Public Assessment Report

Decentralised Procedure

Vancomycin 500 mg Powder for concentrate for solution for infusion
Vancomycin 1000 mg Powder for concentrate for solution for infusion

Procedure No: UK/H/3638-9 and 4491/001-2/DC

UK Licence No: PL 20620/0050-3 and PL 20620/0057-8

NRIM Limited
On 18 January 2011, Austria, Belgium, Bulgaria, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovak Republic and the UK agreed to grant Marketing Authorisations to NRIM Limited for the medicinal products Vancomycin 500 mg and 1000 mg Powder for concentrate for solution for infusion (PL 20620/0050-3 and PL 20620/0057-8; UK/H/3638-9 and 4491/001-2/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 21 February 2011. These are prescription-only medicines (POM) used for the treatment of serious infections caused by certain bacteria, such as infections of the bones, lung tissue infections, skin and muscle (soft tissue) infections, and infection in the heart.

Vancomycin 500 mg and 1000 mg Powder concentrate for solution for infusion contain the active ingredient vancomycin (as vancomycin hydrochloride). Vancomycin hydrochloride is an antibiotic. Antibiotics help the body to fight infections. Vancomycin hydrochloride works by eliminating certain bacteria that cause infection.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Vancomycin 500 mg and 1000 mg Powder for concentrate for solution for infusion outweigh the risks; hence Marketing Authorisations were granted.
### TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module 1: Information about initial procedure</th>
<th>Page 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>Page 5</td>
</tr>
<tr>
<td>Module 3: Product Information Leaflet</td>
<td>Page 23</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>Page 25</td>
</tr>
<tr>
<td>Module 5: Scientific Discussion</td>
<td>Page 28</td>
</tr>
<tr>
<td>1 Introduction</td>
<td></td>
</tr>
<tr>
<td>2 Quality aspects</td>
<td></td>
</tr>
<tr>
<td>3 Non-clinical aspects</td>
<td></td>
</tr>
<tr>
<td>4 Clinical aspects</td>
<td></td>
</tr>
<tr>
<td>5 Overall conclusions</td>
<td></td>
</tr>
<tr>
<td>Module 6 Steps taken after initial procedure</td>
<td></td>
</tr>
</tbody>
</table>
# Module 1

## Information about the initial procedure

| Product Name(s) | UK/H/3638/001/DC: Vancomycin 500 mg Powder for concentrate for solution for infusion  
UK/H/3638/002/DC: Vancomycin 1000 mg Powder for concentrate for solution for infusion  
UK/H/3639/001/DC: Vancomycin 500 mg Powder for concentrate for solution for infusion  
UK/H/3639/002/DC: Vancomycin 1000 mg Powder for concentrate for solution for infusion  
UK/H/4491/001/DC: Vancomycin 500 mg Powder for concentrate for solution for infusion  
UK/H/4491/002/DC: Vancomycin 1000 mg Powder for concentrate for solution for infusion |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td>Active Substances</td>
<td>Vancomycin hydrochloride</td>
</tr>
<tr>
<td>Form</td>
<td>Powder for concentrate for solution for infusion</td>
</tr>
<tr>
<td>Strength</td>
<td>500 mg and 1000 mg</td>
</tr>
</tbody>
</table>
| MA Holder | NRIM Limited  
Marlborough House  
298 Regents Park Road  
Finchley  
London, N3 2UA  
UK |
| Reference Member State (RMS) | UK |
| Concerned Member States (CMS) | UK/H/3638/001-2/DC: Belgium, Bulgaria, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, and Slovak Republic  
UK/H/3639/001-2/DC: Austria, Belgium, Bulgaria, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Lithuania, Luxembourg, Latvia, The Netherlands, Norway, Portugal, Romania, Sweden, Slovenia and Slovak Republic  
UK/H/4491/001-2/DC: Austria, Belgium, Germany, Denmark, Spain, Greece, Finland, France, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Poland, Sweden and Romania |
| Procedure Number(s) | UK/H/3638/001/DC (PL 20620/0050)  
UK/H/3638/002/DC (PL 20620/0051)  
UK/H/3639/001/DC (PL 20620/0052)  
UK/H/3639/002/DC (PL 20620/0053)  
UK/H/4491/001/DC (PL 20620/0057)  
UK/H/4491/002/DC (PL 20620/0058) |
| Timetable | Day 210 – 18 January 2011 |
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Vancomycin 500 mg Powder for concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 500 mg vancomycin (as vancomycin hydrochloride) equivalent to 500,000 IU.

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

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Intravenous vancomycin is indicated in the following severe infections caused by gram-positive bacteria susceptible to vancomycin which cannot be treated or failed to respond or are resistant to other antibiotics such as penicillins and cephalosporins (see section 5.1).
- endocarditis
- infections of the bones (osteomyelitis)
- pneumonia
- soft tissue infections

Where appropriate, vancomycin should be co-administered with other antibacterial agents. This particularly applies to the treatment of endocarditis.

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
Method of administration:
Parenterally vancomycin shall only be administered as slow intravenous infusion (not more than 10 mg/min – over at least 60 min) which is sufficiently diluted (at least 100 ml per 500 mg or at least 200 ml per 1000 mg).

Patients requiring fluid restriction can receive a solution of 500 mg / 50 ml or 1000 mg / 100 ml. With these higher concentrations the risk for infusion related side effects can be increased. Infusion related events may occur, however, at any rate or concentration.

The dose should be individually adapted according to weight, age and renal function. Vancomycin levels can be measured to aid dose adjustments.

