VANCOMYCIN 500MG AND 1000MG POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION

PL 24701/0033-4

UKPAR

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VANCOMYCIN 500MG AND 1000MG POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION

PL 24701/0033-4

LAY SUMMARY

On 15 August 2011, the MHRA granted Nucleus EHF Marketing Authorisations (licences) for Vancomycin 500mg and 1000mg Powder for Concentrate for Solution for Infusion (PL 24701/0033-4).

Vancomycin belongs to a group of medicines called glycopeptides antibiotics.

Vancomycin comes in the form of a powder which is made into a solution using sterile water (for injections). This solution is given as an infusion, a slow injection, by means of a drip through a vein. It can also be given by mouth.

Vancomycin 500mg and 1000mg Powder for Concentrate for Solution for Infusion are used for severe infections caused by bacteria which can resist other antibiotics. They are used in patients who have not responded to treatment with, or have had a bad reaction to, other antibiotics.

They are used to treat various severe infections of the lining or valves of the heart, lungs, bone or soft tissue (flesh) and can also be given before some surgical procedures to prevent infections.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of using Vancomycin 500mg and 1000mg Powder for Concentrate for Solution for Infusion outweigh the risks; hence these Marketing Authorisations have been granted.
VANCOMYCIN 500MG AND 1000MG POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted Marketing Authorisations for the medicinal products Vancomycin 500mg and 1000mg Powder for Concentrate for Solution for Infusion (PL 24701/0033-4) to Nucleus EHF on 15 August 2011. They are prescription only medicines (POM).

Intravenous vancomycin is indicated in the following severe infections caused by gram-positive bacteria susceptible to vancomycin which cannot be treated with, or failed to respond to or are resistant to other antibiotics such as penicillins and cephalosporins:

- endocarditis
- infections of the bones (osteomyelitis)
- pneumonia
- soft-tissue infections

Vancomycin may be used for the perioperative prophylaxis against bacterial endocarditis, in patients at high risk of developing bacterial endocarditis when they undergo major surgical procedures (e.g., cardiac and vascular procedures, etc) and are unable to receive a suitable beta-lactam antibacterial agent.

Vancomycin may be used orally for the treatment of staphylococcal enterocolitis and pseudomembranous colitis due to Clostridium difficile. Parenteral administration of vancomycin is not effective for these indications. Intravenous administration may be used concomitantly if required.

These applications for Vancomycin 500mg and 1000mg Powder for Concentrate for Solution for Infusion are submitted under Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Vancocin CP Injection (500mg and 1000mg Vancomycin) first authorised in the UK to Eli Lilly & Company Limited on 18 April 1994 (PL 00006/507R). This licence then underwent a change of ownership to Flynn Pharma Limited on 26 May 2006 (PL 13621/0033).

Vancomycin is a glycopeptide antibiotic for parenteral use. Vancomycin exerts its bactericidal action by inhibiting the formation of the peptidoglycan polymers of the bacterial cell wall, thus interfering with cell wall synthesis.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Vancomycin hydrochloride


Structure:

![Structure of Vancomycin](image)

Physical form: White to off-white crystalline powder

Solubility: Freely soluble in acetone, methanol, ethanol and acetonitrile; soluble in ethyl acetate and chloroform; sparingly soluble in water; and slightly soluble in ether

Molecular formula: C_{66}H_{75}Cl_{2}N_{9}O_{24}.HCl

Molecular weight: 1485.71

Vancomycin hydrochloride is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof of structure data has been supplied for the active substance. All potential known impurities have been identified and characterised.
An appropriate specification is provided for the active substance, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all reference standards used.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations.

Adequate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

**MEDICINAL PRODUCT**

**Other Ingredients**

Other ingredients are the pharmaceutical excipients sodium hydroxide and hydrochloric acid (both for pH adjustment).

Both ingredients comply with their relevant European Pharmacopoeia monographs.

None of the excipients used contain material of animal or human origin.

**Pharmaceutical Development**

The objective of the development programme was to produce safe, efficacious products containing vancomycin hydrochloride that could be considered generic medicinal products of Vancocin CP Injection.

A suitable product development section has been provided. Justifications for the use and amounts of each excipient have been provided and are valid.

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. In-process controls are satisfactory based on batch data and controls on the finished products. The manufacturing process has been validated with process validation data on pilot-scale batches. A commitment to perform process validation on future commercial-scale batches of both strengths has been provided.

**Finished Product Specification**

The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis for all working standards used have been provided and are satisfactory.

**Container-Closure System**

Both strengths of the powder are packaged in type I glass vials closed with bromobutyl rubber stoppers and aluminium seal with flip off caps. The vials are packaged into cartons. Pack sizes are 1 and 10 vials.

Specifications and Certificates of Analysis have been provided. All primary product packaging complies with EU legislation.
Stability of the Product
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf life of 2 years for the unopened products has been set, with storage instructions “Store below 25°C. Keep the vial in the outer carton in order to protect from light”. This is satisfactory.

From a microbiological point of view, the medicinal products should be used immediately unless reconstitution and dilution has taken place in controlled and validated aseptic conditions. The reconstituted concentrate should be diluted immediately after preparation. For oral use the reconstituted concentrate should be used immediately. However the following instructions are given concerning the storage of the products after dilution: Chemical and physical in-use stability has been demonstrated for 48 hours at both 2-8°C and 25°C and protected from light when diluted with either 0.9% sodium chloride or 5% glucose.

For solutions of the parenteral powder intended for oral administration, these may be stored in a refrigerator (2-8 °C) for 96 hours.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL), Labels
The SmPCs, PIL and labels are pharmaceutically acceptable.

User testing results have been submitted for a typical PIL for these products. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains. A satisfactory bridging report has been submitted.

MAA Forms
These are pharmaceutically satisfactory.

The Quality Overall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
From a pharmaceutical perspective, it is recommended that Marketing Authorisations are granted for these applications.
NON-CLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of vancomycin are well known. As vancomycin hydrochloride is a widely used, well-known active substance, no new non-clinical data have been supplied with these applications and none are required for applications of this type. An overview based on literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

An Environmental Risk Assessment has not been submitted and one is not required for these generic applications.

From a non-clinical perspective, it is recommended that Marketing Authorisations are granted for these applications.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
No bioequivalence studies have been performed and none are required for applications of this type. According to CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98 Rev 1).

EFFICACY
No new data has been provided and none are required.

SAFETY
No new data has been provided and none are required.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL), Labels
The SmPCs, PIL and labels are clinically acceptable. The SmPCs are consistent with those for the reference products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

Clinical Overview
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring.

A satisfactory justification was provided for the absence of a Risk Management Plan.

Conclusion
From a clinical perspective, it is recommended that Marketing Authorisations are granted for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Vancomycin 500mg and 1000mg Powder for Concentrate for Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of vancomycin hydrochloride are well-known, no additional data were required.

EFFICACY
Vancomycin hydrochloride is a widely used, well-known active substance. No bioequivalence studies have been performed and none are required as the products are to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised reference products.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labels are satisfactory and consistent with those for the reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data submitted supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with vancomycin hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
### STEPS TAKEN FOR ASSESSMENT

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<td>1</td>
<td>The MHRA received the marketing authorisation application on 21 July 2010.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 13 August 2010.</td>
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<td>3</td>
<td>Following assessment of the application, the MHRA requested further information relating to the clinical dossier on 22 September 2010. The MHRA requested further information relating to the quality dossier on 10 March 2011.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 18 October 2010 for the clinical section. The applicant provided further information on 16 May 2011 for the quality section.</td>
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<td>5</td>
<td>The application was determined on 15 August 2011. The application was complete on 16 August 2011.</td>
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VANCOMYCIN 500MG AND 1000MG POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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<tr>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Vancomycin 500mg Powder for Concentrate for Solution for Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial contains:
Vancomycin 500mg Powder for Concentrate for Solution for Infusion.
Each vial contains 500mg vancomycin (equivalent to 525,000 IU) (as vancomycin hydrochloride).
When reconstituted with 10ml of water for injections, the resulting concentrate for solution for infusion contains 50mg/ml vancomycin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for concentrate for solution for infusion.

White to off-white powder.

Reconstituted solution pH is 2.5 – 4.5

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Intravenous vancomycin is indicated in the following severe infections caused by gram-positive bacteria susceptible to vancomycin which cannot be treated with or failed to respond or are resistant to other antibiotics such as penicillins and cephalosporins.
- endocarditis
- infections of the bones (osteomyelitis)
- pneumonia
- soft-tissue infections

Endocarditis caused by enterococci, *Streptococcus viridans* or *S. bovis* should be treated with a combination of vancomycin and an aminoglycoside.

Vancomycin may be used for the perioperative prophylaxis against bacterial endocarditis, in patients at high risk of developing bacterial endocarditis when they undergo major surgical procedures (e.g., cardiac and vascular procedures, etc) and are unable to receive a suitable beta-lactam antibacterial agent.

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

Vancomycin may be used orally for the treatment of staphylococcal enterocolitis and pseudomembranous colitis due to *Clostridium difficile*. Parenteral administration of vancomycin is not effective for these indications. Intravenous administration may be used concomitantly if required.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
For intravenous infusion only.

For preparation of solution for infusion please refer to section 6.6.

Concentrations of no more than 5mg/ml are recommended. In selected patients in need of fluid restriction, a concentration up to 10mg/ml may be used; use of such higher concentrations may increase the risk of infusion-related events. Infusions should be given over at least 60 minutes. In adults, if doses exceeding 500mg are used, a rate of infusion of no more than 10mg/min is recommended. Infusion related events may occur, however, at any rate or concentration.

The dose and duration of treatment should be adjusted individually and according to the underlying type and severity of infection, and patient factors such as age and renal function.

Vancomycin levels can be measured to aid dose adjustments.

**Measurement of serum concentrations**
Following multiple intravenous doses, peak serum concentrations, measured two hours after infusion is complete, range from 18-26mg/l. Trough levels measured immediately prior to the next dose should be 5-10mg/l. Ototoxicity has been associated with serum drug levels of 80-100mg/l, but this is rarely seen when serum levels are kept at or below 30mg/l.
Patients with normal renal function

**Adults and children above 12 years of age:**
The recommended daily intravenous dose is 2000mg (2g), given as 500mg every 6 hours or 1000mg (1g) every 12 hours. Improvement is usually seen within 48 to 72 hours. The total duration of administration is determined by the type and severity of the infection and the clinical response of the patient.

For bacterial endocarditis, the generally accepted regimen is 1000mg (1g) vancomycin intravenously every 12 hours for 4 weeks either alone or in combination with other antibiotics. Longer treatment up to 6 weeks may be required, depending on the pathogen involved. National guidelines should be adhered to.

If Vancomycin is co-administrated with aminoglycoside (e.g. gentamycin) patients should be monitored carefully for signs of neurotoxicity and ototoxicity. The dosage should be adjusted when renal disturbance occurs (see section 4.5).

**Peri-operative prophylaxis against bacterial endocarditis:** Adults receive 1000mg (1g) vancomycin intravenously prior to surgery (prior to induction of anaesthesia) and depending on time and type of surgery, the dose of 1000mg (1g) of vancomycin i.v. 12 hours postoperatively can be given.

**Children one month to 12 years of age:**
40 mg/kg/day: The dose must be divided and usually in to four doses (e.g. 10mg/kg every 6 hours). Each dose should be administered over at least 60 min.

**Newborn infants (full-term):**
0-7 days of age: A starting dose of 15mg/kg, followed by 10mg/kg every 12 hours.
7-30 days of age: A starting dose of 15mg/kg, followed by 10mg/kg every 8 hours.
Each dose should be administered over at least 60 min.
Close monitoring of serum vancomycin concentrations may be warranted in these patients.

**The elderly:**
Dosage reduction may be necessary to a greater extent than expected because of decreasing renal function (see below). Monitor auditory function, see Section 4.4.

**Pregnancy:**
It has been reported that significantly increased doses may be required to achieve therapeutic serum concentrations in pregnant patients.

**Patients with impaired renal function**
In patients with impaired renal function the dose must be adjusted to avoid toxic serum levels. Serum levels of vancomycin should be monitored regularly. For most patients with impaired renal function the following nomogram, based on creatinine clearance, can be used to determine the dose needed.
The starting dose should always be at least 15mg/kg. The nomogram is not valid for functionally anephric patients on dialysis.
If the creatine clearance is not available, the following formula may be applied to calculate the creatinine clearance from the patient’s age, sex and serum creatinine:

Men: \[
\frac{\text{Weight (kg)} \times 140 - \text{age (years)}}{72 \times \text{serum creatinine (mg/100 ml)}}
\]

Women: \[0.85 \times \text{value calculated by the above formula.}\n
Where possible, the creatinine clearance should always be determined.

**Patient on hemodialysis**
Serum levels of vancomycin should be monitored regularly.
For anuric patients (without kidney function) on dialysis the starting dose is 15mg/kg and the maintenance dose is approximately 1.9 mg/kg/24 hours. Since individual maintenance doses of 250mg to 1g are convenient, in patients with marked renal impairment a dose may be given every several days rather than on a daily basis. In anuria a dose of 1g every 7-10 days has been recommended

If polysulfone membranes are used for hemodialysis („high flux dialysis“), the half time of vancomycin is shortened. For patients with regular hemodialysis an additional maintenance dose may be necessary.

**Patients with impaired liver function**
The availability of data in patients with impaired liver function is limited. Available data do not indicate the need for dose adjustment in mild or moderate liver function impairment.

**Oral administration**
The contents of vials for parenteral administration may be used.

Adults and the elderly: The usual daily dose given is 500mg in divided doses for 7 to 10 days, although up to 2g/day have been used in severe cases. The total daily dosage should not exceed 2g. Each dose may be reconstituted in 30ml water and either given to the patient to drink, or administered by nasogastric tube.

Children: The usual daily dose is 40mg/kg in three or four divided doses for 7 to 10 days. The total daily dosage should not exceed 2g.

Common flavouring syrups may be added to the solution at the time of administration to improve the taste.
4.3 CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings
Rapid bolus administration (eg, 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 in a dilute solution 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 (see Section 4.2. and Section 4.8).

In case of severe acute hypersensitivity reactions (e.g. anaphylaxis), the treatment with vancomycin has to be discontinued immediately and the usual appropriate emergency measures have to be started.

Vancomycin should be used with caution in patients with allergic reactions to teicoplanin, since cross hypersensitivity reactions between vancomycin and teicoplanin have been reported. Vancomycin should be used with care in patients with renal insufficiency as the possibility of developing toxic effects is much higher in the presence of prolonged high blood concentrations. The dose should be reduced according to the degree of renal impairment. The risk of toxicity is appreciably increased by high blood concentrations or prolonged therapy. Blood levels should be monitored and renal function tests should be performed regularly.

