VANCOMYCIN 500MG POWDER FOR SOLUTION FOR INFUSION
PL 20851/0007

VANCOMYCIN 1G POWDER FOR SOLUTION FOR INFUSION
PL 20851/0008

UKPAR

TABLE OF CONTENTS

VANCOMYCIN 500MG POWDER FOR SOLUTION FOR INFUSION
PL 20851/0007

VANCOMYCIN 1G POWDER FOR SOLUTION FOR INFUSION
PL 20851/0008

LAY SUMMARY

The MHRA granted Wockhardt UK Ltd Marketing Authorisations (licences) for the medicinal products Vancomycin 500mg Powder for Solution for Infusion (PL 20851/0007) and Vancomycin 1g Powder for Solution for Infusion (PL 20851/0008). These are prescription-only medicines (POM) for the treatment of infections caused by bacteria called 'staphylococci' which may be difficult to cure with other antibiotics. It may also be administered as an oral liquid for the treatment of severe diarrhoea.

Vancomycin 500mg &Powder for Solution for Infusion contains the active ingredient vancomycin, which is an antibiotic.

The test product was considered the same as the original product Vancocin CP (Flynn Pharma Ltd). No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Vancomycin 500mg & 1g Powder for Solution for Infusion outweigh the risks, hence Marketing Authorisations have been granted.

VANCOMYCIN 500MG POWDER FOR SOLUTION FOR INFUSION
PL 20851/0007

VANCOMYCIN 1G POWDER FOR SOLUTION FOR INFUSION
PL 20851/0008

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Vancomycin 500mg Powder for Solution for Infusion (PL 20851/0007) and Vancomycin 1g Powder for Solution for Infusion (PL 20851/0008) on 28 September 2007. The products are prescription-only medicines.

These are two strengths of Vancomycin, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic products of the original product Vancocin CP (Flynn Pharma Ltd). The reference product has been authorised in the UK since April 1990 and so the 10-year period of data exclusivity has expired. The Market Authorisation was initially held by Eli Lilly & Company Ltd, but a change of ownership to Flynn Pharma Ltd occurred in May 2006.

The products contain the active ingredient vancomycin, an antibiotic for the treatment of infections caused by Gram-positive cocci.

Vancomycin 500mg and 1g Powder for Solution for Infusion are indicated for infections which cannot be treated with other effective, less toxic antimicrobial drugs and for the treatment of or prophylaxis against endocarditis. Vancomycin may also be used orally for the treatment of staphylococcal enterocolitis and pseudomembranous colitis due to *Clostridium difficile*.

These applications were submitted at the same time. Consequently, all sections of this Scientific Discussion refer to both products.

PHARMACEUTICAL ASSESSMENT

COMPOSITION

The product is formulated as a powder for solution for infusion containing the active pharmaceutical ingredient vancomycin at strengths of 500 mg and 1g. No excipients are present in the formulation.

The powders are presented in Type II colorless glass 10ml (Vancomycin 500mg Powder for Solution for Infusion) or 20ml (Vancomycin 1g Powder for Solution for Infusion) vials stoppered with Type I rubber stoppers capped with a flip-off cap, in packs of 1, 2, 5 or 10 vials.

DRUG SUBSTANCE

Vancomycin

The specification from the active substance manufacturer has been provided. It is in compliance with the European Pharmacopoeia monograph and the certificate of suitability.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the finished product manufacturer during analysis.

Appropriate stability data have been generated supporting a retest period of 24 months, if the product is stored at 2-8°C in an aluminium container with a plastic insert.

DRUG PRODUCT

Other ingredients

Exemplary certificates of analysis for Water for Injections and Nitrogen gas used during manufacture have been provided.

Impurity profiles

The impurity profile for the drug product complies with the requirements of the finished product specification and the BP monograph for vancomycin injection.

Manufacture

A Good Manufacturing Practice (GMP) certificate has been provided for the manufacturing site. A description and flow-chart of the manufacturing method have been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on three batches of each strength. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory and complies with the Ph Eur general monograph for parenteral preparations. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for reference standards.

Container Closure System
Satisfactory specifications and certificates of analysis have been provided for the packaging components. All primary product packaging complies with Ph Eur requirements.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years with no special storage conditions has been set, which is satisfactory. After reconstitution the solution must be used within 24 hours when stored at 2-8°C. Solution intended for parenteral administration should be used immediately.

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

PRECLINICAL ASSESSMENT

These are applications for generic products of Vancocin CP (Flynn Pharma Ltd), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

INTRODUCTION AND BACKGROUND

These are national abridged applications for Marketing Authorisations for Vancomycin Powder for Solution for Infusion, in doses of 500mg and 1g, submitted by Wockhardt UK Ltd under EC Article 10.1 of Directive 2001/83/EEC. The applicant is claiming that the products are generic products of the UK innovator product Vancocin CP (Flynn Pharma) first authorised by Eli Lilly & Company Ltd on 18 April 1990.

There is no paediatric development programme for this medical product.

Vancomycin is a glycopeptide antibiotic obtained from *Streptomyces orientalis* (now known as *Amycolatopsis oreintalis)* in 1956. Vancomycin is a dry off-white powder, which produces a light yellow to light brown transparent solution when reconstituted in water, with pH of 2.5 to 4.5. By parenteral route it is the antibiotic of choice only for the treatment of infections caused by Gram-positive cocci, such as methicillin resistant beta-lactam resistant staphylococci or patients with allergies to beta-lactam antibiotics. Vancomycin was a major therapeutic agent because of its efficacy against penicillin resistant staphylococci until its extensive use was reduced due to the development of semi-synthetic anti-staphylococci penicillins (methicillin) and the toxicity associated with the use of vancomycin preparations. However, there has been renewed interest in recent years due to the increase in nosocomial infections caused by Gram-positive bacteria, which now represents 50% of all infections.

INDICATIONS

The proposed indications are:

> Vancomycin is indicated in potentially life-threatening infections which cannot be treated with other effective, less toxic antimicrobial drugs, including the penicillins and cephalosporins.
>
> Vancomycin is useful in the therapy of severe staphylococcal infections in patients who cannot receive or who have failed to respond to the penicillins and cephalosporins, or who have infections with staphylococci resistant to other antibiotics.
>
> Vancomycin is used in the treatment of endocarditis and as prophylaxis against endocarditis in patients at risk from dental or surgical procedures.
>
> Its effectiveness has been documented in other infections due to staphylococci, including osteomyelitis, pneumonia, septicaemia and soft tissue infections.
>
> Vancomycin may be used orally for the treatment of staphylococcal enterocolitis and pseudomembranous colitis due to *Clostridium difficile*. Parenteral administration of vancomycin is not effective for these indications. Intravenous administration may be used concomitantly if required.

These are considered satisfactory and are consistent with the SPC for Vancocin CP.

