COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Pantoprazol Amarox 40 mg powder for solution for injection

(pantoprazole)

NL/H/4829/001/DC

Date: 15 December 2020

This module reflects the scientific discussion for the approval of Pantoprazol Amarox 40 mg powder for solution for injection. The procedure was finalised at 25 September 2020. 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 Pantoprazol Amarox 40 mg powder for solution for injection, from Amarox Pharma B.V.

The product is indicated for:

- Reflux oesophagitis.
- Gastric and duodenal ulcer.
- Zollinger-Ellison-Syndrome and other pathological hyper secretory conditions.

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 Pantozol 40 mg, powder for solution for injection which has been registered in The Netherlands by Takeda Nederland B.V. since 11 February 1998 via a decentralised procedure (DE/H/0268/003).

The concerned member states (CMS) involved in this procedure were Germany and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Pantoprazol Amarox is a white to off-white powder for solution for injection. Each vial contains 40 mg of pantoprazole (as sodium sesquihydrate). After reconstitution, 1 ml of solution for injection contains 4 mg pantoprazole. For the solution reconstituted with 10 ml of 0.9% NaCl solution the pH is approximately 9-10.5 and the osmolality is approximately 280-340 mOsm/Kg.

The powder is packed in clear glass (type I) vial with a grey rubber stopper and flip off aluminium seal.

The excipients are disodium edetate and sodium hydroxide (E 524) (for pH adjustment).

II.2 Drug Substance

The active substance is pantoprazole sodium sesquihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a white or almost

white powder and freely soluble in water and 96% ethanol. Pantoprazole sodium sesquihydrate does not exist in different polymorphic forms.

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 residual solvents, bacterial endotoxins and microbial quality. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance

The active substance is stable for 5 years when stored under the stated conditions. 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 choice of excipients is justified and their functions explained. Characterisation of the reference product was performed. The excipients used in the formulation are well known. No bioequivalence study has been performed. This is justified for the product. The pharmaceutical development of the product has been adequately performed

Manufacturing process

The manufacturing process consists of compounding, filtration, filling, lyophilisation, sealing, labelling and packing and has been validated according to relevant European guidelines. The process is considered to be a non-standard process, based on the aseptic processing. Process validation data on the product have been presented for three production scale batches in accordance with the relevant European guidelines.

Control of excipients
All excipients comply with their respective Ph. Eur. monograph. 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 appearance, identification, clarity and degree of opalescence, colour of solution, reconstitution time, uniformity of dosage units, pH, water content, assay, related substances, particulate matter, bacterial endotoxins and sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three commercial scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three productions scale batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). No significant changes were observed and all results remained well within the specifications. Based on the provided stability data, the proposed shelf life of 24 months can be granted. This medicinal product does not require any special temperature storage conditions. The photostability study results demonstrate that the proposed product packed in the immediate packaging is susceptible to degradation when exposed to light. No significant changes were observed when the product was stored in the secondary packaging as well. Hence, the product should be kept in the secondary packaging (outer carton) in order to protect the product from light.
Stability data have provided for the product reconstituted with sodium chloride 9 mg/ml (0.9%) solution for injection (10 ml) and as per SmPC further diluted (using 100 ml) with sodium chloride 9 mg/mL (0.9%) solution for injection and glucose 55 mg/mL (5%) solution for injection. These data show that the product remains stable for 12 hours.

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 Pantoprazol Amarox 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 Pantoprazol Amarox 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 Pantozol 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

Pantoprazole 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

Biowaiver

Pantoprazol Amarox 40 mg powder for solution for injection 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Pantoprazol Amarox 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 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 Pantoprazol Amarox.

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

Important identified risks	None
Important potential risks	- Increased risk of Clostridium difficile-associated diarrhoea (CDAD) with PPIs - Childhood asthma following in utero exposure to pantoprazole
Missing information	- Use in children and adolescents

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 Pantozol. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Levetiracetam Hetero 750 mg film-coated tablets and Pantoprazole PCH 40 mg powder for solution for injection or infusion The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pantoprazol Amarox 40 mg powder for solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Pantozol 40 mg, powder for solution for injection. Pantozol 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. A biowaiver has been granted.

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 Pantoprazol Amarox with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 September 2020.

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