

## **Public Assessment Report**

### **Scientific discussion**

**Pantoprazole ADOH 40 mg, powder for solution  
for injection**

**(pantoprazole sodium sesquihydrate)**

**NL/H/3656/001/DC**

**Date: 10 April 2017**

**This module reflects the scientific discussion for the approval of Pantoprazole ADOH 40 mg, powder for solution for injection. The procedure was finalised on 8 December 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
USP	United States Pharmacopoeia

## I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Pantoprazole ADOH 40 mg, powder for solution for injection from ADOH 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 Pantozol i.v. 40 mg powder for solution for injection has been registered in the Netherlands by Takeda B.V. since 11 February 1998 through mutual recognition procedure DE/H/0268/003.

The concerned member state (CMS) involved in this procedure was Germany.

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

## II. QUALITY ASPECTS

### II.1 Introduction

Pantoprazole ADOH is a white to off-white powder for solution for injection with porous appearance and pH between 9.5 and 11 after reconstitution.

The powder is packed in 10 ml clear glass vial (type I) with aluminum cap and grey rubber stopper. Each vial contains as active substance 40 mg of pantoprazole, as 45.1 mg of pantoprazole sodium sesquihydrate.

A ready-to-use solution is prepared in 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 yellowish solution.

The excipients are mannitol (E421) and disodium phosphate dodecahydrate (E339).

### II.2 Drug Substance

The active substance is pantoprazole sodium sesquihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Pantoprazole sodium sesquihydrate is a white to off-white porous cake or 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. For specified related substances, in-house specifications are tighter. The additional test for residual solvents is in accordance with the CEP. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

#### Stability of drug substance

The active substance is stable for four 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 the two different excipients compared to the innovator product is justified and their functions are explained. The choices of the packaging and manufacturing process are also justified. Pantoprazole ADOH powder for solution for infusion has the same pharmaceutical form as the originator. Aseptic filtration and aseptic processing as sterilisation method is accepted. 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 capping. The manufacturing process has been adequately described. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full consecutive batches in accordance with the relevant European guidelines.

#### Control of excipients

The excipients comply and are tested in accordance with their respective Ph.Eur. or United States Pharmacopoeia (USP) 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, water, 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. 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 full scaled batches that were stored at 25°C/60% RH (36 months), 30°C/65% RH (36 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 commercial packaging. At all three storage conditions no clear trends are observed. Also no differences are observed between the vials stored upright and inverted. Based on the results of the photostability study it is recommended to store the product protected from light. The claimed shelf-life of three 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 on the reconstituted product and on the reconstituted product that was diluted further with 100 ml sodium chloride 0.9% or 100 ml glucose 5%. In use stability has been demonstrated for 12 hours at 25°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 Pantoprazole ADOH 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 Pantoprazole ADOH 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**

Pantoprazole sodium sequehydrate 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**

Pantoprazole ADOH 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 qualitative composition differs with that of Pantozol i.v. Mannitol (filler) and disodium phosphate dodecahydrate (for pH adjustment) are present in the test product but not in the reference product. However, these differences are 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 Pantoprazole ADOH.

Summary table of safety concerns as approved in RMP:

Important identified risks	<ul style="list-style-type: none"> <li>• Chronic treatment with proton pump inhibitors (PPIs) and hypomagnesaemia</li> <li>• Increased risk of fractures of the hip, wrist, and spine with the long term use of PPIs</li> <li>• Visual disturbances</li> <li>• Chronic treatment with PPIs decreases absorption of cyanocobalamine (vitamin B12)</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>• Congenital cardiac malformation following in utero exposure</li> <li>• Increased risk of gastrointestinal infection; particularly Clostridium difficile-associated diarrhea (CDAD)</li> <li>• Interactions with warfarin or other coumarin derivatives, atazanavir, nelfinavir, digoxin, methotrexate</li> <li>• Masking of gastro-intestinal malignancies</li> <li>• Off-label use</li> <li>• Chronic use of PPIs and the risk of pneumonia</li> <li>• Decrease in absorption of iron</li> </ul>
Missing information	<ul style="list-style-type: none"> <li>• Use in patients with severe hepatic impairment</li> <li>• Use in pregnancy and during lactation</li> <li>• Use in patients with renal impairment</li> </ul>

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 Pantoprazole ADOH 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 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 PL of medicinal products for human use.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pantoprazole ADOH 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 i.v. 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 Pantoprazole ADOH with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 December 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