For information about the preparation of the solution, please refer to chapter 6.6

Intravenous use (infusion) in patients with normal renal function:
Adults and adolescents above 12 years of age:
The recommended daily intravenous dose is 2000 mg; divided into doses of 500 mg every 6 hours or 1000 mg every 12 hours. Or 30 to 40 mg/kg/day in 2 to 4 daily administrations.

For bacterial endocarditis, the generally accepted regimen is 1000 mg vancomycin intravenously every 12 hours for 4 weeks either alone or in combination with other antibiotics (gentamicin plus rifampicin, gentamicin, streptomycin). Enterococcal endocarditis is treated for 6 weeks with vancomycin in combination with an aminoglycoside. Official guidance should be consulted.
Children one month to 12 years of age:
The usual intravenous dosage is 10mg/kg per dose given every six hours (total daily dosage 40mg/kg of body weight). Each dose should be administered over a period of at least 60 minutes.

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

Each dose should be administered over 60 minutes. Close monitoring of serum vancomycin concentrations may be warranted in these patients.

Pregnancy:
It has been reported that significantly increased doses may be required to achieve therapeutic serum concentrations in pregnant patients - see Section 4.6 Pregnancy and lactation

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

Obese patients:
Modification of the usual daily doses may be required.

Patients with hepatic insufficiency
There is no evidence that the dose has to be reduced in patients with hepatic insufficiency.

Patients with impaired renal function:
Dosage adjustments must be made to avoid toxic serum levels. In premature infants and the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Regular monitoring of serum levels is advised in such patients, as accumulation has been reported, especially after prolonged therapy.

Vancomycin serum concentrations may be determined by use of a micro-biological assay, radioimmunoassay, fluorescence polarisation immunoassay, fluorescence immunoassay or high-pressure liquid chromatography. The following nomogram, based on creatinine clearance values, is provided as a guidance for dose adjustments:

The nomogram is not valid for functionally anephric patients on dialysis. For such patients, a loading dose of 15mg/kg body weight should be given to achieve therapeutic serum levels promptly, and the dose required to maintain stable levels is 1.9mg/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 seven to ten days has been recommended.
If serum creatinine level alone is available, the following formula may be applied to calculate the creatinine clearance:

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

Women: \(0.85 \times \text{value calculated by the above formula}\)

For instructions on the preparation of solutions, see Section 6.6.

Monitoring of vancomycin serum concentrations:
The serum concentration of vancomycin should be monitored at the second day of treatment immediately prior to the next dose, and one hour post infusion. Therapeutic vancomycin blood levels should be between 30 and 40 mg/l (maximum 50 mg/l) one hour after the end of the infusion, the minimum level (short prior to the next administration) between 5 and 10 mg/l.

The concentrations should normally be monitored twice or three times per week.

Duration of treatment
The duration of the treatment depends on the severity of the infection as well as on the clinical and bacteriological progress.

4.3 Contraindications
Hypersensitivity to vancomycin

4.4 Special warnings and precautions for use
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. Posology and method of administration and Section 4.8. Undesirable effects).

Due to its potential ototoxicity and nephrotoxicity, vancomycin should be used with care in patients with renal insufficiency and 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.

Vancomycin should also be avoided in patients with previous hearing loss. If it is used in such patients, the dose should be regulated, if possible, by periodic determination of the drug level in the blood. Deafness may be preceded by tinnitus.

The elderly are more susceptible to auditory damage. Experience with other antibiotics suggests that deafness may be progressive despite cessation of treatment.

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 histaminelike flushing in children.

Use in the elderly: The natural decrement of glomerular filtration with increasing age may lead to elevated vancomycin serum concentrations if dosage is not adjusted (see 'Posology and method of administration').

Precautions
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.

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

Vancomycin is very irritating to tissue, and causes injection site necrosis when injected intramuscularly; it must be infused intravenously. Injection site pain and thrombophlebitis occur in many patients receiving vancomycin and are occasionally severe.

The frequency and severity of thrombophlebitis can be minimised by administering the drug slowly as a dilute solution (2.5 to 5.0g/l) and by rotating the sites of infusion.

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.

As cases of cross hypersensitivity have been reported, Vancomycin must be administered with care in patients with known hypersensitivity to Teicoplanin.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Concurrent or sequential systemic or topical use of other potentially ototoxic, neurotoxic, or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymyxin B, colistin, viomycin or cisplatin, when indicated, requires careful monitoring.

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 and should be therefore used in lactation period only if other antibiotics have failed. Vancomycin should be cautiously given to breast-feeding mothers because of potential adverse reactions in the infant (disturbances in the intestinal flora with diarrhoea, colonisation with yeast-like fungi and possibly sensitisation).

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 are defined using the following MedDRA:
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)

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

**Blood and the lymphatic system disorder:**
Rare (≥1/10,000 to <1/1,000): thrombocytopenia, neutropenia, agranulocytoses, eosinophilia.

**Immune system disorders**
Rare (≥10,000 to ≤1/1,000): anaphylactic reactions, hypersensitivity reactions

**Ear and labyrinth disorders:**
Uncommon (≥1/1,000 to <1/100): Transient or permanent loss of hearing.
Rare (≥1/10,000 to <1/1,000): Tinnitus, dizziness.

**Cardiac disorders:**
Very rare (<1/10,000): cardiac arrest

**Vascular disorders:**
Common (≥1/100 to <1/10): Decrease in blood pressure.
Rare (≥1/10,000 to <1/1,000): Vasculitis

**Respiratory, thoracic and mediastinal disorders:**
Common (≥1/100 to <1/10): Dyspnoea, stridor.

**Gastrointestinal disorders:**
Rare (≥1/10,000 to <1/1,000): Nausea.
Very rare (<1/10,000): Pseudomembranous enterocolitis.

**Skin and subcutaneous tissue disorders:**
Common (≥1/100 to <1/10): Exanthema and mucosal inflammation, pruritus, urticaria.

**Renal and urinary disorders:**
Common (≥1/100 to <1/10): Renal insufficiency manifested primarily by increased serum creatinine.
Rare (≥1/10,000 to <1/1,000): Interstitial nephritis, acute renal failure.

**General disorders and administration site conditions:**
Common (≥1/100 to <1/10): Phlebitis, redness of the upper body and the face.
Rare (≥1/10,000 to <1/1,000): Drug fever, shivering. Pain in the chest and back muscles.

**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).

Ototoxicity may be reversible or permanent, and has been reported mainly in patients given an overdose in patients with a history of reduced hearing, and with concomitant therapy with other ototoxic drugs, such as aminoglycosides.
4.9 Overdose
Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed from the blood by haemodialysis or peritoneal dialysis. Haemoperfusion with Amberlite resin XAD-4 has been reported to be of limited benefit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antibacterials for systemic use Glycopeptide Antibacterials
ATC Code: JO1X 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.

Mechanism of resistance:
Acquired resistance to glycopeptides is most common in enterococci and is based on acquisition of various van gene complexes which modifies the D-alanyl-D-alanine target to D-alanyl-D-lactate or D-alanyl-D-serine which bind vancomycin poorly. Cross-resistance with teicoplanin has been reported for some van genes. Van genes have rarely been found in Staphylococcus aureus, where changes in cell wall structure result in “intermediate” susceptibility, which is most commonly heterogeneous.

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

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Breakpoints
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.

<table>
<thead>
<tr>
<th>Classes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commonly susceptible species</td>
</tr>
<tr>
<td>Gram positive</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>Staphylococcus coagulase negative</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>Clostridium spp.</td>
</tr>
<tr>
<td>Species for which acquired resistance may be a problem</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inherently resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative bacteria</td>
</tr>
<tr>
<td>Chlamydia spp.</td>
</tr>
<tr>
<td>Mycobacteria</td>
</tr>
<tr>
<td>Mycoplasma spp.</td>
</tr>
<tr>
<td>Rickettsia spp.</td>
</tr>
</tbody>
</table>
5.2 Pharmacokinetic properties

Absorption
Vancomycin is administered intravenously for the treatment of systemic infections. In the case of patients with normal renal function, intravenous infusion of multiple doses of 1g vancomycin (15 mg/kg) for 60 minutes produces approximate average plasmatic concentrations of 50-60 mcg/mL, 20-25 mcg/mL and 5-10 mcg/mL, immediately, 2 hours and 11 hours after completing the infusion, respectively. Intravenous infusion of multiple doses of 500 mg for 30 minutes produces average plasmatic concentrations of around 40-50 mg/l, 19-20 mg/l and 10-11 mg/l immediately, 2 hours and 6 hours after completing the infusion, respectively. The plasmatic levels obtained after multiple doses are similar to those achieved after a single dose.

In case of oral use, high-polar vancomycin is virtually not absorbed. It appears after oral administration in active form in the stool, and is therefore a suitable chemotherapeutic for pseudomembranous colitis and staphylococcal colitis.

Distribution
At serum concentrations of vancomycin of 10 mg/l to 100 mg/l, the binding of the drug to plasma proteins is approximately 30-55%, measured by ultra-filtration.

After intravenous administration of vancomycin hydrochloride, inhibitory concentrations are found in the pleural, pericardial, ascitic and sinovial fluids, in the urine and the peritoneal dialysis fluid and in the tissue of the atrial appendix.

In non-inflamed meninges vancomycin passes the blood-brain barrier only to a low extent.

Elimination
The elimination half-life of vancomycin is 4 to 6 hours in patients with normal renal function. In the first 24 hours, approximately 80% of an administered dose of vancomycin is excreted in the urine through glomerular filtration. Renal dysfunction delays the excretion of vancomycin. In anephric patients, the mean half-life is 7.5 days. There is very little metabolism of the drug. Approximately 35-65% of an intraperitoneal dose of vancomycin administered during peritoneal dialysis is absorbed systemically in six hours. Serum concentrations of approximately 8 mg/litre are achieved through intraperitoneal injection of 30 mg/kg vancomycin. Although the vancomycin is not eliminated efficiently by haemodialysis or peritoneal dialysis, there have been reports of an increase in vancomycin clearance with haemoperfusion and haemofiltration. Total systemic and renal clearance of vancomycin may be reduced in persons of advanced age.

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
None

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

**Powder as packaged for sale:**
2 years

**Reconstituted concentrate:**
The reconstituted concentrate should be further diluted immediately after reconstitution.

**Diluted product:**
From a microbiological and physicochemical point of view, the product should be used immediately.

6.4 **Special precautions for storage**

**Powder as packaged for sale:**
Store below 25°C.
Keep the vial in the outer carton in order to protect from light.

**Reconstituted concentrate and diluted product:**
For storage conditions of the reconstituted concentrate and diluted product, see section 6.3.

6.5 **Nature and contents of container**

Colourless type 1, 10 ml glass vial, with a chlorobutyl type 1 silicone coated stopper and a grey aluminium/polypropylene flip-off cap.

Pack sizes: 1 vial

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**

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

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

**Appearance of reconstituted concentrate:**
Clear and colourless solution free from particles.

One ml of reconstituted concentrate contains 50 mg of vancomycin.

For storage conditions of the reconstituted concentrate, see sections 6.3

**Preparation of final diluted solution infusion:**
Reconstituted concentrate containing 50 mg/ml of vancomycin should be further diluted immediately after reconstitution.

**Suitable diluents are:**
Sodium Chloride 9 mg/ml (0.9%) Injection, Glucose 50 mg/ml (5%) Injection, Sodium Chloride 9 mg/ml (0.9 %) and Glucose 50 mg/ml (5%) Injection or Ringer acetate Injection.