Otoxicity, 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. 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. Vancomycin should be avoided in patients with previous hearing loss. If it is used in such patients, the dose should be regulated, by periodic determination of the drug level in the blood. The elderly are more susceptible to auditory damage.

Use in paediatrics: In premature neonates and young infants, it may be appropriate to confirm desired vancomycin serum concentrations. Concomitant administration of vancomycin and anaesthetic agents has been associated with erythema and histamine-like flushing in children (see section 4.5).

Use in the elderly: The natural decrease of glomerular filtration with increasing age may lead to elevated vancomycin serum concentrations if dosage is not adjusted (see section 4.2).

Precautions
Vancomycin is very irritating to tissue and causes injection site necrosis if injected intramuscularly. Pain and thrombophlebitis may occur in many patients receiving 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 6.6) and by changing the sites of infusion regularly.

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

Doses should be titrated on the basis of serum levels. Blood levels should be monitored and renal function tests performed regularly.

It is a general recommendation to monitor the concentrations 2-3 times weekly. Regular monitoring of the blood levels of vancomycin is indicated in 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.

Patients with borderline renal function and individuals over the age of 60 should be given serial tests of auditory function and of vancomycin blood levels. All patients receiving the drug should have periodic haematological studies, urine analysis and renal function tests.
Clinically significant serum concentrations have been reported in some patients being treated for active C. difficile-induced pseudomembranous colitis after multiple oral doses of vancomycin. Therefore, monitoring of serum concentrations may be appropriate in these patients.

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. In rare instances, there have been reports of pseudomembranous colitis, due to C. difficile, developing in patients who received intravenous vancomycin. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of vancomycin. Antiperistaltics are contraindicated.

Excipients:
This medicinal product contains less than 1 mmol sodium (23mg) per vial, i.e. essentially ‘sodium-free’.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

Infusion-related events may be minimised by the administration of vancomycin as a 60-minute infusion prior to anaesthetic induction.

Other potentially nephrotoxic or ototoxic medicinal products
Concurrent or sequential systemic or topical use of other potentially neurotoxic or nephrotoxic drugs, such as gentamycin, amphotericin B, streptomycin, neomycin, kanamycin, amikacin, tobramycin, bacitracin, polymyxin B, colistin, viomycin or cisplatin, may potentiate the nephrotoxicity and/or ototoxicity of vancomycin and consequently requires careful monitoring. See also section 4.2 with regard to dosage adjustment in case of use with an aminoglycoside.

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

4.6 PREGNANCY AND LACTATION

Pregnancy:
No sufficient safety experience is available regarding vancomycin during human pregnancy. Reproduction toxicological studies on animals do not suggest any effects on the development of the embryo, foetus or gestation period (see section 5.3). However, vancomycin penetrates the placenta and a potential risk of embryonal and neonatal ototoxicity and nephrotoxicity cannot be excluded. Therefore vancomycin should be given in pregnancy only if clearly needed and after a careful risk/benefit evaluation.

Lactation:
Vancomycin is excreted in human milk. Caution should be exercised when given to breast-feeding mothers because of potential adverse reactions in the infant (disturbances in the intestinal flora with diarrhoea, colonisation with yeast-like fungi and possibly sensibilisation). Considering the importance of this medicine for nursing mother, the decision to stop breastfeeding should be considered.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Vancomycin has negligible influence on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The adverse reactions listed below is 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).

The most common adverse reactions are phlebitis and pseudo-allergic reactions in connection with too rapid intravenous infusion of vancomycin.

Infusion related events:
During or shortly after rapid infusion anaphylactoid reactions may occur, including hypotension, dyspnea, urticaria or pruritus. Redness of the skin on the upper body (Red man syndrome), pain and cramps in chest or back muscle can occur.
The reactions abate when administration is stopped, generally between 20 minutes and 2 hours. Vancomycin should be infused slowly (for more than 60 minutes - see section 4.4).

Otoxicity has primarily been reported in patients given high doses, or concomitant treatment with other ototoxic medicinal product, or had a pre-existing reduction in kidney function or hearing.

Blood and the lymphatic system disorder:
Rare: Thrombocytopenia, neutropenia, agranulocytosis, eosinophilia.

Immune system disorders
Rare: Anaphylactic reactions, hypersensitivity reactions.

Ear and labyrinth disorders:
Uncommon: Transient or permanent loss of hearing.
Rare: Tinnitus, dizziness.

Cardiac disorders:
Very rare: Cardiac arrest.

Vascular disorders:
Common: Decrease in blood pressure, thrombophlebitis.
Very rare: Vasculitis

Respiratory, thoracic and mediastinal disorders:
Common: Dyspnoea, stridor.

Gastrointestinal disorders:
Rare: Nausea, diarrhoea
Very rare: Pseudomembranous enterocolitis.

Skin and subcutaneous tissue disorders:
Common: Exanthema and mucosal inflammation, pruritus, urticaria.
Very rare: Exfoliative dermatitis, Stevens-Johnson syndrome, linear IgA bullous dermatosis, Lyell's syndrome.

Renal and urinary disorders:
Common: Renal insufficiency manifested primarily by increased serum creatinine.
Rare: Interstitial nephritis, acute renal failure.

General disorders and administration site conditions:
Common: Phlebitis, redness of the upper body and the face, pain and spasm of the chest and back muscles.
Rare: Drug fever, shivering.

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

Measures in case of overdose
• A specific antidote is not known.
• Symptomatic treatment while maintaining renal function is required.
Vancomycin is poorly removed from the blood by haemodialysis or peritoneal dialysis. Haemofiltration or haemoperfusion with polysulfone resins have been used to reduce serum concentrations of vancomycin.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Glycopeptide Antibacterials, ATC code: J01X A01

**Mode 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.

**PK/PD relationship**
Vancomycin activity is considered to be time-dependent – that is, antimicrobial activity depends on the duration that the drug level exceeds the minimum inhibitory concentration (MIC) of the target organism.

**Mechanism of resistance:**
Acquired resistance to glycopeptides is based on acquisition of various *van* gene complexes and alteration of the D-alanyl-D-alanine target to D-alanyl-D-lactate or D-alanyl-D-serine which bind vancomycin poorly, because a critical site for hydrogen bonding is missing. This form of resistance is especially seen in *Enterococcus faecium*.

The reduced susceptibility or resistance to vancomycin in *Staphylococcus* is not well understood. Several genetic elements and multiple mutations are required. Cross-resistance with teicoplanin has been reported.

**Susceptibility:**
Vancomycin is active against gram-positive bacteria. Gram-negative bacteria are resistant.

The MIC breakpoints separating susceptible from resistant organisms are as follows:

| **EUCAST (European Committee on Antimicrobial Susceptibility Testing) recommendations** |
|------------------|------------------|
| **Susceptible** | **Resistant** |
| *Staphylococcus* spp. | ≤2 mg/L >2 mg/L |
| *Enterococcus* spp. | ≤4 mg/L > 4 mg/L |
| *Streptococcus* spp. | ≤2 mg/L >2 mg/L |
| *Streptococcus pneumoniae* | ≤2 mg/L >2 mg/L |
| Gram-positive anaerobes | ≤ 2 mg/L ≤ 2 mg/L |
| Non species related* | ≤ 2 mg/L > 4 mg/L |

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

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.

| **Classes** |
|------------------|------------------|
| **Commonly susceptible species** |
| **Gram positive** |
| *Enterococcus faecalis.* |
| *Staphylococcus aureus* |
| *Staphylococcus coagulase negative* |
| *Streptococcus spp.* |
| *Streptococcus pneumoniae* |
| *Clostridium spp.* |
| **Species for which acquired resistance may be a problem** |
| *Enterococcus faecium* |
5.2 PHARMACOKINETIC PROPERTIES
Vancomycin appears in various body fluids, including pleural, pericardial, synovial and ascetic fluids. A single intravenous dose of 1g in adults produces plasma concentrations of 15 to 30µg/ml 1 hour after 1- to 2-hour infusion.

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

The serum elimination half-life is about 4-6 hours in adults with normal renal-function and 2.2-3 hours in children. In patients with impaired renal function the serum elimination half-life can be significantly increased (up to 7.5 days). The total systematic and renal clearance of vancomycin may be reduced in the elderly due to the natural decrease in glomerular filtration.

The volume of distribution is 0.4–1 L/kg. The binding of vancomycin to protein has been reported in the literature to range from 10% to 50%. Factors that affect the overall activity of vancomycin include its tissue distribution, inoculum size, and protein-binding effects.

Vancomycin is not significantly absorbed from the normal gastro-intestinal tract and is therefore not effective by the oral route for infections other than staphylococcal enterocolitis and pseudomembranous colitis due to *Clostridium difficile*.

Orally administered vancomycin does not usually enter the systemic circulation even when inflammatory lesions are present. Measurable serum concentrations may occur infrequently in patients with active *C. difficile* – induced pseudomembranous colitis and, in the presence of renal impairment, the possibility of accumulation exists.

Administration of vancomycin oral solution, 2g daily for 16 days to anephric patients with no inflammatory bowel disease, gave serum levels of <0.66g/ml. With doses of 2g daily, concentration of 3,100mg/kg can be found in the faeces and levels of <1g/ml can be found in serum of patients with normal renal function who have pseudomembranous colitis.

5.3 PRECLINICAL SAFETY DATA
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. Limited data on mutagenic effects show negative results, long-term studies in animals regarding a carcinogenic potential are not available. In teratogenicity studies, where rats and rabbits received doses approximately corresponding to the human dose based on body surface (mg/m²), no direct or indirect teratogenic effects were observed. Animal studies of the use during the perinatal/postnatal period and regarding effects on fertility are not available.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

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

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
6.3 SHELF LIFE
Shelf life of powder as packaged for sale: 2 years

Shelf-life of reconstituted concentrate: The reconstituted concentrate should be diluted immediately after preparation. For oral use the reconstituted concentrate should be used immediately.

Shelf-life of diluted product:
Chemical and physical in-use stability of the diluted product has been demonstrated for 48 hours at both 2-8°C and 25°C when diluted with either 0.9% sodium chloride or 5% glucose.

From a microbiological point of view, the medicinal product should be used immediately unless reconstitution and dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and the product should be protected from light during storage.

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

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

Solutions of the parenteral powder intended for oral administration may be stored in a refrigerator (2-8 °C) for 96 hours.

6.5 NATURE AND CONTENTS OF CONTAINER
Vancomycin hydrochloride 500mg:
Powder in a glass vial (type I) closed with a rubber stopper (bromobutyl rubber) and aluminium seal with flip off cap.

Pack size: 1 and 10 vials in a carton

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
The powder must be reconstituted and the resulting concentrate must then be immediately diluted further prior to use

Preparation of the reconstituted concentrate
Dissolve the content of each 500mg vial in 10ml of sterile water for injections.

One ml of reconstituted solution contains 50mg of vancomycin. pH of the reconstituted solution is 2.5 to 4.5.

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

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

Preparation of final diluted Solution for infusion
Reconstituted solutions containing 50mg/ml of vancomycin should be further diluted depending on the method of administration.
Suitable diluents are:
5% Glucose Injection
0.9% Sodium Chloride Injection

Intermittent infusion:
Reconstituted solution containing 500mg of vancomycin (50mg/ml) must be diluted further with at least 100ml diluent.

The concentration of vancomycin in Solution for infusion should not exceed 5mg/ml.

The desired dose should be administered slowly by intravenous infusion at a rate of no more than 10mg/minute, for at least 60 minutes or even longer.
For storage conditions of the diluted medicinal product, see sections 6.3

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

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

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

Oral administration
The contents of vials for parenteral administration may be used. Common flavouring syrups may be added to the solution at the time of administration to improve the taste.

7 MARKETING AUTHORISATION HOLDER
Nucleus ehf
Box 55, Naustanes
116 Reykjavik
Iceland

8 MARKETING AUTHORISATION NUMBER(S)
PL 24701/0033

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/08/2011

10 DATE OF REVISION OF THE TEXT
15/08/2011
1 NAME OF THE MEDICINAL PRODUCT
Vancomycin 1000mg Powder for Concentrate for Solution for Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial contains:
Vancomycin 1000mg Powder for Concentrate for Solution for Infusion.
Each vial contains 1000mg vancomycin (equivalent to 1,050,000 IU) (as vancomycin hydrochloride).
When reconstituted with 20ml of water for injections, the resulting concentrate for solution for infusion contains 50mg/ml vancomycin

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for concentrate for solution for infusion.
White to off-white powder.
Reconstituted solution pH is 2.5 – 4.5

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Intravenous vancomycin is indicated in the following severe infections caused by gram-positive bacteria susceptible to vancomycin which cannot be treated with or failed to respond or are resistant to other antibiotics such as penicillins and cephalosporins.
- endocarditis
- infections of the bones (osteomyelitis)
- pneumonia
- soft-tissue infections

Endocarditis caused by enterococci, *Streptococcus viridans* or *S. bovis* should be treated with a combination of vancomycin and an aminoglycoside.

Vancomycin may be used for the perioperative prophylaxis against bacterial endocarditis, in patients at high risk of developing bacterial endocarditis when they undergo major surgical procedures (e.g., cardiac and vascular procedures, etc) and are unable to receive a suitable beta-lactam antibacterial agent.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Vancomycin may be used orally for the treatment of staphylococcal enterocolitis and pseudomembranous colitis due to *Clostridium difficile*. Parenteral administration of vancomycin is not effective for these indications. Intravenous administration may be used concomitantly if required.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
For intravenous infusion only.
For preparation of solution for infusion please refer to section 6.6.
Concentrations of no more than 5mg/ml are recommended. In selected patients in need of fluid restriction, a concentration up to 10mg/ml may be used; use of such higher concentrations may increase the risk of infusion-related events. Infusions should be given over at least 60 minutes. In adults, if doses exceeding 500mg are used, a rate of infusion of no more than 10mg/min is recommended. Infusion related events may occur, however, at any rate or concentration.

The dose and duration of treatment should be adjusted individually and according to the underlying type and severity of infection, and patient factors such as age and renal function.
Vancomycin levels can be measured to aid dose adjustments.