DOSE AND DOSE SCHEDULE

The proposed dose and dose schedule for this product to be used for the above indications are the same as for Vancocin CP.

TOXICOLOGY

No new toxicology data were presented in this application and none are required.

CLINICAL PHARMACOLOGY

In accordance with Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), point 5.1.6, a bioequivalence study is not required if the product is an aqueous intravenous solution containing the same active substance in the same concentration as the currently licensed product.

The products are qualitatively identical to the UK reference product and are presented as the same dosage form (for administration by the same route).

CLINICAL EFFICACY

No new efficacy data were presented in this application and none are required.

CLINICAL SAFETY

No new safety data were presented in this application and none are required.

CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified medical doctor. It is an adequate summary of the clinical data provided in the dossier.

SPC, PIL and LABELS

The SPC, PIL and labels are acceptable.

CONCLUSIONS

Marketing Authorisations should be granted for these products.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

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

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

A bioequivalence study was not required for this product due to the route of administration. The applicant has demonstrated that Vancomycin 500mg & 1g Powder for Solution for Infusion is a generic product of Vancocin CP (Flynn Pharma Ltd).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Vancocin CP.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with vancomycin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

VANCOMYCIN 500MG POWDER FOR SOLUTION FOR INFUSION
PL 20851/0007

VANCOMYCIN 1G POWDER FOR SOLUTION FOR INFUSION
PL 20851/0008

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the Marketing Authorisation applications on 05 May 2005.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 30 August 2005.
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 09 February 2006, and further information relating to the quality dossiers on 02 November 2005, 11 August 2006, 28 February 2007, 10 July 2007 and 20 August 2007.
4	The applicant responded to the MHRA's requests, providing further information on 20 February 2006 for the clinical sections, and again on 11 April 2006, 07 August 2006, 01 December 2006, 26 July 2007 and 17 September 2007 for the quality sections.
5	The applications were determined on 28 September 2007.

VANCOMYCIN 500MG POWDER FOR SOLUTION FOR INFUSION
PL 20851/0007

VANCOMYCIN 1G POWDER FOR SOLUTION FOR INFUSION
PL 20851/0008

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vancomycin 500mg Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For full list of excipients, see 6.1

3 PHARMACEUTICAL FORM

Powder for solution for intravenous infusion

Powder for solution for oral use

'A white to cream coloured porous cake'

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vancomycin is indicated in potentially life-threatening infections which cannot be treated with other effective, less toxic antimicrobial drugs, including the penicillins and cephalosporins.

Vancomycin is useful in the therapy of severe staphylococcal infections in patients who cannot receive or who have failed to respond to the penicillins and cephalosporins, or who have infections with staphylococci resistant to other antibiotics.

Vancomycin is used in the treatment of endocarditis and as prophylaxis against endocarditis in patients at risk from dental or surgical procedures.

Its effectiveness has been documented in other infections due to staphylococci, including osteomyelitis, pneumonia, septicaemia and soft tissue infections.

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

4.2 Posology and method of administration

For intravenous infusion and oral use only and not for intramuscular administration.

Please refer to Section 6.6 for full details on preparation.

Infusion-related adverse events are related to both concentration and rate of administration of vancomycin.

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.

Intravenous infusion in patients with normal renal function

Adults: The usual intravenous dose is 500mg every six hours or 1g every 12 hours, in sodium chloride intravenous infusion or 5% dextrose intravenous infusion Each dose should be administered at no more than 10mg/min. Other patient factors, such as age, obesity or pregnancy, may call for modification of the usual daily dose. The majority of patients with infections caused by organisms sensitive to the antibiotic show a therapeutic response within 48-72 hours. The total duration of therapy is determined by the type and severity of the infection and the clinical response of the patient. In staphylococcal endocarditis, treatment for three weeks or longer is recommended.

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

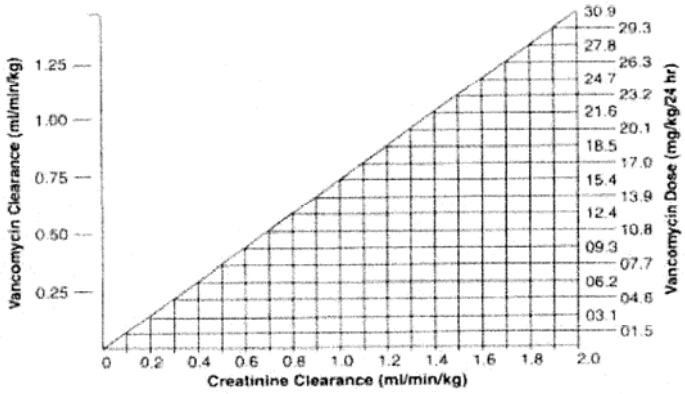
The elderly: Dosage reduction may be necessary to a greater extent than expected because of decreasing renal function (see below). Monitor auditory function – see Section 4.4 Special warnings and precautions for use.

Children: 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.

In neonates and young infants, the total daily dosage may be lower. An initial dose of 15mg/kg is suggested, followed by 10mg/kg every 12 hours in the first week of life and every eight hours thereafter until one month of age. Each dose should be administered over 60 minutes. Close monitoring of serum vancomycin concentrations may be warranted in these patients.

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 microbiological assay, radioimmunoassay, fluorescence polarisation immunoassay, fluorescence immunoassay or high-pressure liquid chromatography. The following nomogram, based on creatinine clearance values, is provided:



Dosage nomogram for vancomycin in patients with impaired renal function

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.

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

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.

Oral administration

The contents of vials for parenteral administration may be used.

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

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

Common flavouring syrups may be added to the solution at the time of administration to improve the taste.

4.3 Contraindications

Hypersensitivity to vancomycin.

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. 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).

Some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption of oral vancomycin and, therefore, may be at risk for the development of adverse reactions associated with the parenteral administration of vancomycin. The risk is greater in patients with renal impairment. It should be noted that the total systemic and renal clearances of vancomycin are reduced in the elderly.

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 histamine-like 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

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.

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.

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 neurotoxic or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymixin B, colistin, viomycin or cisplatin, when indicated, requires careful monitoring.

4.6 Pregnancy and lactation

Use in pregnancy: Teratology studies have been performed at five times the human dose in rats and three times the human dose in rabbits, and have revealed no evidence of harm to the foetus due to vancomycin. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin hydrochloride on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancomycin hydrochloride was found in cord blood. No sensorineural hearing loss or nephrotoxicity attributable to vancomycin was noted. One infant, whose mother received vancomycin in the third trimester, experienced conductive hearing loss that was not attributable to vancomycin. Because vancomycin was administered only in the second and third trimesters, it is not known whether it causes foetal harm. Vancomycin should be given in pregnancy only if clearly needed and blood levels should be monitored carefully to minimise the risk of foetal toxicity. It has been reported, however, that pregnant patients may require significantly increased doses of vancomycin to achieve therapeutic serum concentrations.

Use in nursing mothers: Vancomycin hydrochloride is excreted in human milk. Caution should be exercised when vancomycin is administered to a nursing woman. It is unlikely that a nursing infant can absorb a significant amount of vancomycin from its gastro-intestinal tract.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Infusion-related events: During or soon after rapid infusion of vancomycin, patients may develop anaphylactoid reactions including hypotension, wheezing, dyspnoea, urticaria or pruritus. Rapid infusion may also cause flushing of the upper-body ('red-neck syndrome') or pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may persist for several hours. In animal studies, hypotension and bradycardia occurred in animals given large doses of vancomycin at high concentrations and rates. Such events are infrequent if vancomycin is given by slow infusion over 60 minutes. In studies of normal volunteers, infusion-related events did not occur when vancomycin was administered at a rate of 10mg/min or less.

Nephrotoxicity: Rarely, renal failure, principally manifested by increased serum creatinine or blood urea concentrations, have been observed, especially in patients given large doses of intravenously administered vancomycin. Rare cases of interstitial nephritis have been reported. Most occurred in patients who were given aminoglycosides concomitantly or who had pre-existing kidney dysfunction. When vancomycin was discontinued, azotaemia resolved in most patients.

Ototoxicity: Hearing loss associated with intravenously administered vancomycin has been reported. Most of these patients had kidney dysfunction, pre-existing hearing loss, or concomitant treatment with an ototoxic drug. Vertigo, dizziness and tinnitus have been reported rarely.

Haematological: Reversible neutropenia, usually starting one week or more after onset of intravenous therapy or after a total dose of more than 25g. Neutropenia appears to be promptly reversible when vancomycin is discontinued. Thrombocytopenia has rarely been reported. Reversible agranulocytosis (less than 500 granulocytes per mm^3) has been reported rarely, although causality has not been established.

Miscellaneous: Phlebitis, hypersensitivity reactions, anaphylaxis, nausea, chills, drug fever, eosinophilia, rashes (including exfoliative dermatitis) and rare cases of vasculitis. Vancomycin has been associated with the bullous eruption disorders Stevens-Johnson syndrome, toxic epidermal necrolysis and linear IgA bullous dermatosis. If a bullous disorder is suspected, the drug should be discontinued and specialist dermatological assessment should be carried out.

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

ATC Code: JO1X A (Glycopeptide antibacterial).

Vancomycin is a glycopeptide antibiotic derived from Nocardia orientalis (formerly Streptomyces orientalis), and is active against many Gram-positive bacteria, including Staphylococcus aureus, Staph. epidermidis, alpha and beta haemolytic streptococci, group D streptococci, corynebacteria and clostridia.

5.2 Pharmacokinetic properties

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

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Vancomycin solution has a low pH that may cause chemical or physical instability when it is mixed with other compounds.

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

6.3 Shelf life

Unopened - 36 months

Reconstituted solution intended for parenteral administration

Physical and chemical stability have been demonstrated for a period of 24 hours when stored at 2° to 8°C.

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

Prior to administration, parenteral drug products should be inspected visually for particulate matter and discolouration whenever solution or container permits.

Reconstituted solution intended for oral administration

Solution intended for oral administration may be stored in a refrigerator (2° to 8°C) for up to 24 hours.

6.4 Special precautions for storage

Unopened: Do not store above 25°C

After reconstitution: Store at 2-8^{o}C (see 6.3 Shelf Life).

6.5 Nature and contents of container

Packs* of one, two, five or ten Type II colourless glass 10ml vials stoppered with Type I rubber stopper, capped with a flip-off cap.

*Not all pack sizes may be marketed

6.6 Special precautions for disposal

Preparation of solution: At the time of use, add 10ml of water for injections to the 500mg vial. Vials reconstituted in this manner will give a solution of 50mg/ml.

The reconstituted solution is clear and colourless.

Further dilution is required. Read instructions which follow:

1. Intermittent infusion is the preferred method of administration. Reconstituted solutions containing 500mg vancomycin must be diluted with at least 100ml diluent. 0.9% sodium chloride intravenous infusion or 5% dextrose intravenous infusion are suitable diluents. The desired dose should be given by intravenous infusion over a period of at least 60 minutes. If administered over a shorter period of time or in higher concentrations, there is the possibility of inducing marked hypotension in addition to thrombophlebitis. Rapid administration may also produce flushing and a transient rash over the neck and shoulders.

2. Continuous infusion (should be used only when intermittent infusion is not feasible). 1-2g can be added to a sufficiently large volume of sodium chloride intravenous infusion or 5% dextrose intravenous infusion to permit the desired daily dose to be administered slowly by intravenous drip over a 24 hour period.

3. Oral administration

The contents of vials for parenteral administration may be used.

Common flavouring syrups may be added to the solution at the time of administration to improve the taste.

Vials are for single use only and any unused product or waste material should be disposed of immediately in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited

Ash Road North

Wrexham LL13 9UF

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

Pl 20851/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/09/2007

10 DATE OF REVISION OF THE TEXT

28/09/2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vancomycin 1g Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains vancomycin 1g* (equivalent to 1 000 000* IU) as vancomycin hydrochloride

For full list of excipients, see 6.1

3 PHARMACEUTICAL FORM

Powder for solution for intravenous infusion

Powder for solution for oral use

'A white to cream coloured porous cake'

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vancomycin is indicated in potentially life-threatening infections which cannot be treated with other effective, less toxic antimicrobial drugs, including the penicillins and cephalosporins.

Vancomycin is useful in the therapy of severe staphylococcal infections in patients who cannot receive or who have failed to respond to the penicillins and cephalosporins, or who have infections with staphylococci resistant to other antibiotics.

Vancomycin is used in the treatment of endocarditis and as prophylaxis against endocarditis in patients at risk from dental or surgical procedures.

Its effectiveness has been documented in other infections due to staphylococci, including osteomyelitis, pneumonia, septicaemia and soft tissue infections.

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

4.2 Posology and method of administration

For intravenous infusion and oral use only and not for intramuscular administration.

Please refer to Section 6.6 for full details on preparation.

Infusion-related adverse events are related to both concentration and rate of administration of vancomycin.

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.

Intravenous infusion in patients with normal renal function

Adults: The usual intravenous dose is 500mg every six hours or 1g every 12 hours, in sodium chloride intravenous infusion or 5% dextrose intravenous infusion. Each dose should be administered at no more than 10mg/min. Other patient factors, such as age, obesity or pregnancy, may call for modification of the usual daily dose. The majority of patients with infections caused by organisms sensitive to the antibiotic show a therapeutic response within 48-72 hours. The total duration of therapy is determined by the type and severity of the infection and the clinical response of the patient. In staphylococcal endocarditis, treatment for three weeks or longer is recommended.