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

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

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

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

For storage conditions of the diluted medicinal product, see sections 6.3
Disposal
Vials are for single use only. Unused product must be discarded.

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

7 MARKETING AUTHORISATION HOLDER
NRIM Limited
Marlborough House
298 Regents Park Road
Finchley
London, N3 2UA
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 20620/0050
PL 20620/0052
PL 20620/0057

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/02/2011

10 DATE OF REVISION OF THE TEXT
21/02/2011
1 NAME OF THE MEDICINAL PRODUCT
Vancomycin 1000 mg Powder for concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 1000 mg vancomycin (as vancomycin hydrochloride) equivalent to 1,000,000 IU.

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

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Intravenous vancomycin is indicated in the following severe infections caused by gram-positive bacteria susceptible to vancomycin which cannot be treated or failed to respond or are resistant to other antibiotics such as penicillins and cephalosporins (see section 5.1).
- endocarditis
- infections of the bones (osteomyelitis)
- pneumonia
- soft tissue infections
Where appropriate, vancomycin should be co-administered with other antibacterial agents. This particularly applies to the treatment of endocarditis.
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
Method of administration:
Parenterally vancomycin shall only be administered as slow intravenous infusion (not more than 10 mg/min – over at least 60 min) which is sufficiently diluted (at least 100 ml per 500 mg or at least 200 ml per 1000 mg).
Patients requiring fluid restriction can receive a solution of 500 mg / 50 ml or 1000 mg / 100 ml. With these higher concentrations the risk for infusion related side effects can be increased. Infusion related events may occur, however, at any rate or concentration.
The dose should be individually adapted according to weight, age and renal function. Vancomycin levels can be measured to aid dose adjustments.
For information about the preparation of the solution, please refer to chapter 6.6

Intravenous use (infusion) in patients with normal renal function:
Adults and adolescents above 12 years of age:
The recommended daily intravenous dose is 2000 mg; divided into doses of 500 mg every 6 hours or 1000 mg every 12 hours. Or 30 to 40 mg/kg/day in 2 to 4 daily administrations.
For bacterial endocarditis, the generally accepted regimen is 1000 mg vancomycin intravenously every 12 hours for 4 weeks either alone or in combination with other antibiotics (gentamicin plus rifampicin, gentamicin, streptomycin). Enterococcal endocarditis is treated for 6 weeks with vancomycin in combination with an aminoglycoside. Official guidance should be consulted.
Children one month to 12 years of age:
The usual intravenous dosage is 10mg/kg per dose given every six hours (total daily dosage 40mg/kg of body weight). Each dose should be administered over a period of at least 60 minutes.
Newborn infants (full-term):
0-7 days of age: A starting dose of 15 mg/kg, followed by 10 mg/kg every 12 hours.
7-30 days of age: A starting dose of 15 mg/kg, followed by 10 mg/kg every 8 hours.
Each dose should be administered over 60 minutes. Close monitoring of serum vancomycin concentrations may be warranted in these patients.

Pregnancy:
It has been reported that significantly increased doses may be required to achieve therapeutic serum concentrations in pregnant patients - see Section 4.6 Pregnancy and lactation

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

Obese patients:
Modification of the usual daily doses may be required.

Patients with hepatic insufficiency
There is no evidence that the dose has to be reduced in patients with hepatic insufficiency.

Patients with impaired renal function:
Dosage adjustments must be made to avoid toxic serum levels. In premature infants and the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Regular monitoring of serum levels is advised in such patients, as accumulation has been reported, especially after prolonged therapy.

Vancomycin serum concentrations may be determined by use of a micro-biological assay, radioimmunoassay, fluorescence polarisation immunoassay, fluorescence immunoassay or high-pressure liquid chromatography. The following nomogram, based on creatinine clearance values, is provided as a guidance for dose adjustments:

The nomogram is not valid for functionally anephric patients on dialysis. For such patients, a loading dose of 15mg/kg body weight should be given to achieve therapeutic serum levels promptly, and the dose required to maintain stable levels is 1.9mg/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 seven to ten days has been recommended.
If serum creatinine level alone is available, the following formula may be applied to calculate the creatinine clearance:

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

Women: 0.85 x value calculated by the above formula

For instructions on the preparation of solutions, see Section 6.6.

**Monitoring of vancomycin serum concentrations:**
The serum concentration of vancomycin should be monitored at the second day of treatment immediately prior to the next dose, and one hour post infusion. Therapeutic vancomycin blood levels should be between 30 and 40 mg/l (maximum 50 mg/l) one hour after the end of the infusion, the minimum level (short prior to the next administration) between 5 and 10 mg/l.

The concentrations should normally be monitored twice or three times per week.

**Duration of treatment**
The duration of the treatment depends on the severity of the infection as well as on the clinical and bacteriological progress.

4.3 **Contraindications**
Hypersensitivity to vancomycin

4.4 **Special warnings and precautions for use**
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. Posology and method of administration and Section 4.8 and Undesirable effects).

Due to its potential ototoxicity and nephrotoxicity, vancomycin should be used with care in patients with renal insufficiency and 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.

Vancomycin should also be avoided in patients with previous hearing loss. If it is used in such patients, the dose should be regulated, if possible, by periodic determination of the drug level in the blood. Deafness may be preceded by tinnitus.

The elderly are more susceptible to auditory damage. Experience with other antibiotics suggests that deafness may be progressive despite cessation of treatment.

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 histaminelike flushing in children.

Use in the elderly: The natural decrement of glomerular filtration with increasing age may lead to elevated vancomycin serum concentrations if dosage is not adjusted (see 'Posology and method of administration').

**Precautions**
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.

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

Vancomycin is very irritating to tissue, and causes injection site necrosis when injected intramuscularly; it must be infused intravenously. Injection site pain and thrombophlebitis occur in many patients receiving vancomycin and are occasionally severe.

The frequency and severity of thrombophlebitis can be minimised by administering the drug slowly as a dilute solution (2.5 to 5.0g/l) and by rotating the sites of infusion.

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.

As cases of cross hypersensitivity have been reported, Vancomycin must be administered with care in patients with known hypersensitivity to Teicoplanin.

4.5 Interaction with other medicinal products and other forms of interaction
Concomitant administration of vancomycin and anaesthetic agents has been associated with erythema, histamine-like flushing and anaphylactoid reactions. There have been reports that the frequency of infusion-related events increases with the concomitant administration of anaesthetic agents. Infusion-related events may be minimised by the administration of vancomycin as a 60-minute infusion prior to anaesthetic induction.

Concurrent or sequential systemic or topical use of other potentially ototoxic, neurotoxic, or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymyxin B, colistin, viomycin or cisplatin, when indicated, requires careful monitoring.

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 otoxicity 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 and should be therefore used in lactation period only if other antibiotics have failed. Vancomycin should be cautiously given to breast-feeding mothers because of potential adverse reactions in the infant (disturbances in the intestinal flora with diarrhoea, colonisation with yeast-like fungi and possibly sensitisation).

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 are defined using the following MedDRA:
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)
Intravenous infusion:
The most common adverse reactions are phlebitis and pseudo-allergic reactions in connection with too rapid intravenous infusion of vancomycin.

Blood and the lymphatic system disorder:
Rare (≥1/10,000 to <1/1,000): thrombocytopenia, neutropenia, agranulocytoses, eosinophilia.

Immune system disorders
Rare (≥10,000 to ≤1/1,000): anaphylactic reactions, hypersensitivity reactions

Ear and labyrinth disorders:
Uncommon (≥1/1,000 to <1/100): Transient or permanent loss of hearing.
Rare (≥1/10,000 to <1/1,000): Tinnitus, dizziness.

Cardiac disorders:
Very rare (<1/10,000): cardiac arrest

Vascular disorders:
Common (≥1/100 to <1/10): Decrease in blood pressure.
Rare (≥1/10,000 to <1/1,000): Vasculitis

Respiratory, thoracic and mediastinal disorders:
Common (≥1/100 to <1/10): Dyspnoea, stridor.

Gastrointestinal disorders:
Rare (≥1/10,000 to <1/1,000): Nausea.
Very rare (<1/10,000): Pseudomembranous enterocolitis.

Skin and subcutaneous tissue disorders:
Common (≥1/100 to <1/10): Exanthema and mucosal inflammation, pruritus, urticaria.

Very rare (<1/10,000): Exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome Linear IgA bullous dermatosis,

Renal and urinary disorders:
Common (≥1/100 to <1/10): Renal insufficiency manifested primarily by increased serum creatinine.
Rare (≥1/10,000 to <1/1,000): Interstitial nephritis, acute renal failure.

General disorders and administration site conditions:
Common (≥1/100 to <1/10): Phlebitis, redness of the upper body and the face.
Rare (≥1/10,000 to <1/1,000): Drug fever, shivering. Pain in the chest and back muscles.

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).

Ototoxicity may be reversible or permanent, and has been reported mainly in patients given an overdose in patients with a history of reduced hearing, and with concomitant therapy with other ototoxic drugs, such as aminoglycosides.

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

5.1 Pharmacodynamic properties
Pharmacotherapeutic group, “antibacterials for systemic use 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.

Mechanism of resistance:
Acquired resistance to glycopeptides is most common in enterococci and is based on acquisition of various van gene complexes which modifies the D-alanyl-D-alanine target to D-alanyl-D-lactate or D-alanyl-D-serine which bind vancomycin poorly. Cross-resistance with teicoplanin has been reported for some van genes. Van genes have rarely been found in Staphylococcus aureus, where changes in cell wall structure result in “intermediate” susceptibility, which is most commonly heterogeneous.

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

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Breakpoints
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>Grampositive 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.

5.2 Pharmacokinetic properties
Absorption
Vancomycin is administered intravenously for the treatment of systemic infections. In the case of patients with normal renal function, intravenous infusion of multiple doses of 1g vancomycin (15 mg/kg) for 60 minutes produces approximate average plasmatic concentrations of 50-60 mcg/mL,
20-25 mcg/mL and 5-10 mcg/mL, respectively. Intravenous infusion of multiple doses of 500 mg for 30 minutes produces average plasmatic concentrations of around 40-50 mg/l, 19-20 mg/l and 10-11 mg/l immediately, 2 hours and 6 hours after completing the infusion, respectively. The plasmatic levels obtained after multiple doses are similar to those achieved after a single dose.

In case of oral use, high-polar vancomycin is virtually not absorbed. It appears after oral administration in active form in the stool, and is therefore a suitable chemotherapeutic for pseudomembranous colitis and staphylococcal colitis.

**Distribution**

At serum concentrations of vancomycin of 10 mg/l to 100 mg/l, the binding of the drug to plasma proteins is approximately 30-55%, measured by ultra-filtration.

After intravenous administration of vancomycin hydrochloride, inhibitory concentrations are found in the pleural, pericardial, ascitic and sinovial fluids, in the urine and the peritoneal dialysis fluid and in the tissue of the atrial appendix.

In non-inflamed meninges vancomycin passes the blood-brain barrier only to a low extent.

**Elimination**

The elimination half-life of vancomycin is 4 to 6 hours in patients with normal renal function. In the first 24 hours, approximately 80% of an administered dose of vancomycin is excreted in the urine through glomerular filtration. Renal dysfunction delays the excretion of vancomycin. In anephric patients, the mean half-life is 7.5 days. There is very little metabolism of the drug. Approximately 35-65% of an intraperitoneal dose of vancomycin administered during peritoneal dialysis is absorbed systemically in six hours. Serum concentrations of approximately 8 mg/litre are achieved through intraperitoneal injection of 30 mg/kg vancomycin. Although the vancomycin is not eliminated efficiently by haemodialysis or peritoneal dialysis, there have been reports of an increase in vancomycin clearance with haemoperfusion and haemofiltration. Total systemic and renal clearance of vancomycin may be reduced in persons of advanced age.

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

None

6.2 Incompatibilities

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

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

6.3 Shelf life

Powder as packaged for sale:

2 years

Reconstituted concentrate:
The reconstituted concentrate should be further diluted immediately after reconstitution.
Diluted product:
From a microbiological and physicochemical point of view, the product should be used immediately.

6.4 Special precautions for storage

Powder as packaged for sale:
Store below 25°C.
Keep the vial in the outer carton in order to protect from light.

Reconstituted concentrate and diluted product:
For storage conditions of the reconstituted concentrate and diluted product, see section 6.3.

6.5 Nature and contents of container

Colourless type 1, 20 ml glass vial, with a chlorobutyl type 1 silicone coated stopper and a green aluminium/polypropylene flip-off cap.
Pack sizes: 1 vial
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

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

Appearance of reconstituted concentrate:
Clear and colourless solution free from particles.

One ml of reconstituted concentrate contains 50 mg of vancomycin.

For storage conditions of the reconstituted concentrate, see sections 6.3

Preparation of final diluted solution infusion:
Reconstituted concentrate containing 50 mg/ml of vancomycin should be further diluted immediately after reconstitution.

Suitable diluents are:
Sodium Chloride 9 mg/ml (0.9%) Injection, Glucose 50 mg/ml (5%) Injection, Sodium Chloride 9 mg/ml (0.9 %) and Glucose 50 mg/ml (5%) Injection or Ringer acetate Injection.

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

Intermittent infusion:
Reconstituted concentrate containing 1000 mg of vancomycin (50 mg/ml) must be diluted further with at least 200 ml diluent immediately after reconstitution.

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

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

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

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

Any unused product or waste material should be disposed of in accordance with local requirements.
MARKETING AUTHORISATION HOLDER
NRIM Limited
Marlborough House
298 Regents Park Road
Finchley
London, N3 2UA
UK

MARKETING AUTHORISATION NUMBER(S)
PL 20620/0051
PL 20620/0053
PL 20620/0058

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/02/2011

DATE OF REVISION OF THE TEXT
21/02/2011
Module 3

Please note that the representative leaflet for Vancomycin 500 mg and 1000 mg Powder for concentrate for solution for infusion (PL 20620/0057-8; UK/H/4491//001-2/DC) is shown below. The leaflet details for Vancomycin 500 mg and 1000 mg Powder for concentrate for solution for infusion (PL 20620/0050-3; UK/H/3638-9/001-2/DC) are consistent with this leaflet, with the exception of the list of the member states where the products are authorised (and the corresponding product names).
Vancomycin 500 mg and 1000 mg Powder concentrate for solution for infusion

UK/H/3638-9 & 4491/001-2/DC

The following information is intended for medical or healthcare professionals only.

**Preparation**

**500 mg**
- Dissolve the content of the vial with 10 ml sterile water for injection.
- Dilute the reconstituted solution with at least 100 ml Sodium Chloride 0.9% injection (9%), for infusion, Glucose 50% injection, Sodium Chloride 0.9% injection, Glucose 50% injection, and Sodium Chloride 0.9% injection or Ringer’s acetate injection.

**1000 mg**
- Dissolve the content of the vial with 20 ml sterile water for injection.
- Dilute the reconstituted solution with at least 200 ml Sodium Chloride 0.9% injection, Glucose 50% injection, Sodium Chloride 0.9% injection, Glucose 50% injection, and Sodium Chloride 0.9% injection or Ringer’s acetate injection.

The concentration of vancomycin in the prepared infusion fluid must not exceed 100 mg/l (1%).

In selected patients in need of fluid restriction, a concentration up to 10 mg/l may be used; use of such higher concentrations may increase the risk of infusion-related events.

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

The infusion should not be mixed with other drugs.

**Infusion**

Must be given as slow intravenous infusion over at least 60 minutes at a maximum rate of 10 mg/min. Exceed 2 minutes of an infusion with a concentration of 5 mg/l.

**Dosing**

**Intravenous use**
- The dose is adjusted individually and according to the patient's function. The usual dose is:
  - Adults: 500 mg every 8 hours or 1 every 12 hours given by slow intravenous infusion of 10 to 40 mg/kg/day in 2 to 4 daily administrations.
  - Children: 10 mg/kg body weight every 12 hours given by slow intravenous infusion.

**Storage**

Vancomycin powder for concentrate for solution for infusion should be stored below 25°C. Keep the vial in the outer carton in order to protect from light.

Vancomycin powder for concentrate for solution for infusion should be used after the expiry date which is stated on the carton.

**Reconstitution concentrate**

The reconstituted concentrate should be further diluted immediately after reconstitution.