Measurement of serum concentrations
Following multiple intravenous doses, peak serum concentrations, measured two hours after infusion is complete, range from 18-26mg/l. Trough levels measured immediately prior to the next dose should be 5-10mg/l. Ototoxicity has been associated with serum drug levels of 80-100mg/l, but this is rarely seen when serum levels are kept at or below 30mg/l.
Patients with normal renal function

*Adults and children above 12 years of age:*

The recommended daily intravenous dose is 2000mg (2g), given as 500mg every 6 hours or 1000mg (1g) every 12 hours. Improvement is usually seen within 48 to 72 hours. The total duration of administration is determined by the type and severity of the infection and the clinical response of the patient.

For bacterial endocarditis, the generally accepted regimen is 1000mg (1g) vancomycin intravenously every 12 hours for 4 weeks either alone or in combination with other antibiotics. Longer treatment up to 6 weeks may be required, depending on the pathogen involved. National guidelines should be adhered to.

If Vancomycin is co-administrated with aminoglycoside (e.g. gentamicine) patients should be monitored carefully for signs of neurotoxicity and ototoxicity. The dosage should be adjusted when renal disturbance occurs (see section 4.5).

Peri-operative prophylaxis against bacterial endocarditis: Adults receive 1000mg (1g) vancomycin intravenously prior to surgery (prior to induction of anaesthesia) and depending on time and type of surgery, the dose of 1000mg (1g) of vancomycin i.v. 12 hours postoperatively can be given.

*Children one month to 12 years of age:*

40 mg/kg/day: The dose must be divided and usually in to four doses (e.g. 10mg/kg every 6 hours). Each dose should be administered over at least 60 min.

*Newborn infants (full-term):*

0-7 days of age: A starting dose of 15mg/kg, followed by 10mg/kg every 12 hours.
7-30 days of age: A starting dose of 15mg/kg, followed by 10mg/kg every 8 hours.

Each dose should be administered over at least 60 min.

Close monitoring of serum vancomycin concentrations may be warranted in these patients.

*The elderly:*

Dosage reduction may be necessary to a greater extent than expected because of decreasing renal function (see below). Monitor auditory function, see Section 4.4.

*Pregnancy:*

It has been reported that significantly increased doses may be required to achieve therapeutic serum concentrations in pregnant patients.

Patients with impaired renal function

In patients with impaired renal function the dose must be adjusted to avoid toxic serum levels. Serum levels of vancomycin should be monitored regularly. For most patients with impaired renal function the following nomogram, based on creatinine clearance, can be used to determine the dose needed.

The starting dose should always be at least 15mg/kg.

The nomogram is not valid for functionally anephric patients on dialysis.
If the creatine clearance is not available, the following formula may be applied to calculate the creatinine clearance from the patient’s age, sex and serum creatinine:

Men: \[ \frac{\text{Weight (kg) \times 140} - \text{age (years)}}{72 \times \text{serum creatinine (mg/100 ml)}} \]

Women: \[ 0.85 \times \text{value calculated by the above formula.} \]

Where possible, the creatinine clearance should always be determined.

**Patient on hemodialysis**

Serum levels of vancomycin should be monitored regularly.

For anuric patients (without kidney function) on dialysis the starting dose is 15mg/kg and the maintenance dose is approximately 1.9 mg/kg/24 hours. Since individual maintenance doses of 250mg to 1g are convenient, in patients with marked renal impairment a dose may be given every several days rather than on a daily basis. In anuria a dose of 1g every 7-10 days has been recommended.

If polysulfone membranes are used for hemodialysis ("high flux dialysis"), the half time of vancomycin is shortened. For patients with regular hemodialysis an additional maintenance dose may be necessary.

**Patients with impaired liver function**

The availability of data in patients with impaired liver function is limited. Available data do not indicate the need for dose adjustment in mild or moderate liver function impairment.

**Oral administration**

The contents of vials for parenteral administration may be used.

Adults and the elderly: The usual daily dose given is 500mg in divided doses for 7 to 10 days, although up to 2g/day have been used in severe cases. The total daily dosage should not exceed 2g. Each dose may be reconstituted in 30ml water and either given to the patient to drink, or administered by nasogastric tube.

Children: The usual daily dose is 40mg/kg in three or four divided doses for 7 to 10 days. The total daily dosage should not exceed 2g.

Common flavouring syrups may be added to the solution at the time of administration to improve the taste.
4.3 CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings
Rapid bolus administration (e.g., 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 in a dilute solution 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 (see Section 4.2. and Section 4.8).

In case of severe acute hypersensitivity reactions (e.g., anaphylaxis), the treatment with vancomycin has to be discontinued immediately and the usual appropriate emergency measures have to be started.

Vancomycin should be used with caution in patients with allergic reactions to teicoplanin, since cross hypersensitivity reactions between vancomycin and teicoplanin have been reported. Vancomycin should be used with care in patients with renal insufficiency, as the possibility of developing toxic effects is much higher in the presence of prolonged high blood concentrations. The dose should be reduced according to the degree of renal impairment. The risk of toxicity is appreciably increased by high blood concentrations or prolonged therapy. Blood levels should be monitored and renal function tests should be performed regularly.

Otoxicity, 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. 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 otoxicity, blood levels should be determined periodically and periodic testing of auditory function is recommended.

Vancomycin should be avoided in patients with previous hearing loss. If it is used in such patients, the dose should be regulated, by periodic determination of the drug level in the blood. The elderly are more susceptible to auditory damage.

Use in paediatrics: In premature neonates and young infants, it may be appropriate to confirm desired vancomycin serum concentrations. Concomitant administration of vancomycin and anaesthetic agents has been associated with erythema and histamine-like flushing in children (see section 4.5).

Use in the elderly: The natural decrease of glomerular filtration with increasing age may lead to elevated vancomycin serum concentrations if dosage is not adjusted (see section 4.2).

Precautions
Vancomycin is very irritating to tissue and causes injection site necrosis if injected intramuscularly. Pain and thrombophlebitis may occur in many patients receiving 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 6.6) and by changing the sites of infusion regularly.

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

Doses should be titrated on the basis of serum levels. Blood levels should be monitored and renal function tests performed regularly.

It is a general recommendation to monitor the concentrations 2-3 times weekly. Regular monitoring of the blood levels of vancomycin is indicated in 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.

Patients with borderline renal function and individuals over the age of 60 should be given serial tests of auditory function and of vancomycin blood levels. All patients receiving the drug should have periodic haematological studies, urine analysis and renal function tests.
Clinically significant serum concentrations have been reported in some patients being treated for active C. difficile-induced pseudomembranous colitis after multiple oral doses of vancomycin. Therefore, monitoring of serum concentrations may be appropriate in these patients.

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. In rare instances, there have been reports of pseudomembranous colitis, due to C. difficile, developing in patients who received intravenous vancomycin. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of vancomycin. Antiperistaltics are contraindicated.

Excipients:
This medicinal product contains less than 1 mmol sodium (23mg) per vial, i.e. essentially ‘sodium-free’.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

Infusion-related events may be minimised by the administration of vancomycin as a 60-minute infusion prior to anaesthetic induction.

Other potentially nephrotoxic or ototoxic medicinal products
Concurrent or sequential systemic or topical use of other potentially neurotoxic or nephrotoxic drugs, such as gentamycin, amphotericin B, streptomycin, neomycin, kanamycin, amikacin, tobramycin, bacitracin, polymixin B, colistin, viomycin or cisplatin, may potentiate the nephrotoxicity and/or ototoxicity of vancomycin and consequently requires careful monitoring. See also section 4.2 with regard to dosage adjustment in case of use with an aminoglycoside

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

4.6 PREGNANCY AND LACTATION

Pregnancy:
No sufficient safety experience is available regarding vancomycin during human pregnancy. Reproduction toxicological studies on animals do not suggest any effects on the development of the embryo, foetus or gestation period (see section 5.3). However, vancomycin penetrates the placenta and a potential risk of embryonal and neonatal ototoxicity and nephrotoxicity cannot be excluded. Therefore vancomycin should be given in pregnancy only if clearly needed and after a careful risk/benefit evaluation.

Lactation:
Vancomycin is excreted in human milk. Caution should be exercised when given to breast-feeding mothers because of potential adverse reactions in the infant (disturbances in the intestinal flora with diarrhoea, colonisation with yeast-like fungi and possibly sensibilisation). Considering the importance of this medicine for nursing mother, the decision to stop breastfeeding should be considered.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Vancomycin has negligible influence on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The adverse reactions listed below is 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).

The most common adverse reactions are phlebitis and pseudo-allergic reactions in connection with too rapid intravenous infusion of vancomycin.

Infusion related events:
During or shortly after rapid infusion anaphylactoid reactions may occur, including hypotension, dyspnea, urticaria or pruritus. Redness of the skin on the upper body (Red man syndrome), pain and cramps in chest or back muscle can occur. The reactions abate when administration is stopped, generally between 20 minutes and 2 hours. Vancomycin should be infused slowly (for more than 60 minutes - see section 4.4).

Otoxicity has primarily been reported in patients given high doses, or concomitant treatment with other ototoxic medicinal product, or had a pre-existing reduction in kidney function or hearing.

Blood and the lymphatic system disorder:
Rare: Thrombocytopenia, neutropenia, agranulocytosis, eosinophilia.

Immune system disorders
Rare: Anaphylactic reactions, hypersensitivity reactions.

Ear and labyrinth disorders:
Uncommon: Transient or permanent loss of hearing.
Rare: Tinnitus, dizziness.

Cardiac disorders:
Very rare: Cardiac arrest.

Vascular disorders:
Common: Decrease in blood pressure, thrombophlebitis.
Very rare: Vasculitis.

Respiratory, thoracic and mediastinal disorders:
Common: Dyspnoea, stridor.

Gastrointestinal disorders:
Rare: Nausea, diarrhoea.
Very rare: Pseudomembranous enterocolitis.

Skin and subcutaneous tissue disorders:
Common: Exanthema and mucosal inflammation, pruritus, urticaria.
Very rare: Exfoliative dermatitis, Stevens-Johnson syndrome, linear IgA bullous dermatosis, Lyell's syndrome.

Renal and urinary disorders:
Common: Renal insufficiency manifested primarily by increased serum creatinine.
Rare: Interstitial nephritis, acute renal failure.

General disorders and administration site conditions:
Common: Phlebitis, redness of the upper body and the face, pain and spasm of the chest and back muscles.
Rare: Drug fever, shivering.

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

Measures in case of overdose
• A specific antidote is not known.
• Symptomatic treatment while maintaining renal function is required.
Vancomycin is poorly removed from the blood by haemodialysis or peritoneal dialysis. Haemofiltration or haemoperfusion with polysulfone resins have been used to reduce serum concentrations of vancomycin.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Glycopeptide Antibacterials, ATC code: J01X A01

Mode 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.

PK/PD relationship
Vancomycin activity is considered to be time-dependent – that is, antimicrobial activity depends on the duration that the drug level exceeds the minimum inhibitory concentration (MIC) of the target organism.

Mechanism of resistance:
Acquired resistance to glycopeptides is based on acquisition of various van gene complexes and alteration of the D-alanyl-D-alanine target to D-alanyl-D-lactate or D-alanyl-D-serine which bind vancomycin poorly, because a critical site for hydrogen bonding is missing. This form of resistance is especially seen in Enterococcus faecium. The reduced susceptibility or resistance to vancomycin in Staphylococcus is not well understood. Several genetic elements and multiple mutations are required. Cross-resistance with teicoplanin has been reported.

Susceptibility:
Vancomycin is active against gram-positive bacteria. Gram-negative bacteria are resistant.

The MIC breakpoints separating susceptible from resistant organisms are as follows:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) recommendations

<table>
<thead>
<tr>
<th>Species</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus spp.</td>
<td>≤2 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>≤4 mg/L</td>
<td>&gt;4 mg/L</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>≤2 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>≤2 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td>Gram-positive anaerobes</td>
<td>≤2 mg/L</td>
<td>≤2 mg/L</td>
</tr>
<tr>
<td>Non species related*</td>
<td>≤2 mg/L</td>
<td>&gt;4 mg/L</td>
</tr>
</tbody>
</table>

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

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.

Classes

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

Species for which acquired resistance may be a problem
Enterococcus faecium
5.2 PHARMACOKINETIC PROPERTIES
Vancomycin appears in various body fluids, including pleural, pericardial, synovial and ascetic fluids.
A single intravenous dose of 1g in adults produces plasma concentrations of 15 to 30µg/ml 1 hour after 1- to 2-hour infusion.

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

The serum elimination half-life is about 4-6 hours in adults with normal renal-function and 2.2-3 hours in children. In patients with impaired renal function the serum elimination half-life can be significantly increased (up to 7.5 days).

The total systematic and renal clearance of vancomycin may be reduced in the elderly due to the natural decrease in glomerular filtration.

The volume of distribution is 0.4–1 L/kg. The binding of vancomycin to protein has been reported in the literature to range from 10% to 50%. Factors that affect the overall activity of vancomycin include its tissue distribution, inoculum size, and protein-binding effects.

Vancomycin is not significantly absorbed from the normal gastro-intestinal tract and is therefore not effective by the oral route for infections other than staphylococcal enterocolitis and pseudomembranous colitis due to Clostridium difficile.

Orally administered vancomycin does not usually enter the systemic circulation even when inflammatory lesions are present. Measurable serum concentrations may occur infrequently in patients with active C. difficile – induced pseudomembranous colitis and, in the presence of renal impairment, the possibility of accumulation exists.

Administration of vancomycin oral solution, 2g daily for 16 days to anephric patients with no inflammatory bowel disease, gave serum levels of <0.66g/ml. With doses of 2g daily, concentration of 3,100mg/kg can be found in the faeces and levels of <1g/ml can be found in serum of patients with normal renal function who have pseudomembranous colitis.

5.3 PRECLINICAL SAFETY DATA
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.
Limited data on mutagenic effects show negative results, long-term studies in animals regarding a carcinogenic potential are not available.
In teratogenicity studies, where rats and rabbits received doses approximately corresponding to the human dose based on body surface (mg/m²), no direct or indirect teratogenic effects were observed.
Animal studies of the use during the perinatal/postnatal period and regarding effects on fertility are not available.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

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

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
6.3 SHELF LIFE
Shelf life of powder as packaged for sale: 2 years

Shelf-life of reconstituted concentrate: The reconstituted concentrate should be diluted immediately after preparation. For oral use the reconstituted concentrate should be used immediately.

Shelf-life of diluted product:
Chemical and physical in-use stability of the diluted product has been demonstrated for 48 hours at both 2-8°C and 25°C when diluted with either 0.9% sodium chloride or 5% glucose.

From a microbiological point of view, the medicinal product should be used immediately unless reconstitution and dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and the product should be protected from light during storage.

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

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

Solutions of the parenteral powder intended for oral administration may be stored in a refrigerator (2-8°C) for 96 hours.

6.5 NATURE AND CONTENTS OF CONTAINER
Vancomycin hydrochloride 1000mg:
Powder in a glass vial (type I) closed with a rubber stopper (bromobutyl rubber) and aluminium seal with flip off cap.

Pack size: 1 and 10 vials in a carton

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
The powder must be reconstituted and the resulting concentrate must then be immediately diluted further prior to use

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

One ml of reconstituted solution contains 50mg of vancomycin. pH of the reconstituted solution is 2.5 to 4.5.

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

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

Preparation of final diluted Solution for infusion
Reconstituted solutions containing 50mg/ml of vancomycin should be further diluted depending on the method of administration.

Suitable diluents are:
5% Glucose Injection
0.9% Sodium Chloride Injection

Intermittent infusion:
Reconstituted solution containing 1000mg vancomycin (50mg/ml) must be diluted further with at least 200ml diluent.

The concentration of vancomycin in Solution for infusion should not exceed 5mg/ml.

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

For storage conditions of the diluted medicinal product, see sections 6.3
Before administration, the reconstituted and diluted solutions should be inspected visually for particulate matter and discoloration. Only clear and colourless to pale yellow solution free from particles should be used.

**Disposal**

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

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

**Oral administration**

The contents of vials for parenteral administration may be used. Common flavouring syrups may be added to the solution at the time of administration to improve the taste.

**MARKETING AUTHORITY HOLDER**

Nucleus ehf
Box 55, Naustanes
116 Reykjavik
Iceland

**MARKETING AUTHORITY NUMBER(S)**

PL 24701/0034

**DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**

15/08/2011

**DATE OF REVISION OF THE TEXT**

15/08/2011
UKPAR Vancomycin 500mg and 1g Powder for Solution for Infusion

Vancomycin 500mg and 1000mg
Powder for Concentrate for Solution for Infusion

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
- The full name of this medicine is Vancomycin 500mg and 1000mg Powder for Concentrate for Solution for Infusion but within the leaflet it will be referred to as Vancomycin powder.

In this leaflet:
1. What Vancomycin powder is and what it is used for
2. Read this before you are given Vancomycin powder
3. How to use Vancomycin powder
4. Possible side effects
5. How Vancomycin powder is stored
6. Further information

1. What Vancomycin powder is and what it is used for
What Vancomycin powder is
Vancomycin powder is one of a group of medicines called glycopeptide antibiotics. These are used to treat infections caused by bacteria. Vancomycin comes in the form of a powder which is made into a solution using sterile water (for injections).
This solution is given to you as an infusion, a slow injection, by means of a drip. It will only be given to you through a vein. It can also be given by mouth.

What Vancomycin powder is used for
This medicine is used for severe infections caused by bacteria which can resist other antibiotics. It is used in patients who have not responded to treatment with, or have had a bad reaction to, other antibiotics.

It is used to treat various severe infections of the lining or valves of the heart, lungs, bone or soft tissue (flesh). It can also be given to you before some surgical procedures to prevent infections.

2. Read this before you are given Vancomycin powder
Do not have Vancomycin powder if you
- are allergic to vancomycin hydrochloride or to any of the other ingredients of Vancomycin powder (See Section 6 for a list of these).
- Tell your doctor if you have had any problems with this medicine or any other in the past.

Take special care with Vancomycin powder if you
- suffer from loss of hearing
- have kidney problems
- are elderly (65 years old and over)

Rapid injection of Vancomycin may cause low blood pressure, shock and rarely cardiac arrest. Stopping the infusion usually results in a prompt cessation of the reactions.

Injection site pain, inflammation of the vein wall and blood clotting can occur and is occasionally severe. Slow administration also reduces these side effects. If you are allergic to another antibiotic called teicoplanin you may also be allergic to vancomycin. Please tell your doctor.

If you suffer from kidney failure or receive concomitant treatment with other substances toxic to kidney the possibility of developing toxic effects is much higher.

Your doctor may perform several tests to see if your kidneys and liver are working properly. If you are elderly or have kidney problems your doctor may also perform regular tests on your hearing and measure the amount of vancomycin in your blood.

Deafness, transient or permanent, which may be preceded by noises in ears, can occur in patients with prior deafness, who have received excessive doses, or who receive treatment with another substance toxic to hearing. To reduce this risk, blood levels should be checked periodically and periodic testing of hearing function is recommended.

Prolonged use of Vancomycin powder may result in the overgrowth of resistant organisms; your doctor will monitor this.

Taking other medicines with Vancomycin powder
Tell your doctor if you are also taking:
- gentamycin (antibiotic)
- amphotericin B (antibiotic)
- streptomycin (antibiotic)
- neomycin (antibiotic)
- kanamycin (antibiotic)
- amikacin (antibiotic)
- tobramycin (antibiotic)
- bacitracin (antibiotic)
- polymyxin B (antibiotic)
- colistin (antibiotic)
- viomycin (antibiotic)
- cisplatin (medicinal product used to treat some types of cancer)

The following can also react with vancomycin if taken at the same time:
- anaesthetic agents (if you are going to have a general anaesthetic)
- muscle relaxants (used sometimes during a general anaesthetic)

Please tell your doctor or nurse, if you are taking or have taken recently any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
Ask your doctor for advice before taking any medicine.
Tell your doctor if you are pregnant or think you may be pregnant. Your doctor will then decide whether you should receive Vancomycin powder.
Tell your doctor if you are breast-feeding, because Vancomycin passes into breast milk. A decision will be made as to whether you breast-feed or are treated with Vancomycin powder.

Driving and using machines
Vancomycin powder has very little influence on the ability to drive or to use machinery.

Important information about some of the ingredients of Vancomycin powder
This medicinal product contains less than 1mmol sodium (23mg) per vial, i.e. essentially 'sodium-free'.

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Continued on next page
How to use Vancomycin powder

Vancomycin powder is given to you by hospital staff, using an infusion, (a slow injection by means of a drip). Each infusion will be given slowly, usually lasting for at least one hour. It may also be given to you to drink or via a tube in your nose.

How much will you receive

The dose of Vancomycin powder your doctor gives you will depend on your age, weight, general health condition, the severity of the infection, whether you need certain other medicines and how well you respond to the treatment.

For patients whose kidneys are working normally

Adults and children above 12 years of age: the usual dose is 2000mg daily in two or four doses (or 30mg per kilogram of bodyweight, per day either 500mg every 6 hours or 1g every 12 hours).

Children (from one month to 12 years of age): the usual intravenous dosage is 10mg/kg per dose given every 6 hours (total daily dosage 40mg/kg of body weight).

New-born babies (born full term):

- 0 - 7 days old: a starting dose of 15mg for each kilogram of the child’s weight, followed by 10mg per kilogram, every 12 hours.
- 7 - 30 days old: a starting dose of 15mg for each kilogram of the child’s weight, followed by 10mg per kilogram, every 8 hours.

For patients whose kidneys are not working normally

The doctor will reduce the dose or extend the interval between two doses. Specific tests will be carried out and the dose will be adjusted to meet the results of the tests. If you are elderly, (65 years of age and over), your doctor will also consider how well your kidneys are likely to be working.

For patients whose liver is not working normally

If you have severe liver damage, specific tests will be carried out and the dose will be adjusted to meet the results of the tests.

For patients whose kidneys do not work at all

The starting dose is 15mg for each kilogram of bodyweight, followed by a maintenance dose of approximately 1.5mg for each kilogram of bodyweight, every 24 hours.

Oral doses

Adults and elderly: 500mg a day in divided doses for 7-10 days.
Children: 40mg per kilogram of bodyweight, in 3-4 doses for 7-10 days.

Maximum daily dose of 2000mg

Your doctor will decide when your treatment should end.

If you receive too much Vancomycin

Your doctor monitors the amount of Vancomycin you receive. If the regular blood tests and other tests show that you have too much in your body, the amount of Vancomycin will be reduced or infusion will be stopped. The level remaining in your blood will be lowered.

If you have any further questions about receiving this medicine, please ask your doctor.

Possible side effects

Like all medicines, Vancomycin powder can cause side effects, although not everybody gets them.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse immediately.

Severe allergic reaction:

- Swelling of the face or throat, difficulty in breathing, feeling faint, itchy skin or hives. The consequences could become very serious so, tell your doctor or nurse immediately. Infusion will be halted.

Infusion related events:

- During or shortly after rapid infusion low blood pressure, difficulty breathing, itchy skin rash, redness of the skin of the upper body, pain and cram in chest or back muscle can occur. Vancomycin is given slowly (for more than 60 minutes) to avoid these reactions.

Common side effects (affect 1 to 10 users in 100):

- Shortness of breath, noisy breathing (stridor)
- Low blood pressure
- Vein wall irritation including blood clotting (thrombophlebitis)
- Kidney problems
- Skin reactions such as rash, swelling, itching or hives
- Redness, a burning sensation, swelling of a vein and the area around it
- Redness and soreness at the point where the infusion goes into your body
- Redness of the upper body and the face
- Pain and spasm of the chest and back muscles

Uncommon side effects (affect 1 to 10 users in 1000):

- Temporary or permanent loss of hearing

Rare side effects (affect 1 to 10 users in 10,000):

- Anaphylactic reactions, allergic reactions
- Ringing or buzzing in your ears
- Dizziness
- Feeling sick
- Diarrhoea
- Raised temperature or shivering
- Changes to the number of various types of white blood cells in the blood - an increase or decrease
- A decrease in the number of blood cells important in blood clotting in the blood
- Inflammation of the kidneys
- Acute kidney failure

Very rare side effects (affect less than 1 user in 10,000):

- Cardiac arrest
- Inflammation of the bowel which causes abdominal pain or bloody diarrhoea
- Severe skin reactions such as red and scaly or blistering skin, lesions and flu-like symptoms
- Inflammation of the blood vessels

How Vancomycin powder is stored

Keep out of the reach and sight of children. Do not use Vancomycin powder after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month. Keep the vial in the outer carton in order to protect from light. Store below 25°C. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Further information

What Vancomycin powder contains

- The active substance is vancomycin. Each vial contains either 500mg vancomycin (equivalent to 525,000 IU) (as vancomycin hydrochloride) or 1000mg vancomycin (equivalent to 1,050,000 IU) (as vancomycin hydrochloride).
- The other ingredients are sodium hydroxide, hydrochloric acid.

What Vancomycin powder looks like and the contents of the pack

Vancomycin powder is a freeze-dried, off-white powder. It is vacuum-packed in a glass vial with a rubber stopper and an aluminium seal with flip-off cap. Pack sizes: 1 vial in a carton

Marketing Authorisation Holder:

Nucleus elfi
Box 55, Naustanes
116 Reykjavik
Iceland

Manufacturer:

Actavis Nordic A/S
Onnesgårdevej 16
2820 Gentofte
Denmark

This leaflet was last revised in August 2011
The following information is intended for medical or healthcare professionals only:

Vancomycin powder for concentrate for infusion is for single use only and any unused solution should be discarded.

For intravenous use the powder must be reconstituted and the resulting concentrate must then be immediately diluted further prior to use.

For oral use the powder must be reconstituted; the resulting concentration may be stored in a refrigerator (2 - 8°C) for 96 hours. Discard any unused solution.

Preparation of the reconstituted concentrate
Dissolve the content of each 500mg vial in 10ml of sterile water for injections.
Dissolve the content of each 1000mg vial in 20ml of sterile water for injections.
One ml of reconstituted solution contains 50mg of vancomycin. pH of the reconstituted solution is 2.5 to 4.5. The solution should be clear colourless to pale yellow and free from fibre and visible particulate matters.

Preparation of final diluted Solution for infusion
Reconstituted concentrate containing 50mg/ml of vancomycin should be further diluted depending on the method of administration.
Suitable diluents are: 5% Glucose Injection or 0.9% Sodium Chloride Injection

Intermittent infusion:
Reconstituted concentrate containing 500mg of vancomycin (50mg/ml) must be diluted further with at least 100ml diluent.
Reconstituted concentrate containing 1000mg vancomycin (50mg/ml) must be diluted further with at least 200ml diluent.
The concentration of vancomycin in Solution for infusion should not exceed 5mg/ml.
The desired dose should be administered slowly by intravenous infusion at a rate of no more than 10mg/minute, for at least 60 minutes or even longer.

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

Shelf-life of reconstituted concentrate:
The reconstituted concentrate should be diluted immediately after preparation.

Shelf-life of diluted product:
Chemical and physical in-use stability of the diluted product has been demonstrated for 48 hours at both 2-8°C and 25°C when diluted with either 0.9% sodium chloride or 5% glucose.
From a microbiological point of view, the medicinal product should be used immediately unless reconstitution and dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and the product should be protected from light during storage.

In patients with impaired renal function the dose must be adjusted. Serum levels of vancomycin should be monitored regularly. For most patients with impaired renal function the following nomogram can be used to determine the dose needed. The total daily dose of vancomycin (in kg) should be about 13 times the glomerular filtration rate (in ml/min). The starting dose should always be at least 15mg/kg. The nomogram is not valid for functionally anephric patients on dialysis.

If the creatinine clearance is not available, the following formula may be applied to calculate the creatinine clearance from the patient’s age, sex and serum creatinine:

Men: \[ \text{Weight (kg)} \times 140 \times \text{age (years)} \]
72 \times \text{serum creatinine (mg/100ml)}

Women: \[ 0.85 \times \text{value calculated by the above formula.} \]
The reconstituted concentrate should be diluted immediately after preparation.
Single use only.
Read the package leaflet before use.
Each vial contains 500mg vancomycin.
PL 24701/0033

Carton Size: 32 x 32 x 65mm
Pack: 1 Vial in a carton
UKPAR Vancomycin 500mg and 1g Powder for Solution for Infusion

The reconstituted concentrate should be diluted immediately after preparation. Single use only. Read the package leaflet before use. Each vial contains 1000mg vancomycin.

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Vancomycin
Powder for Concentrate for Solution for Infusion
For intravenous or oral use after reconstitution and dilution

Each vial contains 1000mg vancomycin (equivalent to 1,050,000 IU) (as vancomycin hydrochloride).

When reconstituted as directed, the resulting concentrate contains 50mg/ml vancomycin.

Contains sodium hydroxide and hydrochloric acid.

PL 24701/0034

Codo No.: K92DRUGS/KTK26/3656

Batch
Exp.

Carton Size: 45 x 45 x 75mm
Pack: 1 Vial in a carton

actavis
Batch
Exp.

MA Holder: Nudius ohf
Box 15, Naantali, 11644, Finland