# IPAR

IRISH MEDICINES BOARD

**PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE**

Scientific discussion

Vancocin 1g powder for concentrate for solution for infusion and powder for oral solution
VANCOMYCIN HYDROCHLORIDE
PA 1226/5/4

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the IMB for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the IMB leading to the approval of the medicinal product for marketing in Ireland.

# I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Vancocin 1g powder for concentrate for solution for infusion and powder for oral solution, from Flynn Pharma Ltd on 11th June 2010 for;

1) potentially life−threatening infections which cannot be treated with other effective, less toxic antimicrobial drugs, including the penicillins and cephalosporins
2) 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
3) in the treatment of endocarditis and as prophylaxis against endocarditis in patients at risk from dental or surgical procedures, and
4) for the treatment of staphylococcal enterocolitis and pseudomembranous colitis due to *Clostridium difficile*.
5) in other infections due to staphylococci including: osteomyelitis, pneumonia, septicaemia and soft tissue infections

This is an abridged application under Article 8(3) of Directive 2001/83 as amended, and is a line extension to add an additional strength to a medicinal product previously authorised under this Article. The applicant has not received any scientific advice related to this procedure.

The submission of a Paediatric Investigation Plan was not required for this application, as the application was received prior to the commencement of Article 7 of the Paediatric Regulation 1901/2006.

The prescription status of the product is prescription only which may not be renewed.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at www.imb.ie

| | |
|---|---|
| Name of the product | Vancocin 1 g powder for concentrate for solution for infusion and powder for oral solution |
| Name(s) of the active substance(s) (INN) | VANCOMYCIN HYDROCHLORIDE |
| Pharmacotherapeutic classification (ATC code) | A07AA09 (Antibiotics)<br>J01XA01 (Glycopeptide antibacterials) |
| Pharmaceutical form and strength(s) | powder for concentrate for solution for infusion and powder for oral solution<br>1 g |
| Marketing Authorisation Number(s) in Ireland (PA) | PA 1226/5/4 |
| Marketing Authorisation Holder | Flynn Pharma Ltd |

# II QUALITY ASPECTS

## II.1. Introduction

This application is for Vancocin 1 g powder for concentrate for solution for infusion and powder for oral solution.

## II.2 Drug substance

The active substance is Vancomycin Hydrochloride, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

## II.3 Medicinal product

P.1 Composition

Brief description of the dosage form
Powder for concentrate for solution for infusion and powder for oral solution
Off-white lyophilised plug. When reconstituted with Water for Injections, it forms a clear sterile solution.

Composition of the medicinal product
Active substance

| | |
|---|---|
| Vancomycin | 1 g |
| as Vancomycin Hydrochloride Ph. Eur. | |

Excipients
Hydrochloric Acid Ph. Eur.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances)*

All ingredients comply with Ph. Eur. specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the parenteral preparations and relevant ICH Guidelines, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented in 20 ml Type I glass vial with a rubber closure, aluminium collar and a polypropylene cap

Evidence has been provided that the container closure complies with the requirements as described in the Ph. Eur. for Glass Containers for Pharmaceutical Use and with the requirements of the Ph. Eur. for Rubber Closures for Containers for Aqueous Preparations for Parenteral Use.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 2 years when stored below 25°C as packaged for sale. *After reconstitution:* The reconstituted concentrate for solution for infusion, diluted solution for infusion or a reconstituted oral solution should be used immediately.

### II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Vancocin 1 g powder for concentrate for solution for infusion and powder for oral solution.

## III NON-CLINICAL ASPECTS

This active substance has been available on the European/Irish market for many (more than 50) years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available. Relevant preclinical information has been assessed during the originator product authorisation.

## IV CLINICAL ASPECTS

### IV.1 Introduction

Vancomycin hydrochloride is a well known active substance with established efficacy and tolerability. As this is an abridged application under Article 8(3) of the Directive, reference is made in the application to the original application for Vancocin 500mg powder for solution for infusion and oral solution, made under the same Article. As such, no additional information has been provided nor is necessary. Bioequivalence studies are not required for this product, in accordance with the guideline on the demonstration of bioequivalence, as published by the European Medicines Agency.

The content of the SPC approved during this national procedure is in accordance with that accepted for the reference product Vancocin 500mg powder for solution for infusion and oral solution marketed by the MAH.

The schedule for PSUR submissions should be harmonised with that of the originator product.

### IV.2 Pharmacokinetics

Vancomycin is given intravenously for therapy of systemic infections.
The mean elimination half-life of vancomycin from the plasma is 4 to 6 hours in patients with normal renal function. About 75% of an administered dose of vancomycin is excreted in urine by glomerular filtration in the first 24 hours. Mean plasma clearance is about 0.058 l/kg/h, and mean renal clearance is about 0.048 l/kg/h.

Renal vancomycin clearance is fairly constant and accounts for 70% to 80% of vancomycin elimination. The volume of distribution ranges from 0.3 to 0.43 l/kg. There is no apparent metabolism of the drug. Vancomycin is 55% protein bound as measured by ultrafiltration at vancomycin serum levels of 10 to 100 mg/l. After IV administration of vancomycin hydrochloride, inhibitory concentrations are present in pleural, pericardial, ascitic, atrial appendage tissue and synovial fluid, as well as urine and peritoneal fluid. Vancomycin does not readily penetrate the cerebrospinal fluid unless the meninges are inflamed.

Renal dysfunction slows excretion of vancomycin. In anephric patients, the average half-life of elimination is 7.5 days.

The total systemic and renal clearance of vancomycin may be reduced in the elderly due to the natural decrement of glomerular filtration.
Vancomycin is poorly absorbed after oral administration, and can be thought to have local activity only.

### IV.3 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.

*In vitro* vancomycin is generally active against gram-positive microorganisms including: *Staphylococcus aureus* and *Staphylococcus epidermidis (*including heterogeneous methicillin-resistant strains), *Streptococcus pyogenes, Streptococcus pneumoniae (*including penicillin-resistant strains), *Streptococcus agalactiae,* the viridans group, *Streptococcus bovis,* and enterococci (e.g. *Enterococcus faecalis); Clostridium difficile (*e.g. toxigenic strains implicated in pseudomembranous enterocolitis) and diptheroids. Other organisms that are susceptible to vancomycin *in vitro* include *Listeria monocytogenes, Lactobacillus* species, *Acintomyces* species, *Clostridium* species and *Bacillus* species.

*In vitro* resistance to vancomycin has been reported among some enterococcal and staphylococcal isolates. The combination of vancomycin and an aminoglycoside acts synergistically in vitro against many strains of *S. aureus,* nonenterococcal group D streptococci, enterococci, and *Streptococcus* species (viridans group).
Vancomycin is not active *in vitro* against gram-negative bacilli, mycobacteria or fungi.

### IV.4 Clinical Efficacy

The clinical efficacy of this product is well established, and described in the product information. As this is a solution for intravenous use, no bioequivalence studies have been provided in support of this application, and these are not required in accordance with the guideline on the demonstration of bioequivalence, published by the European Medicines Agency. Additionally, as the oral solution is the same concentration as the I.V. solution, is poorly absorbed and generally acts in a local manner, bioequivalence studies for this route are also not required.

### IV.5 Clinical Safety

The clinical safety profile of this product is well known. No additional clinical safety studies have been provided in support of this application nor are required.

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance system, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

Risk Management Plan (usual pharmacovigilance requirements +/- additional requirements)

The schedule for Periodic Safety Update Reports (PSUR) submission should be harmonised with that of the originator product. *(PhV to adapt as necessary)*

### IV.6 Discussion on the clinical aspects

Vancomycin hydrochloride has a well established efficacy and safety profile. As this is an abridged application under Article 8(3) of the Directive and references the original medicinal product application under the same Article, no additional clinical studies have been provided nor are required. The applicant has correctly stated that as this is a solution for both intravenous and oral administration, no bioequivalence studies are required.

## V OVERALL CONCLUSIONS

### BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Vancocin 1 g powder for concentrate for solution for infusion and powder for oral solution has been submitted as a line extension of the existing marketing authorisation of Vancocin 500mg 1 g powder for concentrate for solution for infusion and powder for oral solution. Vancocin 500mg 1 g powder for concentrate for solution for infusion and

powder for oral solution is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has not been required to be shown to be in compliance with the CHMP guidance documents. The SPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The IMB, on the basis of the data submitted considered that Vancocin 1g powder for solution for infusion and oral solution was the same as the reference product and therefore granted a marketing authorisation.