your body weight. The usual infusion dose is 10 to 15 mg for each kg of body weight. It is usually given every 6 hours.

Preterm and term newborn infants (from 0 to 27 days)

The dosage will be calculated according to 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).

The elderly, pregnant women and patients with a kidney disorder, including those on dialysis, may need a different dose.

[For parenteral formulations authorised for intraperitoneal use:]

Intraperitoneal administration

Adults and children

When using for the treatment of infections related to peritoneal dialysis, your doctor will decide exactly how much vancomycin you need.

[For parenteral formulations authorised for oral use:]

Oral administration

Adults and adolescents (from 12 to 18 years)

The recommended dose is 125 mg every 6 hours. In some cases, your doctor may decide to give a higher daily dose of up to 500 mg every 6 hours. The maximum daily dose should not exceed 2 g.

If you suffered other episodes (infection of the mucosa) before you may need different dose and different duration of the therapy.

Use in children

Neonates, infants and children less than 12 years old

The recommended dose is 10 mg for each kg of body weight. It is usually given every 6 hours. The maximum daily dose should not exceed 2 g.

Method of administration

Intravenous infusion means that the medicinal product flows from an infusion bottle or bag through a tube to one of your blood vessels and into your body. Your doctor, or nurse, will always give vancomycin into your blood and not in the muscle.

Vancomycin will be given into your vein for at least 60 minutes.

[For parenteral formulations authorised for intraperitoneal use:]

If given for the treatment of of infections related to peritoneal dialysis, vancomycin will be added to the dialysate solution in the long-dwell exchange.

[For parenteral formulations authorised for oral use:]

If given for treatment of gastric disorders (so called Pseudomembranous colitis), the medicinal product must be administrated as a solution for oral use (you will take the medicine by mouth).

Duration of treatment

The length of treatment depends on the infection you have and may last a number of weeks.

The duration of the therapy may be different depending on the individual response to treatment for every patient.

During the treatment, you might have blood tests, be asked to provide urine samples and possibly have hearing tests to look for signs of possible side effects.

4. Possible side effects

[This section should read as follows:]

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Vancomycin can cause allergic reactions, although serious allergic reactions (anaphylactic shock) are rare. Tell your doctor immediately if you get any sudden wheeziness, difficulty in breathing, redness on the upper part of the body, rash or itching.

[For parenteral formulations authorised for oral use:]

The absorption of vancomycin from the gastrointestinal tract is negligible. However, if you have an inflammatory disorder of the digestive tract, especially if you also have a kidney disorder, side effects that occur when vancomycin is administered by infusion may appear.

Common side effects (may affect up to 1 in 10 people):

- Fall in blood pressure
- Breathlessness, noisy breathing (a high pitched sound resulting from obstructed air flow in the upper airway)
- Rash and inflammation of the lining of the mouth, itching, itching rash, hives

- Kidney problems which may be detected primarily by blood tests
- Redness of upper body and face, inflammation of a vein

Uncommon side effects (may affect up to 1 in 100 people):

- Temporary or permanent loss of hearing

Rare side effects (may affect up to 1 in 1,000 people):

- Decrease in white blood cells, red blood cells and platelets (blood cells responsible for blood clotting)

  Increase in some of the white cells in the blood.
- Loss of balance, ringing in your ears, dizziness
- Blood vessel inflammation
- Nausea (feeling sick)
- Inflammation of the kidneys and kidney failure
- Pain in the chest and back muscles
- Fever, chills

Very rare side effects (may affect up to 1 in 10,000 people):

- Sudden onset of severe allergic skin reaction with skin flaking blistering or peeling skin. This may be associated with a high fever and joint pains
- Cardiac arrest
- Inflammation of the bowel which causes abdominal pain and diarrhea, which may contain blood

Not known (frequency cannot be estimated from the available data):

- Being sick (throwing up), diarrhoea
- Confusion, drowsiness, lack of energy, swelling, fluid retention, decreased urine
- Rash with swelling or pain behind the ears, in the neck, groin, under the chin and armpits (swollen lymph nodes), abnormal blood and liver function tests
- Rash with blisters and fever.

Reporting of side effects

If you get any side effects, talk to your doctor, hospital pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

6. Contents of the pack and other information

Other sources of information

<u>Advice / medical education</u>

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.

If your doctor has prescribed antibiotics, you need them precisely for your current illness.

Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.

Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:

- dosage

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- duration of treatment

Consequently, to preserve the efficacy of this drug:

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2 - Strictly follow the prescription.

3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.