CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Pantoprazol SUN 40 mg, powder for solution for injection
Sun Pharmaceutical Industries Europe B.V., the Netherlands

pantoprazole (as sodium sesquihydrate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1376/001/DC
Registration number in the Netherlands: RVG 102490

14 October 2010

Pharmacotherapeutic group:	drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), proton pump inhibitors
ATC code:	A02BC02
Route of administration:	intravenous
Therapeutic indication:	treatment of duodenal ulcer, gastric ulcer, moderate and severe reflux esophagitis, Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions.
Prescription status:	prescription only
Date of authorisation in NL:	30 August 2010
Concerned Member States:	Decentralised procedure with DE, ES, FR, IT, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Pantoprazol SUN 40 mg, powder for solution for injection from Sun Pharmaceutical Industries Europe B.V. The date of authorisation was on 30 August 2010 in the Netherlands.

The product is indicated for treatment of:

- 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 SPC.

Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific action on the proton pumps of the parietal cells (a gastric proton pump inhibitor, (PPI). Pantoprazole is converted to its active form in the acidic environment in the parietal cells where it inhibits the H+, K+ ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. As other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, the substance can affect hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is given orally or intravenously.

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 Germany by Altana Pharma since 31 July 1997. In the Netherlands Pantozol i.v., 40 mg powder for solution for injection (NL License RVG 22084) has been registered since 11 February 1998 through MRP DE/H/268/003. In addition, reference is made to Pantozol authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Pantoprazol SUN 40 mg, powder for solution for injection is a product for parenteral use in aqueous solution, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is pantoprazole sodium sesquihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white powder, which is freely soluble in water and ethanol, and insoluble in hexane. The substance is a racemic mixture, chiral through the Sulphur atom. The substance shows polymorphism and several hydrate forms are known. One crystalline form is used.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
A four step process is used to obtain pantoprazole sodium sesquihydrate. Acceptable specifications for the starting materials and solvents have been provided. The active substance has been adequately characterized.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. monograph. Additional requirements for particle size, bioburden, bacterial endotoxins and residual solvents have been included. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three production-scale batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The batches were adequately stored. The stability data sufficiently support a re-test period of 2 years.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Each vial of pantoprazol SUN 40 mg contains 40 mg of pantoprazole (as 45.12 mg sodium sesquihydrate). It is a white to almost white powder with pH between 9.0 and 10.0 after reconstitution.

The powder for solution for injection is packed in 10 ml clear type I tubular glass vials, closed with 20 mm grey bromobutyl rubber stoppers and sealed with red flip-off aluminium seal.

No excipients are present in the product; water for injections is used as production adjuvant and nitrogen is used as protective gas.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation development has been adequately performed. No bioequivalence study is deemed necessary as the drug product is administered as a liquid parenteral product. The drug product is sterilized by means of aseptic filtration. The choice of this method has been sufficiently justified. No overages are needed. The absence of a buffer system, as present in the innovator product, was justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is divided into several steps: preparation of a bulk solution, sterile filtration followed by aseptic filling and lyophilisation. The process is therefore considered non-standard. Adequate in-process controls have been laid down. Validation data has been provided for three batches. The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients
The excipients comply with the requirements of their Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification (pantoprazole and sodium), pH, water content, completeness and clarity of solution, uniformity of dosage units, absorbance, transmittance, reconstitution time, particulate matter, sterility, bacterial endotoxins, related substances and assay. The release and shelf-life limits differ in limits for water content and individual and total impurities. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three production-scale batches, demonstrating compliance with the release specification.

Microbiological attributes
The integrity of the container closure system was tested by microbial challenge tests. No growth was observed in the test vials, showing that the integrity of the system was satisfactory.

Stability of drug product
Stability data on the product has been provided of three production-scale batches stored at 25°C/60% RH (9 months), 30°C/65% RH (9 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 clear type I glass vials with grey bromobutyl rubber stoppers and aluminium seals. The product was demonstrated to be photostable. Out-of-specification results (OOS) were observed after 2 months under accelerated storage conditions. During intermediate and long-term stability studies a decrease in assay and an increase in related substances and water content were observed. The results for several impurities after 9 months of storage under intermediates conditions are at the specified limit. Therefore, no extrapolation can be allowed and a shelf-life of only 9 months was granted. The applicable storage condition is ‘store below 25°C’.

Compatibility/In-use stability
The stability of the powder for solution for injection after reconstitution with 10 ml 0.9% NaCl has been studied at 20-25°C for 12 hours. The solution was stable up to 12 hours at controlled room temperature (20-25°C). The stability of the solution after mixing with the diluents 0.9% NaCl and 5% glucose was tested. After reconstitution of the powder with 10 ml 0.9% NaCl to 4 mg/ml, the solution was injected with a calibrated syringe into 100 ml infusion (plastic) bottles of 0.9% NaCl or 5% glucose. The admixtured solutions were stored at controlled room temperature (20-25°C) and were found to be stable over a period of 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.2 Non-clinical aspects

This product is a generic formulation of Pantozol 40 mg, powder for solution for injection, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of pantoprazole released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Pantoprazole is a well-known active substance with established efficacy and tolerability.

Pantoprazol SUN 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 SUN 40 mg 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.

Risk management plan
Pantoprazole was first approved in 1994, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of pantoprazole can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Pantozol.

Readability test
The package leaflet 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 a pilot test with 5 participants, followed by one round with 15 participants. The overall score of the two rounds of user testing, using the total respondents that could locate the information, was 100% for giving the correct answers. The overall conclusion was that the PIL did not need any amendements.
The test has been performed with the PIL which was proposed by the MAH at the beginning of the procedure. In the meantime, after the readability test, an article 30 referral for Protium (Pantozol) has been finalized. The PIL has been harmonised with the outcome of the article 30 Referral. This is acceptable, as readability has been demonstrated for this harmonised PIL.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Pantoprazol SUN 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.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 40 mg, powder for solution for injection with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 1 July 2010. Pantoprazol SUN 40 mg, powder for solution for injection was authorised in the Netherlands on 30 August 2010.

A European harmonised birth date has been allocated (23 August 1994) and subsequently the first data lock point for pantoprazole is August 2012. The first PSUR will cover the period from July 2010 to August 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 1 July 2015.

The following post-approval commitments have been made during the procedure:

<u>Quality - medicinal product</u>

- The MAH committed to review the release and shelf-life limits for water content and total impurities at the end of the stability study.
- The MAH committed to provide additional stability data of the ongoing stability studies with the drug product, covering the whole shelf life.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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