**Diluted product**

- From a microbiological and physical/chemical point of view, the product should be used immediately.
Vancomycin 500 mg and 1000 mg Powder concentrate for solution for infusion

UK/H/3638-9 & 4491/001-2/DC

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

Common side effects:
• Headache
• Dizziness
• Nausea
• Vomiting
• Diarrhoea
• Abdominal pain
• Indigestion

Very rare side effects:
• Severe allergic reaction (anaphylactic shock), which may cause death
• Difficulty in breathing
• Wheezing
• Swelling of the face, lips, tongue or throat
• Chest pain

What Vancomycin looks like and contents of the pack:
Vancomycin 500 mg powder for concentrate for solution for infusion:
• A vial to reconstitute powder in a glass vial with a grey flip-top cap (Pack size: 1 vial).
Vancomycin 1000 mg powder for concentrate for solution for infusion:
• A vial to reconstitute powder in a glass vial with a green flip-top cap (Pack size: 1 vial).

The medicine is a powder that has to be dissolved before you use it.

Manufacturing Authorisation Holder:
MHRM Limited
Marborough House
288 Regent Park Road
Rickmansworth
Hertfordshire	nw3 1ua
UK

Manufacturer:
Jota Pharmaceuticals ApS
Dalslandvej 11
2380 Copenhagen S
Denmark

This medicinal product is authorised in the Member States under the following names:

Austria: Vancomycin Nellix
Belgium: Vancomycine
Denmark: Vancomycin Nellix
Finland: Vancomycin Nellix
France: Vancomycin Nellix
Germany: Vancomycin Nellix
Greece: Nellixie
Ireland: Vancomycin Nellix
Italy: Vancomycin Nellix

How to Store VANCOMYCIN:
Your doctor will be responsible for storing the medicine.

6. HOW TO STORE VANCOMYCIN
Your doctor will be responsible for storing the medicine.

7. How to use Vancomycin:
Do not use Vancomycin after the expiry date which is stated on the outer container and not on the bottle. The expiry date refers to the last day of that month.

Vancomycin 500 mg and 1000 mg Powder concentrate for solution for infusion:
• Each vial contains 500 mg vancomycin (as vancomycin hydrochloride) equivalent to 500,000 IU.

Vancomycin 1000 mg powder for concentrate for solution for infusion:
• Each vial contains 1000 mg vancomycin (as vancomycin hydrochloride) equivalent to 1,000,000 IU.

25
Module 4

Please note that representative labelling for Vancomycin 500 mg and 1000 mg Powder for concentrate for solution for infusion (PL 20620/0057-8; UK/H/4491/001-2/DC) is shown below. The labelling text details for Vancomycin 500 mg and 1000 mg Powder for concentrate for solution for infusion (PL 20620/0050-3; UK/H/3638-9/001-2/DC) are consistent with these labels, with the exception of the product licence numbers.
Vancomycin 500 mg and 1000 mg Powder concentrate for solution for infusion

For intravenous use after reconstitution and dilution.

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

Store below 25°C.

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

Do not use unless the prepared solution is clear.

Read the package leaflet before use.

MA holder: NRIIM Limited
Marborough House
285 Regents Park Road
Finchley, London, N3 2UA, UK

Do not use unless the prepared solution is clear.

For single use only.

Keep out of the reach and sight of children.

Vancomycin for solution for infusion for solution for infusion

Released for dispensing label

1 vial

NRIIM

UK/H/3638-9 & 4491/001-2/DC
Vancomycin 500 mg and 1000 mg Powder concentrate for solution for infusion

For intravenous use after reconstitution and dilution.
Each vial contains 1000 mg vancomycin (as vancomycin hydrochloride) equivalent to 1,000,000 IU.
Store below 25°C.
Keep the vial in the outer carton in order to protect from light.
Do not use unless the prepared solution is clear.
Read the package leaflet before use.

MA holder: NRIM Limited
Marlborough House
298 Regents Park Road
Finchley, London, N3 2UA, UK
Do not use unless the prepared solution is clear
For single use only.
Discard any unused solution appropriately.
Keep out of the reach and sight of children.

Reserved for dispensing label
1 vial
NRIM
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Vancomycin 500 mg and 1000 mg Powder for concentrate for solution for infusion (PL 20620/0050-3 and PL 20620/0057-8; UK/H/3638-9 and 4491/001-2/DC) could be approved. The products are prescription-only medicines (POM) used for the treatment of the following severe infections caused by gram-positive bacteria susceptible to vancomycin, which cannot be treated 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

Where appropriate, Vancomycin Powder for concentrate for solution for infusion should be co-administered with other antibacterial agents. This particularly applies to the treatment of endocarditis.

Vancomycin Powder for concentrate for solution for infusion may also 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.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Austria, Belgium, Bulgaria, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Ireland, Iceland, Italy, Lithuania Luxembourg, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, and Slovak Republic as Concerned Member States (CMS). The applications were submitted under Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Vancocin® 500 mg and 1000 mg Powder for solution for infusion (Flynn Pharma Limited), which were first authorised in the UK on 18 April 1990.

The active ingredient vancomycin (as vancomycin hydrochloride) 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 that gives the cell wall its strength, vancomycin hydrochloride 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.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.
No new clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years. A bioequivalence study was not necessary to support these applications for parenteral products.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 18 January 2011. After a subsequent national phase, licences were granted in the UK on 21 February 2011.
### II. ABOUT THE PRODUCT

| Names of the products in the Reference Member State | UK/H/3638/001/DC: Vancomycin 500 mg Powder for concentrate for solution for infusion  
UK/H/3638/002/DC: Vancomycin 1000 mg Powder for concentrate for solution for infusion  
UK/H/3639/001/DC: Vancomycin 500 mg Powder for concentrate for solution for infusion  
UK/H/3639/002/DC: Vancomycin 1000 mg Powder for concentrate for solution for infusion  
UK/H/4491/001/DC: Vancomycin 500 mg Powder for concentrate for solution for infusion  
UK/H/4491/002/DC: Vancomycin 1000 mg Powder for concentrate for solution for infusion |
| Name(s) of the active substance(s) (INN) | Vancomycin hydrochloride |
| Pharmacotherapeutic classification (ATC code) | Antibacterials for systemic use Glycopeptide antibiotics”;  
(ATC Code: J01XA01) |
| Pharmaceutical form and strength(s) | Powder for concentrate for solution for infusion;  
500mg and 1000mg |
| Reference numbers for the Decentralised Procedure | UK/H/3638/001/DC (PL 20620/0050)  
UK/H/3638/002/DC (PL 20620/0051)  
UK/H/3639/001/DC (PL 20620/0052)  
UK/H/3639/002/DC (PL 20620/0053)  
UK/H/4491/001/DC (PL 20620/0057)  
UK/H/4491/002/DC (PL 20620/0058) |
| Reference Member State (RMS) | United Kingdom |
| Concerned Member States (CMS) | UK/H/3638/001-2/DC: Belgium, Bulgaria, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia and Slovak Republic  
UK/H/3639/001-2/DC: Austria, Belgium, Bulgaria, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, The Netherlands, Norway, Portugal, Romania, Sweden, Slovenia and Slovak Republic  
UK/H/4491/001-2/DC: Austria, Belgium, Germany, Denmark, Spain, Greece, Finland, France, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Poland, Sweden and Romania |
| Marketing Authorisation Number(s) | PL 20620/0050-3  
PL 20620/0058-9 |
| Name and address of the authorisation holder | NRIM Limited  
Marlborough House  
298 Regents Park Road  
Finchley,  
London, N3 2UA, UK |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Vancomycin hydrochloride
Chemical name: The monohydrochloride of \((3S,6R,7R,22R,23S,26S,36R,38aR)-3-(2\text{-amino-2\text{oxyethyl}})-44-[[2\text{-0-(3-amino-2,3,6-trideoxy-3-C- methyl-a-L-lyxo-hexopyranosyl}-pD-glucopyranosyl]}\text{oxy-10,19-dichloro-7,22,28,30,32-pentahydroxy-6-[2(R)-4-methyl-2-(methylamino)pentanoyl]-amino}]2, 5, 24, 38, 39-penta oxo - 2, 3, 4, 5, 6, 7, 23, 24, 25,26, 36, 37, 38, 38a-tetradeca hydro-22H-8, II: 18, 21-dietheno-23, 36- (iminomethano)-13, 16: 31, 35-dimetheno- IH, 13H-[1, 6, 9] oxadiazacycloc hexadecino [4, 5- m] [10, 2, 16]benzo diazacyclotetracosine-26- carboxylic acid (Vancomycin B).

Structure:

Molecular formula: \(C_{66}H_{75}Cl_2N_9O_{24}\cdot\text{HCl}\)
Molecular Mass: 1486
Appearance: Vancomycin hydrochloride is a white or almost white powder, odourless and hygroscopic, freely soluble in water, slightly soluble in alcohol.

Vancomycin hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance vancomycin hydrochloride are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

MEDICINAL PRODUCT

Other Ingredients
There are no pharmaceutical excipients in these products.

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the originator products Vancocin® 500 mg and 1000 mg powder for solution for infusion and oral solution (Flynn Pharma Limited).

Suitable pharmaceutical development data have been provided for these applications.
Comparative impurity profiles have been provided for these products and the UK originator products Vancocin® 500 mg and 1000 mg Powder for solution for infusion and oral solution (Flynn Pharma Limited).

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of the products, together with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Control of Finished Product**
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**
The finished products are supplied in 10ml (500 mg) and 20ml (1000 mg) colourless type 1 glass vials with chlorobutyl type 1 silicone-coated stoppers and coloured aluminium/polypropylene flip-off caps (grey for the 500 mg strength and green for the 1000 mg strength). The glass vials are individually packed in carton boxes in pack sizes of 1.

Satisfactory specifications and Certificates of Analysis for all packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines concerning materials in contact with parenteral products.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years with the storage conditions “Store below 25°C. Keep the vial in the outer carton in order to protect from light.” has been proposed for products stored in the unopened vials.

The reconstituted concentrate should be further diluted immediately after reconstitution.

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

**Bioequivalence/Bioavailability**
A bioequivalence study was not necessary to support these applications for parenteral products.

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

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet 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.
MAA Forms
The MAA forms are pharmaceutically satisfactory.

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

Conclusion
The grant of Marketing Authorisations is recommended.
III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of vancomycin hydrochloride are well-known, no new non-clinical data have been submitted and none are required.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the non-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

The grant of Marketing Authorisations is recommended.
III.3 CLINICAL ASPECTS

Clinical Pharmacology
No new clinical pharmacology data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support these applications for parenteral products.

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

Safety
No new safety data have been submitted with these applications and none are required.

Summaries 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 originator 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 Expert Report
The clinical expert report 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 applicant, fulfils the requirements and provides adequate evidence that the applicant 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 either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for these products.

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

QUALITY
The important quality characteristics of Vancomycin 500 mg and 1000 mg 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
No new clinical data were submitted for these applications. A bioequivalence study was not necessary to support these applications for parenteral products.

SAFETY
No new data were submitted and none are required for these types of applications. As the safety profile of vancomycin hydrochloride is well-known, no additional data were required.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with those for the originator products, where appropriate, and consistent with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied supports the claim that these products are generic medicinal products of the originator products, Vancocin® 500 mg and 1000 mg Powder for solution for infusion and oral solution (Flynn Pharma Limited). Extensive clinical experience with vancomycin hydrochloride is considered to have demonstrated the therapeutic value of the products. The benefit-risk is, therefore, considered to be positive.
Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>