CBG MEB

Public Assessment Report

Scientific discussion

Pantoprazol SUN Pharma 40 mg, powder for solution for injection

(pantoprazole sodium sequihydrate)

NL/H/3573/001/DC

Date: 17 February 2017

This module reflects the scientific discussion for the approval of Pantoprazol SUN Pharma 40 mg, powder for solution for injection. The procedure was finalised on 25 August 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PPI	Proton Pump Inhibitor
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 SUN Pharma 40 mg, powder for solution for injection from SUN Pharmaceutical Industries Europe B.V.

The product is indicated for:
- Reflux oesophagitis
- Gastric and duodenal ulcer
- Zollinger-Ellison-Syndrome and other pathological hypersecretory 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 Anagastra 40 mg powder for solution for injection which has been registered in Spain by Takeda GmbH since 1 July 1998. In the Netherlands, Pantozol i.v. 40 mg powder for solution for injection has been registered by Takeda B.V. since 11 February 1998 by the mutual recognition procedure DE/H/0268/003.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Pantoprazol SUN Pharma is a white or off-white powder for solution for injection with porous appearance and pH between 9 and 11 after reconstitution.

The powder is packed in a 10 ml type-I colourless glass vial sealed with a grey chlorobutyl stopper, sealed with an aluminium cap made mainly of aluminium or flip-off opening. Each vial contains as active substance 40 mg of pantoprazole, as 45.1 mg of pantoprazole sodium sequihydrate.

A ready-to-use solution is prepared by injecting 10 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection into the vial containing the powder. The appearance of the product after reconstitution is a clear colourless solution, practically free from particles.

The excipient is disodium edetate.

II.2 Drug Substance

The active substance is pantoprazole sodium sequihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Pantoprazole sodium sequihydrate is a white to almost white powder. It is freely soluble in water and in ethanol (96%), and practically insoluble in hexane. As the active substance is dissolved during the manufacturing process of the finished product, any potential polymorphism is not considered as a critical parameter.

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 tests for residual solvents, bacterial endotoxins and microbiological quality. The additional test for residual solvents is in accordance with the CEP. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
The active substance is stable for three 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. The main development study performed was the characterisation of the reference product. The excipient used in the formulation is well known and is the same as present in the reference product. The choice for aseptic filtration and aseptic processing as sterilisation method is considered sufficiently justified. Since the product is a powder for solution for injection no bioequivalence study is required. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are the preparation of the bulk solution, sterile filtration, filling, lyophilisation and stoppering. The manufacturing process is considered a non-standard process given the combination of sterile filtration, aseptic filling and lyophilisation. Sufficient details on the manufacturing process development have been provided and it has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three production scale batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply and are tested in accordance with their respective Ph.Eur. monographs. 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, pH, moisture, air-tightness, reconstitution time, clarity of the solution, colour of the solution, uniformity of dosage units, assay, related substances, bacterial endotoxins, sterility, visible particles and sub-visible particles. Except for assay, related substances and moisture content, the release and shelf-life requirements are identical. The specification is acceptable. 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 full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Microbiological attributes
Microbial quality is adequately controlled in the drug product.

Stability of drug product
Stability data on the product has been provided on three pilot scaled and three full scaled batches that were stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. At all three storage conditions a change in the colour of the solution was observed which was most pronounced at accelerated conditions. Also an increase in moisture content was observed at all three storage conditions as well as an increase in impurities

leading to out-of-specification results for one of the specified impurities and total impurities at accelerated conditions. No clear trends or changes were observed in the other tested parameters. Based on the results of the photostability study it is recommended to store the product protected from light. The claimed shelf-life of two years with storage condition 'Store below 30°C' and 'Keep the vial in the outer carton in order to protect it from light' is justified.

Stability data has been provided demonstrating that the product remains stable for 12 hours when stored at 25°C and 2-8°C following reconstitution with 10 ml of sodium chloride 0.9% solution and also when stored for 12 hours at 2-8°C after further dilution with 100 ml sodium chloride 0.9% or 100 ml glucose 5%. Stability data for one batch of drug product at the end of its shelf-life stored for 12 hours at 25°C after reconstitution and further dilution showed an increase in total impurities, but the results remained within the specified limits.

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 SUN Pharma 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 SUN Pharma 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 i.v. 40 mg powder for solution for injection 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

Pantoprazol sodium sequihydrate 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

Pantoprazol SUN Pharma 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 authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Pantoprazol SUN Pharma 40 mg is entirely the same as the originator. The qualitative composition is identical with that of Pantozol i.v. except for sodium hydroxide (for pH adjustment) is not present in the test product compared to the reference product. However, this component is not expected to affect the disposition of the drug substance. 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 SUN Pharma.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Chronic treatment with pantoprazole and hypomagnesaemia • Increased risk of fractures of the hip, wrist, and spine with the long term use of proton pump inhibitors (PPIs). • Chronic treatment with PPIs decreases absorption of cyanocobalamin (vitamin B12) • Visual disturbances
Important potential risks	• Increased risk of Clostridium difficile–associated diarrhoea (CDAD) with PPIs • Chronic use of PPIs and the risk of pneumonia • Congenital cardiac malformation following in utero exposure. • Decrease in absorption of iron • Off-label use
Missing information	• Use in pregnancy and during lactation • Use in patients with renal impairment

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 i.v. No new clinical studies were conducted. The MAH demonstrated that Pantoprazol SUN Pharma is therapeutically equivalent to the 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 test consisted of: two pilot tests, followed by two rounds with sufficient 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 PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pantoprazol SUN Pharma 40 mg, powder for solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Pantozol i.v. 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.

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 SUN Pharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 August 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure	NL/H/3573/ 1/IA/001	IA	8-11-2016	8-12-2016	Approval	No