COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Vancomycine Strides 125 and 250 mg hard capsules

(vancomycin hydrochloride)

NL/H/4771/001-002/DC

Date: 30 June 2021

This module reflects the scientific discussion for the approval of Vancomycine Strides. The procedure was finalised at 22 March 2021 For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Vancomycine Strides 125 and 250 mg hard capsules, from Strides Pharma Limited.

The product is indicated in patients 12 years and older for the treatment of clostridium difficile infection (CDI).

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Vancocin Matrigel 125 mg hard capsules which has been registered in Ireland by Flynn Pharma Limited since 1985.

The concerned member states (CMS) involved in this procedure were Croatia, France and Hungary.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC as amended. This application concerns a hybrid application as vancomycin is a locally acting drug with no systemic absorption after oral administration.

II. QUALITY ASPECTS

II.1 Introduction

Vancomycine Strides 125 mg hard capsules is a grey/pink hard capsule, containing white to off white congealed liquid mixture as solid mass.

Vancomycine Strides 250 mg hard capsules is a brown hard capsule, containing white to off white congealed liquid mixture as solid mass.

Vancomycine Strides contain as active substance 125 mg and 250 mg of vancomycin hydrochloride equivalent to 125,000 and 250,000 international units (IU) vancomycin.

The capsules are packed in AL-PVC/PE/Aclar blister packs.

The excipients are:

Capsule content - polyethylene glycol (macrogol) 6000

Capsule cap and body - gelatin, iron oxide yellow (E172), iron oxide red (E172), titanium dioxide (E171) and iron oxide black (E172).

The content of the two capsule strengths are dose proportional.

II.2 Drug Substance

The active substance is Vancomycin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is a white or almost white powder and is freely soluble in water, slightly soluble in alcohol and insoluble in ether and in chloroform. Vancomycin hydrochloride does not exhibit polymorphism.
For the drug substance vancomycin hydrochloride a CEP is used.

The CEP procedure is used for the active substance. Under the official certification procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional parameters for microbiological assay, residual solvents, particle size, microbial limits, bulk density and foreign matter. Batch analytical data demonstrating compliance with this specification have been provided for two production scaled batches analysed by the MAH and three production scaled batches analysed by the supplier of the active substance.

Stability of drug substance
The active substance is stable for 24 months when stored at a temperature between 2°C and 8°C in a double polyethylene bag placed in an aluminium drum or metal drum or aluminium foil bag filled with nitrogen. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The aim of the formulation development was to develop a stable and reproducible capsules form of vancomycin hydrochloride capsules 125 mg and 250 mg that is equivalent to the reference product. A

melting and mixing process for the drug product was developed. The selection and optimisation of the manufacturing process has been adequately described. The critical manufacturing process steps are identified and the risks were mitigated. A waiver for *in-vivo* bioequivalence testing for this abridged application is discussed . Overall, the pharmaceutical development of the product is considered adequate.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scaled batches per strength in accordance with the relevant European guidelines. The manufacturing process of the drug product consists of the following steps: sifting, melting, mixing, filling and packaging.

Control of excipients

The excipients comply with the Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, identification of titanium dioxide and iron oxide, average weight, uniformity of filled capsule weight, uniformity of dosage units by mass variation, dissolution, water content, related substances, assay by microbiology and microbiological enumeration. In general the limits at release and shelf life are similar with exception of the limits for related substances. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The identification of the colorants and uniformity of weight and average weight of filled capsules are not included in the shelf life specifications. The impurities are identified and in line with the Ph.Eur. monograph. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 14 batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Initially, stability data on the product has been provided three full scaled batches per strength tested as per previous specification. Description, dissolution, assay by microbiology remained stable up to 24 months. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed PVC/PE/Aclar-Al blister packaging.