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

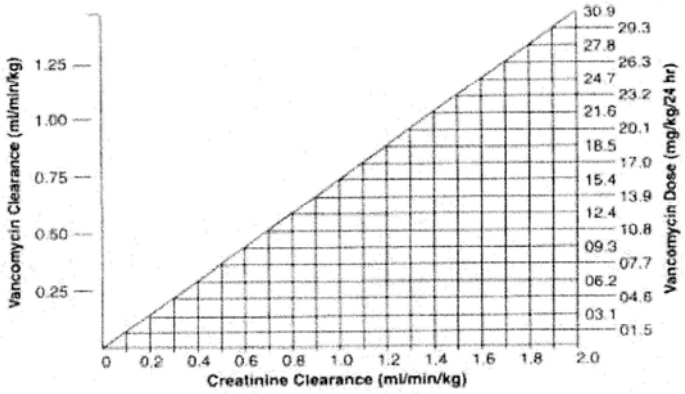
The elderly: Dosage reduction may be necessary to a greater extent than expected because of decreasing renal function (see below). Monitor auditory function - see Section 4.4.Special warnings and precautions for use.

Children: 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.

In neonates and young infants, the total daily dosage may be lower. An initial dose of 15mg/kg is suggested, followed by 10mg/kg every 12 hours in the first week of life and every eight hours thereafter until one month of age. Each dose should be administered over 60 minutes. Close monitoring of serum vancomycin concentrations may be warranted in these patients.

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 microbiological assay, radioimmunoassay, fluorescence polarisation immunoassay, fluorescence immunoassay or high-pressure liquid chromatography. The following nomogram, based on creatinine clearance values, is provided:



Dosage nomogram for vancomycin in patients with impaired renal function

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.

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

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.

Oral administration

The contents of vials for parenteral administration may be used.

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

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

Common flavouring syrups may be added to the solution at the time of administration to improve the taste.

4.3 Contraindications

Hypersensitivity to vancomycin.

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. 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).

Some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption of oral vancomycin and, therefore, may be at risk for the development of adverse reactions associated with the parenteral administration of vancomycin. The risk is greater in patients with renal impairment. It should be noted that the total systemic and renal clearances of vancomycin are reduced in the elderly.

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 histamine-like 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 Section 4.2 Posology and method of administration).

Precautions

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.

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.

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 neurotoxic or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymixin B, colistin, viomycin or cisplatin, when indicated, requires careful monitoring.

4.6 Pregnancy and lactation

Use in pregnancy: Teratology studies have been performed at five times the human dose in rats and three times the human dose in rabbits, and have revealed no evidence of harm to the foetus due to vancomycin. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin hydrochloride on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancomycin hydrochloride was found in cord blood. No sensorineural hearing loss or nephrotoxicity attributable to vancomycin was noted. One infant, whose mother received vancomycin in the third trimester, experienced conductive hearing loss that was not attributable to vancomycin. Because vancomycin was administered only in the second and third trimesters, it is not known whether it causes foetal harm. Vancomycin should be given in pregnancy only if clearly needed and blood levels should be monitored carefully to minimise the risk of foetal toxicity. It has been reported, however, that pregnant patients may require significantly increased doses of vancomycin to achieve therapeutic serum concentrations.

Use in nursing mothers: Vancomycin hydrochloride is excreted in human milk. Caution should be exercised when vancomycin is administered to a nursing woman. It is unlikely that a nursing infant can absorb a significant amount of vancomycin from its gastro-intestinal tract.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Infusion-related events: During or soon after rapid infusion of vancomycin, patients may develop anaphylactoid reactions including hypotension, wheezing, dyspnoea, urticaria or pruritus. Rapid infusion may also cause flushing of the upper-body ('red-neck syndrome') or pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may persist for several hours. In animal studies, hypotension and bradycardia occurred in animals given large doses of vancomycin at high concentrations and rates. Such events are infrequent if vancomycin is given by slow infusion over 60 minutes. In studies of normal volunteers, infusion-related events did not occur when vancomycin was administered at a rate of 10mg/min or less.

Nephrotoxicity: Rarely, renal failure, principally manifested by increased serum creatinine or blood urea concentrations, have been observed, especially in patients given large doses of intravenously administered vancomycin. Rare cases of interstitial nephritis have been reported. Most occurred in patients who were given aminoglycosides concomitantly or who had pre-existing kidney dysfunction. When vancomycin was discontinued, azotaemia resolved in most patients.

Ototoxicity: Hearing loss associated with intravenously administered vancomycin has been reported. Most of these patients had kidney dysfunction, pre-existing hearing loss, or concomitant treatment with an ototoxic drug. Vertigo, dizziness and tinnitus have been reported rarely.

Haematological: Reversible neutropenia, usually starting one week or more after onset of intravenous therapy or after a total dose of more than 25g. Neutropenia appears to be promptly reversible when vancomycin is discontinued. Thrombocytopenia has rarely been reported. Reversible agranulocytosis (less than 500 granulocytes per mm^3) has been reported rarely, although causality has not been established.

Miscellaneous: Phlebitis, hypersensitivity reactions, anaphylaxis, nausea, chills, drug fever, eosinophilia, rashes (including exfoliative dermatitis) and rare cases of vasculitis. Vancomycin has been associated with the bullous eruption disorders, Stevens-Johnson syndrome, toxic epidermal necrolysis and linear IgA bullous dermatosis. If a bullous disorder is suspected, the drug should be discontinued and specialist dermatological assessment should be carried out.

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

ATC Code: JO1X A (Glycopeptide antibacterial)

Vancomycin is a glycopeptide antibiotic derived from *Nocardia orientalis* (formerly *Streptomyces orientalis*), and is active against many Gram-positive bacteria, including *Staphylococcus aureus, Staph. epidermidis,* alpha and beta haemolytic streptococci, group D streptococci, corynebacteria and clostridia.

5.2 Pharmacokinetic properties

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

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Vancomycin solution has a low pH that may cause chemical or physical instability when it is mixed with other compounds.

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

6.3 Shelf life

Unopened - 36 months

Reconstituted solution intended for parenteral administration

Physical and chemical stability have been demonstrated for a period of 24 hours when stored at 2° to 8°C.

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

Prior to administration, parenteral drug products should be inspected visually for particulate matter and discolouration whenever solution or container permits.

Reconstituted solution intended for oral administration

Solution intended for oral administration may be stored in a refrigerator (2° to 8°C) for up to 24 hours.

6.4 Special precautions for storage

Unopened: Do not store above 25°C

After reconstitution: Store at 2-8^{o}C (see 6.3 Shelf Life).

6.5 Nature and contents of container

Packs* of one, two, five or ten Type II colourless glass 20ml vials stoppered with Type I rubber stopper, capped with a flip-off cap.

*Not all pack sizes may be marketed

6.6 Special precautions for disposal

Preparation of solution: At the time of use, add 20ml of water for injections to the 1g vial. Vials reconstituted in this manner will give a solution of 50mg/ml.

The reconstituted solution is clear and colourless.

Further dilution is required. Read instructions which follow:

1. Intermittent infusion is the preferred method of administration. Reconstituted solutions containing 1g vancomycin must be diluted with at least 200ml diluent. 0.9% sodium chloride intravenous infusion or 5% dextrose intravenous infusion are suitable diluents. The desired dose should be given by intravenous infusion over a period of at least 60 minutes. If administered over a shorter period of time or in higher concentrations, there is the possibility of inducing marked hypotension in addition to thrombophlebitis. Rapid administration may also produce flushing and a transient rash over the neck and shoulders.

2. Continuous infusion (should be used only when intermittent infusion is not feasible). 1-2g can be added to a sufficiently large volume of sodium chloride intravenous infusion or 5% dextrose intravenous infusion to permit the desired daily dose to be administered slowly by intravenous drip over a 24 hour period.

3. Oral administration

The contents of vials for parenteral administration may be used.

Common flavouring syrups may be added to the solution at the time of administration to improve the taste.

Vials are for single use only and any unused product or waste material should be disposed of immediately in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited

Ash Road North

Wrexham LL13 9UF

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

Pl 20851/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/09/2007

10 DATE OF REVISION OF THE TEXT

28/09/2007

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET
VANCOMYCIN 500MG and 1G POWDER FOR SOLUTION FOR INFUSION
Vancomycin hydrochloride powder for solution for intravenous infusion or powder for solution for oral use

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 further questions, please ask your doctor or nurse.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

The name of your medicine is vancomycin 500mg or 1g powder for solution for infusion.

Each vial contains the active substance vancomycin (as vancomycin hydrochloride), as a powder for solution for intravenous infusion or powder for solution for oral use. There are no other ingredients included in the product.

Vancomycin powder for solution for infusion comes in a glass vial with a rubber stopper capped with a flip-off cap. The powder is a white to cream coloured solid. Each 500mg vial contains 500,000IU vancomycin. Each 1g vial contains 1,000,000IU vancomycin.

It is available in packs of one, two, five or ten vials. Not all pack sizes may be marketed.

Manufactured by Laboratorio Reig Jofré, Gran Capitán, nº 10, 08970 Sant Joan Despí, Barcelona, Spain. The Marketing Authorisation holder is Wockhardt UK Limited, Ash Road North, Wrexham LL13 9UF, UK (PL 20851/0007 and PL 20851/0008).

1. WHAT VANCOMYCIN POWDER FOR SOLUTION FOR INFUSION IS AND WHAT IT IS USED FOR

Vancomycin is an antibiotic.

Vancomycin works by killing some types of bacteria that can cause various sorts of infections in people. Like all antibiotics, vancomycin is only able to kill some types of bacteria so it is only suitable for treating some types of infection. It is sometimes necessary to give another antibiotic at the same time as vancomycin so as to be sure that all the types of bacteria causing an infection will be killed.

Vancomycin can be used to treat infections caused by bacteria called 'staphylococci' which may be difficult to cure with penicillin or other antibiotics called cephalosporins. It is sometimes given before an operation to prevent you getting an infection.

If you are given this medicine as a liquid to swallow then it is being used to treat severe diarrhoea.

2. BEFORE YOU ARE GIVEN VANCOMYCIN POWDER FOR SOLUTION FOR INFUSION

Vancomycin is not suitable for everyone.

You should not be given vancomycin if the answer to the following question is YES for you (or for a child if you are the legal guardian of the child). If you are not sure about anything, ask your doctor or nurse before you are given vancomycin:

- Have you ever had an allergic reaction to vancomycin?

Tell your doctor if you have ever had or think you may have had any sort of allergic reaction to any antibiotic in the past. Your doctor will advise you if you can still have vancomycin.

Take special care

Vancomycin may or may not be suitable for you if the answer to any of the following questions is YES. Your doctor will advise you if vancomycin is right for you.

- Are you hard of hearing? Your doctor may test your hearing during treatment, particularly if you are elderly.
- Have you ever been told that your kidneys do not work very well or are you having any sort of treatment (like dialysis) for kidney failure? You may still be given vancomycin but you may need a lower dose.
- Have you ever had inflammation of the large bowel, called colitis or any other severe disease affecting your gut?
- Are you going to have an operation? If you are then tell your doctor that you have been given vancomycin.

Your doctor may carry out blood tests during your treatment, particularly if you are elderly, a baby or child, pregnant, have kidney problems, or are being given Vancomycin for Infusion by mouth for severe bowel infection (colitis).

Pregnancy and breastfeeding

- Are you or do you think you might be pregnant? Vancomycin is not known to harm the unborn child but, like all medicines, it will only be given to a pregnant woman if it is really needed.
- Are you breastfeeding? Small amounts of vancomycin enter the milk. If you cannot stop breastfeeding while you have vancomycin, you should watch your baby carefully for any signs of diarrhoea or any other illness and tell your doctor if you notice anything wrong.

Driving and operating machinery

Vancomycin should not affect your ability to drive or operate machinery.

Taking other medicines

Taking another medicine while you are being given vancomycin powder for solution for infusion can affect how it or the other medicine works. Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those you may have bought yourself without a prescription. Please check with your doctor if you are taking

---

THE FOLLOWING INFORMATION IS INTENDED FOR HEALTHCARE PROFESSIONALS ONLY:

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vancomycin 500mg Powder for Solution for Infusion
Vancomycin 1g Powder for Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vancomycin 500mg Powder for Solution for Infusion - Each vial contains vancomycin 500mg* (equivalent to 500 000* IU) as vancomycin hydrochloride
Vancomycin 1g Powder for Solution for Infusion - Each vial contains vancomycin 1g* (equivalent to 1 000 000* IU) as vancomycin hydrochloride
For full list of excipients, see 6.1

3. PHARMACEUTICAL FORM

Powder for solution for intravenous infusion
Powder for solution for oral use
'A white to cream coloured porous cake'

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Vancomycin is indicated in potentially life-threatening infections which cannot be treated with other effective, less toxic antimicrobial drugs, including the penicillins and cephalosporins.

Please refer to Section 6.6 for full details on preparation.

Vancomycin is useful in the therapy of severe staphylococcal infections in patients who cannot receive or who have failed to respond to the penicillins and cephalosporins, or who have infections with staphylococci resistant to other antibiotics.

Vancomycin is used in the treatment of endocarditis and as prophylaxis against endocarditis in patients at risk from dental or surgical procedures.

Its effectiveness has been documented in other infections due to staphylococci, including osteomyelitis, pneumonia, septicaemia and soft tissue infections.

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

4.2. Posology and method of administration

For intravenous infusion and oral use only and not for intramuscular administration.

Infusion-related adverse events are related to both concentration and rate of administration of vancomycin.

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.

Intravenous infusion in patients with normal renal function

Adults: The usual intravenous dose is 500mg every six hours or 1g every 12 hours, in sodium chloride intravenous infusion or 5% dextrose intravenous infusion. Each dose should be administered at no more than 10mg/min. Other patient factors, such as age, obesity or pregnancy, may call for modification of the usual daily dose. The majority of patients with infections caused by organisms sensitive to the antibiotic show a therapeutic response within 48-72 hours. The total duration of therapy is determined by the type and severity of the infection and the clinical response of the patient. In staphylococcal endocarditis, treatment for three weeks or longer is recommended.

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). Monitor auditory function - see Section 4.4. Special warnings and precautions for use.

Children: 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.

In neonates and young infants, the total daily dosage may be lower. An initial dose of 15mg/kg is suggested, followed by 10mg/kg every 12 hours in the first week of life and every eight hours thereafter until one month of age. Each dose should be administered over 60 minutes. Close monitoring of serum vancomycin concentrations may be warranted in these patients.

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 microbiological assay, radioimmunoassay, fluorescence polarisation immunoassay, fluorescence immunoassay or high-pressure liquid chromatography. The following nomogram, based on creatinine clearance values, is provided:

Dosage nomogram for vancomycin in patients with impaired renal function

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.

For instructions on the preparation of solutions before administration, see section 6.6.

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.

Oral administration

The contents of vials for parenteral administration may be used.

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

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

Common flavouring syrups may be added to the solution at the time of administration to improve the taste.

4.3. Contraindications

Hypersensitivity to vancomycin.

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. 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).

Some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption of oral vancomycin and, therefore, may be at risk for the development of adverse reactions associated with the parenteral administration of vancomycin. The risk is greater in patients with renal impairment. It should be noted that the total systemic and renal clearances of vancomycin are reduced in the elderly.

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 histamine-like 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

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.

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

any of the following (or any other medication):
- Anaesthetics
- Certain other antibiotics, used to treat infections: amphotericin B, aminoglycosides, bacitracin, polymixin B, colistin
- Cisplatin, used to treat some tumours

3. HOW VANCOMYCIN POWDER FOR SOLUTION FOR INFUSION IS GIVEN

Vancomycin will be given by a doctor or nurse by injection into a 'drip' into a vein (intravenous infusion) over a period of time which is usually an hour. Vancomycin may also be given by mouth as a solution.

Vancomycin powder for solution for infusion is supplied as a powder, so before it can be given it must be diluted and made into a solution. A doctor, nurse or pharmacist will do this. Only some types of solutions can be used to mix up the powder ready for use. Your doctor, nurse or pharmacist will make sure that only the right types are used.

The usual dose of vancomycin given as an infusion in adults is 500mg every six hours or 1g every 12 hours.

The usual dose of vancomycin given as an infusion in children is 10mg for every kilogram of bodyweight every six hours.

The usual dose of vancomycin given by mouth in adults is 500mg a day, divided into more than one dose, for seven to ten days.

The usual dose of vancomycin given by mouth in children is 40mg for every kilogram of bodyweight each day, divided into three to four doses, for seven to ten days.

Dosage may be reduced if you are elderly, a baby or have kidney problems, and increased if you are pregnant.

Since a doctor or nurse will give you vancomycin, it is very unlikely that you will be given too much or that you will miss a dose. If you think you may have missed a dose or have received too much medicine please tell your doctor or nurse.

As with all antibiotics it is important that you are given vancomycin for infusion regularly and that the full course is completed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, vancomycin can have side effects.

Vancomycin can cause an allergic reaction, with low blood pressure, breathing difficulties and feeling wheezy, rash, and itchiness. Rarely, a more severe allergic reaction may be associated with an extensive rash, feeling unwell, headache, fever, pain in the joints and sore eyes. If you think you are having an allergic reaction, you must tell your doctor or nurse immediately.

Flushing of the neck and chest and pain in the chest and back muscles may occur if vancomycin is given into a vein too quickly.

Pain and irritation of the veins can occur at the site of injection.

Vancomycin can upset the normal working of the kidneys during treatment and this is usually picked up by abnormal blood test results.

Vancomycin can also reduce the numbers of different cells in the blood (symptoms can include tiredness, sore throat, mouth ulcers, new infections and easy bruising or bleeding).

Other side effects include deafness, dizziness, giddiness, ringing in the ears, feeling sick, and chills.

If you experience any other side effects that are not mentioned above, or if you feel unwell or have any unusual discomfort you don't understand, tell your doctor or nurse as soon as possible.

5. STORING VANCOMYCIN POWDER FOR SOLUTION FOR INFUSION

Vancomycin must be kept out of the reach and sight of children.

Your doctor, nurse or pharmacist will usually be responsible for storing and preparing vancomycin before use and for checking that the vials have not passed their expiry date.

The vials will be stored below 25°C. Made-up solutions may be stored for up to 24 hours in a refrigerator (2°C - 8°C).

An expiry date will be stated on the carton and label. Do not use the medicine after the expiry date. This product is for single use only and any out of date or unused vancomycin for infusion should be returned to your doctor or pharmacist for disposal.

Other formats:

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge:

0800 198 5000 (UK Only)

Please be ready to give the following information:

Product Name	Reference Number
Vancomycin 500mg Powder for Solution for Infusion	20851/0007
Vancomycin 1g Powder for Solution for Infusion	20851/0008

Date of Leaflet preparation: May 2007

WOCKHARDT®

103385/1

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.

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 neurotoxic or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymixin B, colistin, viomycin or cisplatin, when indicated, requires careful monitoring.

4.6. Pregnancy and lactation

Use in pregnancy: Teratology studies have been performed at five times the human dose in rats and three times the human dose in rabbits, and have revealed no evidence of harm to the foetus due to vancomycin. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin hydrochloride on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancomycin hydrochloride was found in cord blood. No sensorineural hearing loss or nephrotoxicity attributable to vancomycin was noted. One infant, whose mother received vancomycin in the third trimester, experienced conductive hearing loss that was not attributable to vancomycin. Because vancomycin was administered only in the second and third trimesters, it is not known whether it causes foetal harm. Vancomycin should be given in pregnancy only if clearly needed and blood levels should be monitored carefully to minimise the risk of foetal toxicity. It has been reported, however, that pregnant patients may require significantly increased doses of vancomycin to achieve therapeutic serum concentrations.

Use in nursing mothers: Vancomycin hydrochloride is excreted in human milk. Caution should be exercised when vancomycin is administered to a nursing woman. It is unlikely that a nursing infant can absorb a significant amount of vancomycin from its gastro-intestinal tract.

4.7. Effects on ability to drive and use machines

Not applicable

4.8. Undesirable effects

Infusion-related events: During or soon after rapid infusion of vancomycin, patients may develop anaphylactoid reactions including hypotension, wheezing, dyspnoea, urticaria or pruritus. Rapid infusion may also cause flushing of the upper-body ('red-neck syndrome') or pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may persist for several hours. In animal studies, hypotension and bradycardia occurred in animals given large doses of vancomycin at high concentrations and rates. Such events are infrequent if vancomycin is given by slow infusion over 60 minutes. In studies of normal volunteers, infusion-related events did not occur when vancomycin was administered at a rate of 10mg/min or less.

Nephrotoxicity: Rarely, renal failure, principally manifested by increased serum creatinine or blood urea concentrations, have been observed, especially in patients given large doses of intravenously administered vancomycin. Rare cases of interstitial nephritis have been reported. Most occurred in patients who were given aminoglycosides concomitantly or who had pre-existing kidney dysfunction. When vancomycin was discontinued, azotaemia resolved in most patients.

Ototoxicity: Hearing loss associated with intravenously administered vancomycin has been reported. Most of these patients had kidney dysfunction, pre-existing hearing loss, or concomitant treatment with an ototoxic drug. Vertigo, dizziness and tinnitus have been reported rarely.

Haematological: Reversible neutropenia, usually starting one week or more after onset of intravenous therapy or after a total dose of more than 25g. Neutropenia appears to be promptly reversible when vancomycin is discontinued. Thrombocytopenia has rarely been reported. Reversible agranulocytosis (less than 500 granulocytes per mm^3) has been reported rarely, although causality has not been established.

Miscellaneous: Phlebitis, hypersensitivity reactions, anaphylaxis, nausea, chills, drug fever, eosinophilia, rashes (including exfoliative dermatitis) and rare cases of vasculitis. Vancomycin has been associated with the bullous eruption disorders Stevens-Johnson syndrome, toxic epidermal necrolysis and linear IgA bullous dermatosis. If a bullous disorder is suspected, the drug should be discontinued and specialist dermatological assessment should be carried out.

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

ATC Code: J01X A (Glycopeptide antibacterial).

Vancomycin is a glycopeptide antibiotic derived from Nocardia orientalis (formerly Streptomyces orientalis), and is active against many Gram-positive bacteria, including Staphylococcus aureus, Staph. epidermidis, alpha and beta haemolytic streptococci, group D streptococci, corynebacteria and clostridia.

5.2. Pharmacokinetic properties

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

5.3. Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

None

6.2. Incompatibilities

Vancomycin solution has a low pH that may cause chemical or physical instability when it is mixed with other compounds.

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

6.3. Shelf life

Unopened - 36 months

Reconstituted solution intended for parenteral administration

Physical and chemical stability have been demonstrated for a period of 24 hours when stored at 2 to 8°C.

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

Prior to administration, parenteral drug products should be inspected visually for particulate matter and discolouration whenever solution or container permits.

Reconstituted solution intended for oral administration

Solution intended for oral administration may be stored in a refrigerator (2 to 8°C) for up to 24 hours.

6.4. Special precautions for storage

Unopened: Do not store above 25°C

After reconstitution: Store at 2 to 8°C (see 6.3 Shelf Life).

6.5. Nature and contents of container

Vancomycin 500mg Powder for Infusion:-

Packs* of one, two, five or ten Type II colourless glass 10ml vials stoppered with Type I rubber stopper, capped with a flip-off cap.

Vancomycin 1g Powder for Infusion:-

Packs* of one, two, five or ten Type II colourless glass 20ml vials stoppered with Type I rubber stopper, capped with a flip-off cap.

*Not all pack sizes may be marketed

6.6. Special precautions for disposal

Preparation of solution: At the time of use, add 10ml of water for injections to the 500mg vial. And add 20ml of water for injections to the 1g vial. Vials reconstituted in this manner will give a solution of 50mg/ml.

The reconstituted solution is clear and colourless.

Further dilution is required. Read instructions which follow:

1. Intermittent infusion is the preferred method of administration. Reconstituted solutions containing 500mg vancomycin must be diluted with at least 100ml diluent. Reconstituted solutions containing 1g vancomycin must be diluted with at least 200ml diluent. 0.9% sodium chloride intravenous infusion or 5% dextrose intravenous infusion are suitable diluents. The desired dose should be given by intravenous infusion over a period of at least 60 minutes. If administered over a shorter period of time or in higher concentrations, there is the possibility of inducing marked hypotension in addition to thrombophlebitis. Rapid administration may also produce flushing and a transient rash over the neck and shoulders.
2. Continuous infusion (should be used only when intermittent infusion is not feasible). 1-2g can be added to a sufficiently large volume of sodium chloride intravenous infusion or 5% dextrose intravenous infusion to permit the desired daily dose to be administered slowly by intravenous drip over a 24 hour period.
3. Oral administration

   The contents of vials for parenteral administration may be used.

   Common flavouring syrups may be added to the solution at the time of administration to improve the taste.

Vials are for single use only and any unused product or waste material should be disposed of immediately in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited, Ash Road North, Wrexham LL13 9UF, United Kingdom

8. MARKETING AUTHORISATION NUMBER

Vancomycin 500mg Powder for Infusion - PL 20851/0007

Vancomycin 1g Powder for Infusion - PL 20851/0008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

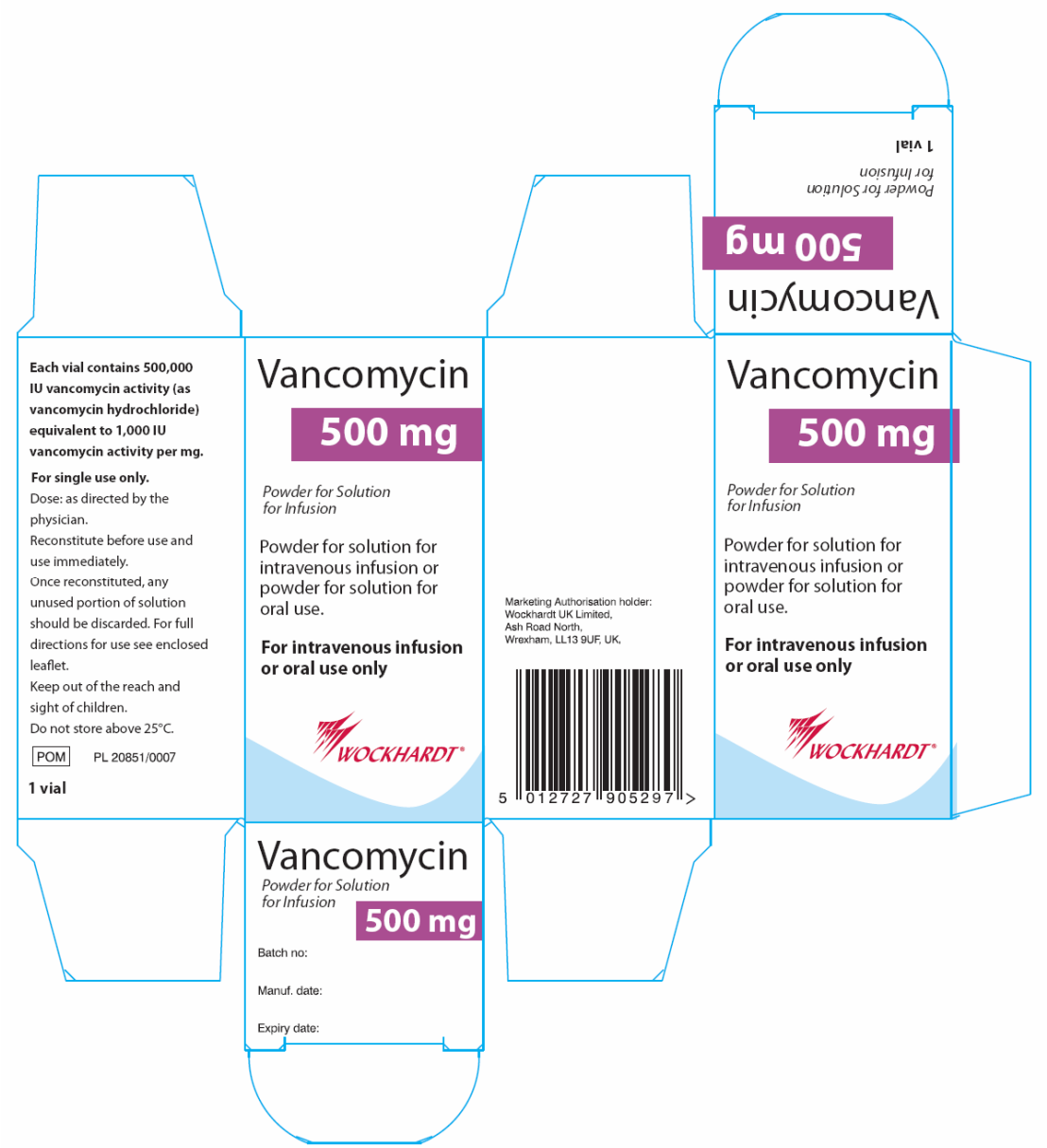
10. DATE OF REVISION OF THE TEXT

December 2006

103385/1

WOCKHARDT®

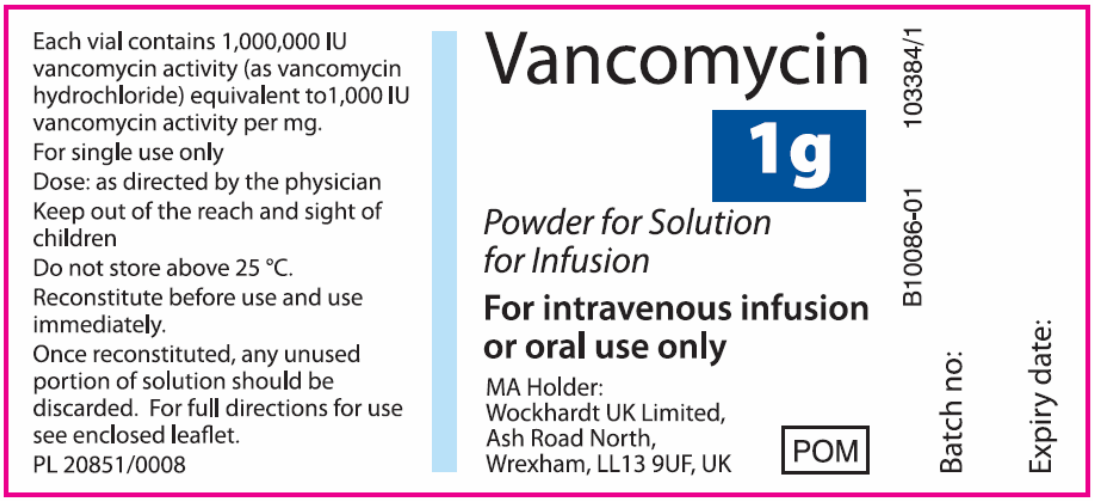
LABELLING



Each vial contains 500,000 IU vancomycin activity (as vancomycin hydrochloride) equivalent to1,000 IU vancomycin activity per mg.
For single use only
Dose: as directed by the physician
Keep out of the reach and sight of children
Do not store above 25 °C.
Reconstitute before use and use immediately.
Once reconstituted, any unused portion of solution should be discarded. For full directions for use see enclosed leaflet.
PL 20851/0007

Vancomycin
500mg
Powder for Solution for Infusion
For intravenous infusion or oral use only
MA Holder:
Wockhardt UK Limited,
Ash Road North,
Wrexham, LL13 9UF, UK
POM
103387/1
Batch no:
Expiry date:


Each vial contains 1,000,000 IU vancomycin activity (as vancomycin hydrochloride) equivalent to 1,000 IU vancomycin activity per mg.
For single use only.
Dose: as directed by the physician.
Reconstitute before use and use immediately.
Once reconstituted, any unused portion of solution should be discarded. For full directions for use see enclosed leaflet.
Keep out of the reach and sight of children.
Do not store above 25˚C.
POM
PL 20851/0008
1 vial
Vancomycin
1g
Powder for Solution for Infusion
Powder for solution for intravenous infusion or powder for solution for oral use
For intravenous infusion or oral use only
WOCKHARDT
103383/1
Marketing Authorisation holder:
Wockhardt UK Limited,
Ash Road North,
Wrexham, LL13 9UF, UK.
5 012727 905280
Vancomycin
1g
Powder for Solution for Infusion
Batch no:
Manuf. date:
Expiry date:
Vancomycin
1g
Powder for Solution for Infusion
1 vial
103383/1
103383/1
103383/1
103383/1


Each vial contains 1,000,000 IU vancomycin activity (as vancomycin hydrochloride) equivalent to1,000 IU vancomycin activity per mg.
For single use only
Dose: as directed by the physician
Keep out of the reach and sight of children
Do not store above 25 °C.
Reconstitute before use and use immediately.
Once reconstituted, any unused portion of solution should be discarded. For full directions for use see enclosed leaflet.
PL 20851/0008
Vancomycin
1g
Powder for Solution for Infusion
For intravenous infusion or oral use only
MA Holder:
Wockhardt UK Limited,
Ash Road North,
Wrexham, LL13 9UF, UK
POM
B10086-01
103384/1
Batch no:
Expiry date: