VANCOMYCIN CAPSULES 125 MG

MODULE 2.5

CLINICAL OVERVIEW

[redacted]

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CONTENTS

Abbreviations:

AUC	Area Under the Curve
GIT	Gastro-intestinal tract
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin-Resistant *Staphylococcus aureus*
NF	National Formulary
PEG	Polyethylene Glycol
Ph. Eur.	European Pharmacopeia
RNA	Ribonucleic Acid
SPCs	Summaries of Product Characteristics

2.5.1 PRODUCT DEVELOPMENT RATIONALE

In anticipation of the patent expiry, the principle objective was to develop a generic product with formulation and pharmaceutical properties as close as possible to the original Innovator product.

The innovator product is marketed in [redacted] as Vancocin Matrigel Capsules 125 mg containing 125 mg Vancomycin base. Vancocin Matrigel Capsules are used orally for the treatment of staphylococcal enterocolitis and pseudomembranous colitis due to Clostridium difficile.

The proposed Vancomycin 125 mg Capsules also contain the same active ingredient and are indicated for the same therapeutic indications as the innovator product.

According to the Article 10.1 of European Directive 2001/83/EC, as amended, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.

A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product. The 'ten year rule' applies and, in accordance with these provisions, therefore, the Applicant has not conducted clinical studies in support of this Application.

Since Vancomycin is expected to have its pharmacological action within GIT for the said indication, it is not significantly absorbed from the normal gastrointestinal tract (i.e. it acts locally in GIT). Section 5.1.8 of the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98, EMEA 2001) describes exemption from in vivo bioequivalence studies for locally acting drug (after oral, nasal, inhalation, ocular, dermal, rectal, vaginal, etc. administration). Thus, in accordance with this guidance, the applicant is not required to submit a bioequivalence study.

Vancomycin acts by interfering with bacterial cell wall biosynthesis. It affects cell wall production at both the transglycosylase step, in which disaccharide building blocks are transferred to the growing glycan chain, and the transpeptidase step, in which different peptidoglycan strands are cross-linked. Vancomycin can block the transglycosylase step by sequestering the substrate of the transglycosylation enzyme and/or by steric blockade of the enzyme's access to the growing glycan chain. The drug blocks the transpeptidation step by sequestering the muramyl peptide that is a substrate for the transpeptidase reaction.[1]

A detailed discussion and critical review of all the published clinical literature data on Vancomycin is therefore not warranted in this Overview as essential similarity to a product with an established and favorable risk-benefit profile has been demonstrated.

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

The proposed product Vancomycin capsules 125 mg contains the same active substance in the same concentration as the currently authorised product Vancocin Matrigel Capsules 125 mg. Since Vancomycin is expected to have its pharmacological action within GIT for the said indication, it is not significantly absorbed from the normal gastrointestinal tract (i.e. it acts locally in GIT). Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98, EMEA 2001) describes exemption from in vivo bioequivalence studies for locally acting drug. Hence, the waiver for a bioequivalence study is adequately justifiable.

[redacted]

* The quantities include [redacted] overages.

[redacted] mg of Vancomycin hydrochloride is equivalent to [redacted] mg of Vancomycin.

The quantity of Vancomycin hydrochloride is to be dispensed based on [redacted] µg/mg assay value (on as such basis). The difference in quantity of Vancomycin hydrochloride is to be adjusted with [redacted] as per formula.

[redacted]

[redacted]

[redacted] hence it is concluded that the test and reference products are pharmaceutically equivalent.

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

Pharmacodynamics

Vancomycin is a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis*. The bactericidal action of vancomycin results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin may alter bacterial cell membrane permeability and RNA synthesis. There is no cross-resistance between vancomycin and other classes of antibiotics.[2]

Orally administered vancomycin is active against *C. difficile* (e.g. toxigenic strains implicated in pseudomembranous enterocolitis). It is also active against staphylococci, including *Staphylococcus aureus*.[2]

Vancomycin is not active *in vitro* against gram-negative bacilli, mycobacteria or fungi.[2]

Demonstration of therapeutic equivalence between the test and reference products

Vancomycin Capsules 125 mg was developed essentially similar to the brand-leader, Vancocin Matrigel Capsules 125 mg ([redacted] Thus, the proposed product contains the same active substance in the same concentration as the currently authorised product. Vancomycin Hydrochloride is a highly soluble drug and it is expected to have its pharmacological action within GIT for the said indication (locally active drug). Vancomycin is not significantly absorbed from the normal gastro-intestinal tract and is therefore not effective by the oral route for other types of infection. Hence, the applicant has not performed a bioequivalence study with the justification that "Section 5.1.8 of the *Note for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98, EMEA 2001) describes exemption from in vivo bioequivalence studies for locally acting drug."

In order to demonstrate therapeutic equivalence, although a clinical trial would normally be considered, EU Guidance (CPMP/EWP/239/95) also allows cases where other models may be used or developed. Reference is therefore made to the draft FDA Guidance (2008)[8] on circumstances where an *in vitro* option may be a suitable alternative to an *in vivo* clinical trial. This FDA Guidance is specific to Vancomycin hydrochloride in the form of oral capsules and states:
"If the test product formulations are qualitatively (Q1) (i.e., contain all of the same inactive ingredients) and quantitatively (Q2) the same as the reference listed drug (RLD) with respect to inactive ingredients, bioequivalence (BE) of all capsule strengths may be established based on comparative dissolution."

It is confirmed that both Q1 and Q2 conditions are met for the proposed product as it contains only the same inactive ingredient as the innovator or RLD, namely [redacted], and contains the same active ingredient.

Further, data is not available in the public domain to confirm the quantity of [redacted] in the EU originator. Qualitatively (Q1), the proposed formulation should be the same as it contains only one inactive ingredient as the innovator, namely [redacted] In order to demonstrate

Quantitative (Q2) similarity, the following comparisons were done between the Test and EU reference:

[redacted]

Further, as the only excipient in the formulation is [redacted] the following measures have been taken to ensure batch to batch consistency of the excipient. As the molecular weight of PEG 6000 is a criteria to be monitored as per USP, the PEG 6000 sourced from [redacted] confirms to a limit of average molecular weight of NLT [redacted] to NMT [redacted] of the labeled nominal value, as confirmed by the supplier and the supplier CoA has a limit of [redacted] Further, the supplier has confirmed the specific grade PEG 6000 (Macrogol) used in the formulation is devoid of any preservatives. Therefore, both Q1 and Q2 conditions are satisfied.

Moreover, as per [redacted], there was no change in urine or serum levels of the antibiotic when (reference product) capsules containing [redacted] were compared with oral solutions, therefore minor differences in the PEG content cannot be expected to alter the absorption of vancomycin from the GIT. Thus, it can be concluded that these negligible differences would not affect the clinical efficacy and safety of the proposed product.

Accordingly, then the applicant has conducted dissolution studies under the same conditions as recommended in the FDA guidance. The multimedia data provided in the Module m3-2-p, clearly shows that drug release of more then 90% of the labeled claim within 45 minutes was observed for both test and reference product. Drug release profiles for test and reference product were comparable in all three dissolution media across the pH range of 1 to 6.8.

In addition, an [redacted] testing was carried out to determine the equivalence of the test Vancomycin capsules 125 mg as against the reference Vancocin Matrigel Capsules 125 mg [redacted]

The results of this comparative study are as follows:

[redacted]

As per the UK SPC of Vancocin Matrigel Capsules 125 mg, Vancomycin is indicated for the treatment of staphylococcal enterocolitis and pseudomembranous colitis due to *Clostridium difficile*. Hence, the comparative study using the ATCC strain of *Clostridium difficile* is scientifically justifiable. It can be clearly observed that in the intestinal fluid medium (which is the site of action of the drug); the results are comparable between the test and reference Vancomycin 125 mg capsules. The difference in the results in gastric fluid could be attributed solely to the double dilution factor used in testing method and would hence not be clinically significant.

On the basis of aforementioned grounds, having shown pharmaceutical equivalence, comparable dissolution and comparable MIC, therapeutic equivalence between the test and reference Vancomycin capsules is clearly demonstrated.

Pharmacokinetics

Orally administered vancomycin does not usually enter the systemic circulation even when inflammatory lesions are present. Measurable serum concentrations may infrequently occur in patients with active *C. difficile*-induced pseudomembranous colitis, and, in the presence of renal impairment, the possibility of accumulation exists.[2]

Vancomycin is poorly absorbed from the gastro-intestinal tract. During multiple dosing of 250 mg every [redacted] hours for [redacted] doses, faecal concentrations of vancomycin, in volunteers, exceeded 100 mg/kg in the majority of samples. No blood concentrations were detected and urinary recovery did not exceed [redacted] [2]

Administration of vancomycin oral solution, [redacted] g daily for [redacted] days, to anephric patients with no inflammatory bowel disease, gave serum levels of [redacted] µg/ml. With doses of [redacted] g daily, concentrations of [redacted] mg/kg can be found in the feces, and levels of [redacted] µg/ml can be found in the serum of patients with normal renal function who have pseudomembranous colitis.[2]

There are very few human studies evaluating the pharmacodynamics of vancomycin, and the findings of most of those studies have not been conclusive in determining which parameter has the most value in predicting patient outcome. The majority of studies have involved relatively small patient populations and patients with a variety of infection types. One prospective evaluation randomized [redacted] patients with *S. aureus* infections, including bacteremia and endocarditis, to achieve [redacted] different trough concentration targets of [redacted] mg/L, [redacted] mg/L, and [redacted] mg/L. No relationships were found between peak concentrations, trough concentrations, or pharmacodynamic parameters (e.g., peak/MIC, time above the MIC, or AUC/MIC) and organism eradication or overall patient outcome.[3]

Interaction with other drugs

Concurrent and/or sequential systemic or topical use of other potentially ototoxic and/or nephrotoxic drugs requires careful monitoring.[2]

2.5.4 OVERVIEW OF EFFICACY

The proposed Vancomycin Capsules 125 mg contains same active ingredient, the same pharmaceutical form and are indicated for identical indications as the innovator product. The proposed formulation is a generic formulation; hence the applicant has not conducted pre-clinical and clinical studies in support of this application. Review of some publications on the efficacy is described below.

Glycopeptide antibiotics, such as teicoplanin and vancomycin, are active against staphylococci (including methicillin resistant strains), streptococci, enterococci and Clostridium spp. Vancomycin and teicoplanin are both widely used in the treatment of infections caused by Gram-positive organisms.[4]

Vancomycin is one of only a few antibiotics available to treat patients infected with methicillin-resistant *Staphylococcus aureus* and methicillin-resistant, coagulase-negative *Staphylococcus* species. Vancomycin is a concentration-independent antibiotic, and there are factors that affect its clinical activity, including variable tissue distribution, inoculum size, and emerging resistance.[3]

Clinical studies

Vancomycin has become a de facto standard comparison agent for recent clinical trials evaluating new antimicrobials with activity against Gram-positive pathogens. A clinical trial was designed to compare linezolid with vancomycin in the treatment of infections due to methicillin-resistant *Staphylococcus aureus* (MRSA). This randomized, open-label, multicentre study enrolled more than [redacted] hospitalized patients in each arm; approximately one-half of these were proven to have MRSA infection. [redacted] percent of patients in each group achieved clinical cure. The proportions of patients with successful microbiological outcomes were, likewise, equivalent: [redacted] of those treated with linezolid and [redacted] of those treated with vancomycin. Vancomycin was also the comparator agent in a study of linezolid for treatment of Gram-positive nosocomial pneumonia. This was a randomized, double-blind, multi-national trial, with approximately [redacted] patients in each study arm. Aztreonam could be administered if needed because of concern about Gram-negative pathogens. Clinical and microbiological cure rates with vancomycin ([redacted] and [redacted] respectively, among evaluable patients) were equivalent to those observed with linezolid. In another study of hospital-acquired pneumonia, the clinical success rate among bacteriologically-evaluable patients with vancomycin ([redacted] was equivalent to that obtained with quinupristin/dalfopristin ([redacted]).[5]

Vancomycin and teicoplanin are glycopeptides active against a wide range of gram-positive bacteria. For 30 years following the discovery of vancomycin in 1956, vancomycin resistance was not detected among normally susceptible bacteria recovered from human specimens. Since 1986, however, bacteria resistant to vancomycin or teicoplanin or both have been described. Strains of the genera Leuconostoc, Lactobacillus, Pediococcus, and Erysipelothrix seem inherently resistant to glycopeptides. Species and strains of enterococci and coagulase-negative staphylococci appear to have acquired or developed resistance. There are at least two categories of glycopeptide resistance among enterococci, characterized by either high-level resistance to

vancomycin (MIC, greater than or equal to 64 mg/liter) and teicoplanin (MIC, greater than or equal to 8 mg/liter) or lower-level vancomycin resistance (MIC, 32 to 64 mg/liter) and teicoplanin susceptibility (MIC, less than or equal to 1 mg/liter). The two categories appear to have similar resistance mechanisms, although genetic and biochemical studies indicate that they have arisen independently. Among coagulase-negative staphylococci, strains for which vancomycin MICs are up to 20 mg/liter or teicoplanin MICs are 16 to 32 mg/liter have been reported, but cross-resistance between these glycopeptides varies. The selective advantage accorded to glycopeptide-resistant bacteria and the observation that high-level resistance in enterococci is transferable suggests that such resistance may be expected to increase in incidence.[6]

The glycopeptides have proven remarkably useful antibiotics in clinical practice. Their spectrum of activity broadly addresses hospital-acquired as well as community-onset infections caused by Gram-positive bacteria. Activities of these agents against MRSA and methicillin-resistant coagulase-negative staphylococci have been especially important. These agents have provided important therapeutic alternatives to b-lactam antibiotics in patients allergic or otherwise intolerant of the latter. The pharmacokinetic and safety profiles of the available agents, vancomycin and teicoplanin, are such that they can be used effectively not only in the hospital, but also in the home or in specialized nursing environments.[5]

2.5.5 OVERVIEW OF SAFETY

The Summaries of Product Characteristics (SPCs) for the proposed Vancomycin Capsules 125 mg is based on very closely on the SPCs for Vancocin Matrigel Capsules 125 mg [redacted] and there are no significant differences in the contraindications, precautions and warnings.

Contraindication

Vancomycin is contraindicated in patient with known hypersensitivity to the drug.[2]

Use in Pregnancy

Pregnancy Category B.[7]

Teratology studies have been performed at [redacted] imes the human dose in rats and [redacted] 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. [redacted] 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 [redacted] and [redacted] trimesters, it is not known whether it causes foetal harm. Therefore vancomycin should be given to a pregnant woman only if clearly needed.[2]

Use in Nursing Mothers

Vancomycin hydrochloride is excreted in human milk. Caution should be exercised when vancomycin is administered to a nursing woman.[2]

Overdose

Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed by dialysis. Haemofiltration and haemoperfusion with Amberlite resin XAD-4 have been reported to be of limited benefit.[2]

Adverse effects

Since vancomycin is not usually significantly absorbed from the gastro-intestinal tract, the toxicity encountered with parenteral therapy is unlikely to occur after oral administration.[2]

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.[2,7]

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.[2,7]

Haematological: Reversible neutropenia, usually starting one week or more after onset of intravenous therapy or after a total dose of more than [redacted] g. Neutropenia appears to be promptly reversible when vancomycin is discontinued. Thrombocytopenia and reversible agranulocytosis (granulocyte count less than 500/mm^3) have been reported rarely.[2,7]

Miscellaneous: Hypersensitivity reactions, anaphylaxis, chills, drug fever, eosinophilia, hypotension, wheezing, dyspnoea, urticaria, pruritus, flushing of the upper body ("red neck" syndrome), pain, muscle spasm of the chest and back, nausea and rashes, including exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis and rare cases of vasculitis.[2]

2.5.6 BENEFITS AND RISKS CONCLUSION

The proposed Vancomycin Capsules 125 mg have been shown to be essentially similar to the UK innovator product (Vancocin Matrigel Capsules 125 mg, [redacted] Both proposed and innovator products contain the same active ingredient at the same strengths.

THERAPEUTIC JUSTIFICATION

Vancomycin Capsules 125 mg is an established therapeutic product with the defined therapeutic indications. The proposed indications for the product concerned in this Application are identical to the indications for the currently-marketed brand product.

Efficacy

When used as directed, Vancomycin Capsules 125 mg is efficacious and has defined role for the treatment of staphylococcal enterocolitis and pseudomembranous colitis due to Clostridium difficile

Safety

Vancomycin preparation is associated with a low & well-defined incidence of adverse events. The warnings and side effects listed in the Summary of Product Characteristics will need to be identical to those listed for the reference product and adequate to ensure safe and appropriate usage.

CONCLUSIONS AS TO RISK/BENEFIT

In view of the established use of Vancomycin Capsules 125 mg for the intended indications and the essential similarity to the innovator product, a favorable risk/benefit ratio can be expected when the proposed product is used in accordance with the instructions in the Summary of Product Characteristics.

2.5.7 References