The MAH was requested to provide additional stability studies as the submitted data was not complete because of modified specifications. Additionally, not all the impurities were stated. Therefore, stability data on the product have been provided for an additional 14 batches in accordance with applicable European guidelines demonstrating the stability of the product for 18 months. On basis of the data submitted, a shelf life was granted of 18 months when stored in the PVC/PE/Aclar-Al blister packaging. Based on the provide batch analyses data and the previous stability data the proposed shelf life can be granted provided that a commitment is made by the applicant to perform stability studies on three commercial batches and any out of specification will be notified to agency with the proposed action. The MAH should submit

the data confirming the proposed shelf-life of 18 months when available or earlier if trends are observed. Photostability studies were performed, compliance with ICH recommendations is claimed. The studies demonstrated that the product is stable when exposed to light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM for gelatin have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Vancomycine Strides has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to carry out formal stability studies according to the principles detailed in the ICH guidelines on three commercial batches for each dosage strengths, manufactured in compliance with the corrected batch formula (in agreement with EMA requirements).
- The MAH committed to submit the above data as soon as available for the dossier lifecycle, via an adequate variation application to confirm the granted shelf life of 18 months.
- The MAH committed to notify the RMS and the CMS of any out of specification result occurring before the end of shelf life, with the proposed action.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Vancomycine Strides is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Vancocin Matrigel which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and

toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Vancomycin is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

The MAH has submitted several comparative dissolution studies between Vancomycine Strides and the reference product Vancocin Matrigel 125 (Flynn Pharma). Additionally, comparative dissolution data against Vancocin CP capsules 250 mg HGC manufactured by Eurocept BV was provided by the MAH.

IV.2 Pharmacokinetics

Biowaiver

Vancomycin is a locally acting drug without systemic absorption and a pharmacokinetic bioequivalence study is therefore not suitable to test therapeutic equivalence, nor necessary for a safety evaluation of comparable systemic absorption. This conclusion is supported and the reasoning behind the lack of bioequivalence studies is agreed. The MAH has requested a biowaiver of strengths for both the 125 mg and 250 mg capsules. The MAH separately compared both requested strengths (125 and 250 mg) to the reference product using comparative dissolution. During these studies the 125 mg capsules have been compared to the reference product (125 mg) and the 250 mg capsules to two capsules of the reference product (125 mg). However, the comparison between the 250 mg capsule and two capsules of the reference product was initially not considered adequate. Therefore, comparative dissolution data against Vancocin CP capsules 250 mg HGC manufactured by Eurocept BV have been provided (instead of using two capsules of the 125 mg reference product). However, considering that Vancocin Matrigel 125 mg hard capsules is declared as a reference product in the application form, dissolution data against Vancocin CP capsules 250 mg HGC cannot be considered supportive of the biowaiver. However, since this application concerns locally acting product which is not absorbed and not systemically acting, comparative dissolution data against two Vancocin Matrigel 125 mg hard capsules and 250 mg test product is considered acceptable. This data has been submitted and discussed and is considered acceptable. Similarity in dissolution has been demonstrated for the 250 mg capsule. Thus, a biowaiver to both the 125 and the 250 mg capsule, can be granted.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Vancomycine Strides.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Use in patients with inflammatory disorders of intestinal mucosa • Use in renal impairment • Ototoxicity • Neutropenia • Use in breast-feeding women • Hypersensitivity to vancomycin • Super infection under prolonged use.
Important potential risks	• Use in pregnancy
Missing information	• Effect on fertility

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Vancocin. No new clinical studies were conducted. The MAH demonstrated through dissolution studies that the dissolution profile of the product is similar to the dissolution profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English. The test consisted of a pilot test with four participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Vancomycine Strides 125 and 250 mg hard capsules have a proven chemical-pharmaceutical quality and are a generic forms of Vancocin. Vancocin is a well-known medicinal product with an established favourable efficacy and safety profile.

No bioequivalence has been shown to be in compliance with the requirements of European guidance documents. However, as vancomycin is a locally acting drug without systemic absorption a pharmacokinetic bioequivalence study is not suitable to test therapeutic equivalence, nor necessary for a safety evaluation of comparable systemic absorption. This conclusion is supported and the reasoning behind the lack of bioequivalence studies is agreed.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). However, a referral to the CMD(h) was started on 31st of January 2021. The MAH provided additional batch analyses data on the comparison of the methods, information of the impurities, and compliance with the related substance specifications for several batches stored up to 26 months. In addition the previously agreed commitments were amended and the shelf life could be granted. Therefore, no discussion was needed and the CMD(h) procedure ended on 31 March 2021 with consensus. Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Vancomycine Strides with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 March 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse