Public Assessment Report

Decentralised Procedure

VANCOMYCIN 500MG POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION
VANCOMYCIN 1G POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION

UK/H/1937/001-2/DC
UK licence no: PL 24701/0022-3

Nucleus ehf
VANCOMYCIN 500MG POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION
VANCOMYCIN 1G POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION

LAY SUMMARY

On 20\textsuperscript{th} March 2010, Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, the Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden and the UK agreed to grant marketing authorisations to Nucleus ehf for the medicinal products Vancomycin 500mg Powder for Concentrate for Solution for Infusion and Vancomycin 1g Powder for Concentrate for Solution for Infusion. The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, licences were granted in the UK on 18\textsuperscript{th} May 2010.

Vancomycin Powder for Concentrate for Solution is a prescription-only medicine (POM) used for the treatment of 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.

This product contains vancomycin hydrochloride, which is one of a group of medicines called glycopeptide antibiotics. These are used to treat infections caused by bacteria.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Vancomycin Powder for Concentrate for Solution outweigh the risks, hence Marketing Authorisations have been granted.
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# Module 1

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<th>Vancomycin 500mg and 1g Powder for Concentrate for Solution for Infusion</th>
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<td>Generic application, Article 10.1</td>
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<tr>
<td><strong>Form</strong></td>
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</tr>
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<td><strong>Strength</strong></td>
<td>500mg and 1g</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Nucleus ehf, Box 55, Naustanes, 116 Reykjavik, Iceland</td>
</tr>
<tr>
<td><strong>RMS</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, the Netherlands, Norway, Poland, Portugal, Romania, Spain and Sweden</td>
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<td>UK/H/1937/001-2/DC</td>
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<td>Day 210 – 20th March 2010</td>
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Module 2
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.

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

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.

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.

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. 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, 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:

<table>
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<th>EUCAST (European Committee on Antimicrobial Susceptibility Testing) recommendations</th>
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<tr>
<td>Susceptible</td>
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<td>Staphylococcus spp.</td>
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<tr>
<td>Enterococcus spp.</td>
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<tr>
<td>Streptococcus spp</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>Gram-positive anaerobes</td>
</tr>
<tr>
<td>Non species related*</td>
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</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*

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

### 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.

### 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.

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.

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.

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**MARKETING AUTHORISATION HOLDER**

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Iceland
Tel: 00 354 893 4482
e-mail: nucleus@simnet.is

**MARKETING AUTHORISATION NUMBER(S)**

PL 24701/0022

**DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

18/05/2010

**DATE OF REVISION OF THE TEXT**

18/05/2010
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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 a 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: \[
\text{Weight (kg)} \times 140 \text{ - age (years)} \over 72 \times \text{serum creatinine (mg/100 ml)}
\]

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.

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.

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. 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, 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
Pharmaco-therapeutic 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></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.
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 reduces 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.

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.

*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.

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 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 of 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.

7 MARKETING AUTHORISATION HOLDER
Nucleus ehf
Box 55, Naustanes
116 Reykjavik
Iceland
Tel: 00 354 893 4482
e-mail: nucleus@simnet.is

8 MARKETING AUTHORISATION NUMBER(S)
PL 24701/0023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/05/2010

10 DATE OF REVISION OF THE TEXT
18/05/2010
Module 3

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
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 injection.

This solution is given as an infusion, a slow injection, by means of a drip. It will only be given to you through a vein.

Vancomycin powder is used for
This medicine is used for severe infections caused by bacteria which can no longer be treated with 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 (endocarditis), bone or skin tissue (osteitis), or any part of the body.

2. Read this before you are given Vancomycin powder
Do not have Vancomycin powder if you
- are allergic to vancomycin or other medicines in the group of glycopeptide antibiotics
- have had an allergic reaction to Vancomycin powder

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 in mass causes low blood pressure, shock and serious cardiac arrest. Stopping the infusion usually results in a prompt cessation of the symptoms. Injection site pain, inflammation of the vein wall and blood clots can occur and 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 require constant treatment with other substances toxic to kidneys the possibility of developing toxic effects is much higher.

Your doctor may perform several tests to see if your kidneys are fully 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.

Dialysis, haemodialysis or peritoneal, which may be provided by nurses in care, 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 you are taking:
- gentamicin (antibiotic)
- amphotericin B (antibiotic)
- streptomycin (antibiotic)
- neomycin (antibiotic)
- kanamycin (antibiotic)
- tobramycin (antibiotic)
- bacitracin (antibiotic)
- polymyxin B (antibiotic)
- colistimethate sodium (antibiotic)
- vancomycin (antibiotic)
- cephalosporin antibiotic product used to treat some types of cancer

The following can also react with vancomycin if taken at the same time:
- hypnotic 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 breastfeeding
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 breastfeeding, because Vancomycin passes into breast milk. A decision will be made as to whether you breastfeed or are treated with Vancomycin powder.

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

Intermittent infusion
Reconstituted concentrate containing 50mg/ml of vancomycin must be diluted further with at least 100ml of normal saline or at least 250ml of dextrose 5% in water. 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 1mg/min, 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.

Sheath-life of reconstituted concentrate
The reconstituted concentrate should be discarded immediately after preparation.

Sheath-life of diluted product:
Chemical and physical 4-year stability of the diluted product has been demonstrated for 48 hours at both 2°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 a controlled and validated aseptic environment. If not used immediately, in storage conditions and times prior to use are the responsibility of the user and the product should be protected from light during storage.
How to use Vancomycin powder

Vancomycin powder is given to you by hospital staff using an infusion, i.e. slow injection by means of a drip. Each infusion will be given slowly, usually lasting for at least one hour.

How much you will 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 or not 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 500mg in two or four doses (or 1g per kilogram of bodyweight, per day) either 500mg every 6 hours (or 4g every 12 hours).

Children (from one month to 12 years of age): the usual intravenous dosage is 15mg/kg per dose given every 6 hours (total daily dosage 45mg/kg of bodyweight).

New born babies (even smaller ones):

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

For patients whose kidneys are not working normally

The doctor will reduce the dose or extend the interval between two doses. Special tests will be carried out and the dose will be adjusted to meet the needs of the tests. If you are elderly, 65 years of age or 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, special tests will be carried out and the dose will be adjusted to meet the needs of the tests.

For patients whose kidneys do not work at all

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

Your doctor will advise on your treatment schedule.

If you receive too much Vancomycin

Your doctor will determine the amount of Vancomycin you receive. If the level of Vancomycin is too high, your doctor will advise on your treatment schedule.

Possible side effects

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

Some of the side effects listed below are not serious and will not last. However, if you notice any side effects not listed in this leaflet, please tell your doctor or nurse immediately.

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

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

- Infusion related events:
  - During or shortly after rapid infusion, blood pressure, difficulty breathing, rashes, skin rash, and swelling. Your doctor may stop the infusion or change the dose.
  - Infusion related events can occur in Vancomycin patients who have had an infusion of more than 15 mg/kg of Vancomycin per hour.

- Common side effects (affect 1 to 10 users in 100):
  - Shivering of the face or throat, difficulty in swallowing, difficulty breathing, rashes, skin rash, and swelling. Your doctor may stop the infusion or change the dose.
  - Infusion related events can occur in Vancomycin patients who have had an infusion of more than 15 mg/kg of Vancomycin per hour.

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

- Temporary or permanent loss of hearing

If you would like a leaflet with larger text, please contact 01271 311257.
Module 4
Labelling

Vancomycin 500mg and 1g Powder for Conc for Sol for Inf

The reconstituted concentrate should be diluted immediately after preparation.
Do not use unless the prepared solution is clear.
Store below 25°C.
Keep the vial in the outer carton in order to protect from light.
For single use only.
Read the package leaflet before use.
Use as directed by a doctor.
Keep out of the reach and sight of children.

Each vial contains 500mg vancomycin (equivalent to 25,000 IU) (as vancomycin hydrochloride).
When reconstituted as directed, the resulting concentrate (which must be further diluted before use) contains 50mg/mL vancomycin.
Contains sodium hydroxide and hydrochloric acid.
PL 24701/0022

Code No: L87/051H30
MA Holder: Nadeus ehf,
Box 5S, Naustanes,
116 Reykjavik, Iceland

10 box: 10 x 500mg vial
1 box: 1 x 500mg vial

Please note: 1 will be updated
Vancomycin

Powder for Concentrate for Solution for Infusion

For intravenous use after reconstitution and dilution

10 x 1000mg vials

- The reconstituted concentrate should be diluted immediately after preparation.
- Do not use unless the prepared solution is clear.
- Store below 25°C.
- Keep the vial in the outer carton in order to protect from light.
- For single use only.
- Use as directed by a doctor.

Each vial contains 500mg vancomycin equivalent to 1.25g (500mg vancomycin hydrochloride). When reconstituted as directed, the resulting concentrate (which must be further diluted before use) contains sodium hydroxide and hydrochloric acid.

Read the package leaflet before use. Keep out of the reach and sight of children.

POM

Batch EXP
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

On 20th March 2010, Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, the Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden and the UK agreed to grant marketing authorisations to Nucleus ehf for the medicinal products Vancomycin 500mg and 1g Powder for Concentrate for Solution for Infusion (UK/H/1937/001-2/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, licences were granted in the UK on 18th May 2010 (PL 24701/0022-3).

These applications were made under Article 10.1 of Directive 2001/83 EC for Vancomycin 500mg and 1g Powder for Concentrate for Solution for Infusion, containing the known active substance vancomycin hydrochloride. The reference medicinal products for these applications are Vancocin CP, which were first licensed in the Netherlands to Eurocept BV in December 1985.

Vancomycin is a glycopeptide antibiotic with primary bactericidal action against a variety of Gram-positive bacteria. It exerts its action by inhibiting the formation of the peptidoglycan polymers of the bacterial wall. Unlike penicillins, which act primarily to prevent the cross-linking of peptidoglycans which gives the cell wall its strength, vancomycin prevents the transfer and addition of the muramylpentapeptide building blocks that make up the peptidoglycan molecule itself. Vancomycin may also exert some effects by damaging the cytoplasmic membrane of the protoplast, and by inhibiting bacterial RNA synthesis.

The drug products correspond to the current EU definition for generic medicinal products because it complies with the criteria of having the same qualitative and quantitative composition in terms of active substance, and the same dosage form as the reference medicinal products stated above.

The proposed products are developed using an approved drug substance that is to be administered as an aqueous intravenous solution, containing the same drug substance in the same concentration as the reference medicinal products stated above. Therefore, a bioequivalence study is not required in support of these applications.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Vancomycin 500mg Powder for Solution for Infusion  
| Vancomycin 1000mg Powder for Solution for Infusion |
| Name(s) of the active substance(s) (USAN) | Vancomycin hydrochloride |
| Pharmacotherapeutic classification (ATC code) | Glycopeptide antibacterials (J01XA01) |
| Pharmaceutical form and strength(s) | Powder for Solution for Infusion, 500mg and 1g |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1937/001-2/DC |
| Reference Member State | United Kingdom |
| Member States concerned | Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, the Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden, Slovak Republic and the UK |
| Marketing Authorisation Number(s) | PL 24701/0022-3 |
| Name and address of the authorisation holder | Nucleus ehf, Box 55, Naustanesi 116, Reykjavik, Iceland |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Vancomycin hydrochloride


Structure:

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Molecular formula: C_{66}H_{75}Cl_{2}N_{9}O_{24}.HCl
Molecular weight: 1485.71
Physical form: A white or almost white powder, odourless and hygroscopic, freely soluble in water, slightly soluble in alcohol.
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Vancomycin B is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. All impurities have been appropriately characterised and certificates of analysis have been provided for any working standards used. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications for all materials used in the active substance packaging have been provided. The primary packaging meets the requirements for materials in contact with food.
Appropriate stability data have been generated, from studies carried out in accordance with ICH conditions. A suitable retest period has been set, based on the stability data provided.

**DRUG PRODUCT**

**Other ingredients**
Other ingredients consist of pharmaceutical excipients sodium hydroxide and hydrochloric acid. All excipients are controlled to their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used are sourced from materials of animal or human origin.

**Pharmaceutical Development**
The objective of the pharmaceutical development programme was to obtain stable products containing vancomycin hydrochloride that could be considered generic medicinal products of Vancocin CP Injections. Suitable pharmaceutical development data have been provided for these applications.

**Manufacture**
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished products. Process validation has been carried out on batches of each product. The results appear satisfactory.

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

**Container Closure System**
The finished products are supplied in Type I glass vials, which are closed with a bromobutyl rubber stopper and an aluminium seal equipped with a flip-off cap. Pack sizes are 1 and 10 vials.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines concerning materials in contact with parenteral products.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set when the product is unopened, with the storage conditions “Store below 25°C. Keep the vial in the outer carton in order to protect from light.”

It has been stipulated that the contents of the reconstituted concentrate should be used immediately after preparation. However, the following instructions are also given concerning storage of the product after dilution:

*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.

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling**
The SPC, PIL and labelling are pharmaceutically satisfactory.

The applicant has submitted results of PIL user testing. 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.

**Pharmacovigilance System and Risk Management Plan**
An acceptable justification for not submitting a European Risk Management Plan has been provided. Other documentation relating to pharmacovigilance system have been provided.

**MAA Forms**
The MAA forms are pharmaceutically satisfactory.

**Expert Report**
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.

**III.2 PRE-CLINICAL ASPECTS**
**PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY**
The pharmacological, pharmacokinetic and toxicological properties of vancomycin hydrochloride are well-known. As vancomycin hydrochloride is a well-known active substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

**ENVIRONMENTAL RISK ASSESSMENT**
A formal Environmental Risk Assessment has not been performed as the product is intended for generic substitution. Hence no increase in environmental risk is to be expected compared to that of the reference product.

**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**
The SPC is satisfactory from a preclinical viewpoint.

**PRE-CLINICAL EXPERT REPORT**
The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

**OVERALL CONCLUSION ON THE PRE-CLINICAL PART**
The applicant has provided an adequate review of the available pre-clinical data. There were no new pre-clinical data identified in the literature review that would change the risk-benefit analysis for vancomycin hydrochloride.
There are no objections to the grant of marketing authorisations from a pre-clinical point of view.

III.3 CLINICAL ASPECTS

Pharmacokinetics

No new data have been submitted and none are required for applications of this type.

Vancomycin 500mg and 1g Powder for Concentrate for Solution for Infusion is the generic version of Vancocin CP. The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredient, vancomycin hydrochloride.

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, subpoint 5.1.6, Parenteral solutions).

Pharmacodynamics

No new data have been submitted and none are required for applications of this type.

Clinical efficacy

No new data have been submitted and none are required for applications of this type.

Clinical safety

Vancomycin hydorchloride has an acceptable adverse events profile. No novel safety data are supplied or required for these generic applications. Vancomycin hydorchloride has a well-established side-effect profile and is generally well-tolerated. The applicant has provided a review of clinical trials published in the literature confirming the safety of vancomycin hydorchloride.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and labelling

The SPC, PIL and labelling are medically satisfactory and consistent with those for the reference products.

Clinical Expert Report

The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA Forms

The MAA Forms are medically satisfactory.

Clinical Conclusion

The grant of Marketing Authorisations is recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Vancomycin 500mg and 1g 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.

PRE-CLINICAL
The pre-clinical data submitted have not revealed any evidence of potential risks to human health from treatment with Vancomycin 500mg and 1g Powder for Concentrate for Solution for Infusion beyond those already described.

Efficacy
No new data have been submitted and none are required for applications of this type.

Vancomycin 500mg and 1g Powder for Concentrate for Solution for Infusion is the generic version of Vancocin CP. The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredient, vancomycin hydrochloride.

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, subpoint 5.1.6, Parenteral solutions). Thus, bioequivalence has been shown between these products and their respective reference products.

No new safety data are supplied or required for this generic application. Vancomycin hydrochloride has a well-established side-effect profile and is generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s product and the innovator product 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.
Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

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