COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Vancomycine Sandoz 500 mg and 1000 mg powder for solution for infusion

(vancomycin hydrochloride)

NL/H/4445/001/DC

Date: 17 July 2018

This module reflects the scientific discussion for the approval of Vancomycine Sandoz 500 mg and 1000 mg powder for solution for infusion. The procedure was finalised on 15 October 2009 with the United Kingdom as RMS (UK/H/1383/001-002/DC). The current RMS is the Netherlands (NL/H/4445/001-002/DC). 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
RMS	Reference Member State
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 Sandoz 500 mg and 1000 mg powder for solution for infusion from Sandoz B.V.

The product is indicated in the therapy of severe, potentially life-threatening infections due to susceptible gram-positive microorganisms which cannot be treated with or failed to respond to other effective, less toxic antimicrobial medicinal products, such as penicillins and cephalosporins.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Vancocin 500 mg and 1000 mg powder for solution for infusion and oral solution, which has been registered in the UK since 15 April 1990 and currently marketed by Flynn Pharma Limited. In the Netherlands, Vancocin CP 500 mg and 1000 mg, powder for solution for infusion has been registered since 4 December 1985 by a national procedure, however recently withdrawn.

The reference member state (RMS) of the initial procedure was the United Kingdom and the concerned member states involved in this procedure were Latvia, Italy, Finland, Spain, the Netherlands, Estonia, Denmark, Czech Republic, Bulgaria, Slovak Republic, Slovenia, Sweden, Portugal, Germany, Luxembourg and Poland. The role of RMS was transferred to the Netherlands on 30 April 2018 and the concerned member states in this procedure were Belgium, Bulgaria, Denmark, Estonia, Finland, Sweden, Slovenia, Slovak republic and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Vancomycin Sandoz is a white or almost white powder. Each vial contains 500 mg vancomycin (hydrochloride) equivalent to 500,000 IU. After reconstitution a solution is obtained with a pH of approximately 3.

The powder for solution for infusion is packed in colourless type I glass vials, with a bromobutyl rubber stopper and an aluminium/plastic flip-off cap.

The product contains no other excipients.

II.2 Drug Substance

The active substance is vancomycin hydrochloride and is an established substance. It is a white or almost white powder, hygroscopic. Vancomycin is freely soluble in water and slightly soluble in alcohol.

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. Suitable pharmaceutical development data have been provided for these applications.
The physico-chemical properties of the drug product have been compared with those of the originator product. These data demonstrate that the proposed products can be considered generic medicinal products of Vancocin 500 and 1000 mg powder for solution for infusion and oral solution.

Manufacturing process
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results are satisfactory.

Quality control of drug product
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used. In addition, all primary packaging complies with guidelines concerning materials in contact with parenteral products.

Stability of drug product
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years has been set for the unopened product, with the storage instructions ‘Store below 25 degree C’.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Vancomycin Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Vancomycin Sandoz is intended for generic 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 generic formulation of Vancocin 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 hydrochloride 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.

IV.2 Pharmacokinetics

Vancomycine Sandoz 500 mg and 1000 mg powder for solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of

Vancomycine Sandoz is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Risk Management Plan

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 a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Vancomycine Sandoz 500 mg and 1000 mg powder for solution for infusion have a proven chemical-pharmaceutical quality and are generic forms of Vancocin 500 mg and 1000 mg powder for solution for infusion and oral solution. Vancocin is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). 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 Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 October 2009.

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
UK/H/1383/IB/001/G	Change in medicinal product name and MAH in Denmark and Estonia	-	14-04-2010	Approved	-
UK/H/1383/IB/002/G	Change in medicinal product name in Belgium, Latvia, Sweden and the Slovak Republic due to a MAH-transfer	-	14-04-2010	Approved	-
UK/H/1383/1-2/IB/003	Change in the (invented) name of the medicinal product; for nationally authorised products; in the Netherlands	-	27-04-2010	Approved	-
UK/H/1383/1-2/IB/004	Follow Up Measure/Specific Obligation, data submitted under Article 45/46 of Regulation (EC) No 1901/2006, or amendments to reflect a competent authority Core SPC; implementation of agreed wording change(s) for which no new additional data are submitted by the MAH	-	27-08-2010	Approved	-
UK/H/1383/IB/005/G	Change in the (invented) name of the medicinal product; for nationally authorised products; in Czech Republic and Finland.	-	06-08-2010	Approved	-
UK/H/1383/1-2/IA/006	Change in address of the MAH	-	12-01-2010	Approved	-
UK/H/1383/IB/007/G	- Change in name of the product in Bulgaria, Poland and Slovenia - Introducing a new DDPS	-	28-09-2011	Approved	-
UK/H/1383/IB/008/G	Change in medicinal product name and MAH in Italy and Spain	-	08-12-2011	Approved	-
UK/H/1383/IB/009/G	- register an updated EDQM certificate of suitability - register of new certificate from a new manufacturer (replacement of addition)	-	03-04-2011	Approved	-
UK/H/1383/IA/011/G	- Addition of a new specification parameter of the specification with its corresponding test method - Other changes to a test	-	15-02-2013	Approved	-

	procedure (including replacement or addition)				
UK/H/1383/1-2/II/010	Change to the immediate packaging of the finished product; sterile medicinal products and biological/immunological medicinal products	yes	21-06-2013	Approved	-
UK/H/1383/IB/012/G	- Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product; other variation - Change in the batch size (including batch size ranges) of the finished product; up to 10-fold compared to the originally approved batch size - Change to in-process tests or limits applied during the manufacture of the finished product; other variation	-	16-05-2013	Approved	-
UK/H/1383/1-2/IA/014/G	Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use; introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	-	25-03-2014	Approved	-
UK/H/1383/1-2/IA/015	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability; european Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph; updated certificate from an already approved manufacturer	-	01-05-2014	Approved	-
UK/H/1383/1-2/IA/016/G	Change in the specification parameters and/or limits of the immediate packaging of the finished product: - Addition of a new specification parameter to the specification with its	-	09-12-2014	Approved	-

	corresponding test method - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
UK/H/1383/1-2/IA/017/G	Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites); the activities for which the manufacturer/importer is responsible do not include batch release	-	23-02-2015	Approved	-
UK/H/1383/1-2/IB/018	Change in the shelf-life or storage conditions of the finished product; reduction of the shelf life of the finished product; as packaged for sale	-	13-04-2015	Approved	-
UK/H/1383/1-2/II/019	Change in the specification parameters and/or limits of the finished product; change outside the approved specifications limits range	-	28-04-2017	Withdrawn	-
UK/H/1383/1-2/IB/020/G	Change in the specification parameters and/or limits of the immediate packaging of the finished product; addition of a new specification parameter to the specification with its corresponding test method; deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	-	18-01-2017	Approved	-
UK/H/1383/1-2/IB/021/G	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure; the medicinal product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure and no new additional data is required to be submitted by the MAH	-	16-04-2018	Approved	-