CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Pantogerolan 20 mg, gastro-resistant tablets M.R. Pharma GmbH, Germany

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/1852/001/DC
Registration number in the Netherlands: RVG 105947

5 April 2011

Pharmacotherapeutic group:	drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), proton pump inhibitors
ATC code:	A02BC02
Route of administration:	oral
Therapeutic indication:	short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults
Prescription status:	non prescription
Date of authorisation in NL:	28 March 2011
Concerned Member States:	Decentralised procedure with AT, BG, CZ, EE, HU, LT, LV, RO
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 Pantogerolan 20 mg, gastro-resistant tablets from M.R. Pharma GmbH. The date of authorisation was on 28 March 2011 in the Netherlands.
The product is indicated for short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

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 blockade of the proton pumps of the parietal cells (a gastric proton pump inhibitor, (PPI)). Pantoprazole is converted to its active form, a cyclic sulphenamide, 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. In most patients, freedom from heartburn and acid reflux symptoms is achieved in 1 week. Pantoprazole reduces acidity in the stomach and thereby increases gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the active substance is given orally or intravenously.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Pantozol 20 mg gastro-resistant tablets (NL License RVG 23513) which has been registered in the Netherlands by Altena Pharma since 28 December 1998 through MRP DE/H/0268/001. The current MAH is Nycomed B.V. 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. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Pantozol 20 and 40 mg, gastro-resistant tablets registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic 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 practically insoluble in hexane. Pantoprazole sodium exists in two polymorphic forms: monohydrate and sesquihydrate. Pantoprazole has a chiral atom, therefore two possible enantiomers exist. Both manufacturers produce a racemic mixture.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of 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
The manufacturing process of pantoprazole sodium sesquihydrate consists of 2 steps. The drug substance has been adequately characterized and acceptable specifications have been adopted for the solvents and reagents.

Quality control of drug substance
One overall drug substance specification has been composed from the specifications from the drug substance manufacturers and the Ph.Eur. The specification is acceptable and in line with the various European guidelines and the Ph.Eur. Batch analytical data have been provided for three batches per drug substance supplier, analysed at the drug product manufacturing sites. The MAH committed to provide additional batch analysis data on drug substance from one of the suppliers.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches from one supplier, and four full-scale batches from the other. The batches were stored at 25°C/60% RH (18 months for 1 supplier, 36 months for the other) and 40°C/75% RH (6 months for both).
All parameters tested are considered to be stable, no trends were observed. Therefore the proposed retest periods of 30 months for the first supplier, and 4 years for the other supplier could be granted without special storage conditions.

** 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
Pantogerolan 20 mg contains as active substance 20 mg pantoprazole (as sodium sesquihydrate) and is a yellow, oval tablet.

The gastro-resistant tablets are packed in oPA/Alu/PVC-Aluminium blisters or HDPE bottles with PP closure with a desiccant container.

The excipients are:
Tablet core - maltitol (E965), crospovidone type B, carmellose sodium, anhydrous sodium carbonate, calcium stearate.
Tablet coating - poly(vinyl alcohol), talc, titanium dioxide (E 171), macrogol 3350, soya lecithin, iron oxide yellow (E 172), sodium carbonate, anhydrous, methacrylic acid-ethyl acrylate copolymer (1:1), sodium laurilsulfate, polysorbate 80, triethyl citrate.

Pharmaceutical development
The development of the drug product has been adequately described, the choice of excipients is justified and their functions explained. The MAH's objective was to produce pantoprazole delayed release tablets 20 that would be essentially similar to the reference product Pantozol®.
The pantoprazole batches of 20 mg are used in bioequivalence studies. The dissolution profile is obtained conform the method as described in the Ph.Eur. monograph on dissolution testing for delayed-release solid dosage forms. The biobatches demonstrated similar dissolution profiles.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of wet granulation, blending of the granules, compression and film-coating. The product is manufactured using conventional manufacturing techniques. Process validation has been performed on three production-size batches per manufacturing site. It has been adequately demonstrated that the manufacturing process can adequately produce a product that is in line with the specification. The results from the process validation have been included in the dossier.

Control of excipients
All excipients except lecithin and iron oxide yellow are specified according to the Ph.Eur. Iron oxide yellow and lecithin are specified according to an in-house specification. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification of pantoprazole and colorants, water content, dissolution, assay, related substances, uniformity of dosage units and microbial limits. The release and shelf-life specifications are identical with the exception of related substance impurity and total impurities.
The analytical methods have been adequately described and validated. Batch analytical data from all proposed production-sites have been provided, demonstrating compliance with the release specification.

Stability of drug product
Three batches per strength have been included in the stability study. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in HDPE-bottles with PP cap and 2g desiccant PE container, Al/Al blister and in bulk packaging. Six months accelerated and 36 months long term data are available for the tablets packed in HDPE-bottles, and 48 month long term data for the Al-Al blister packed tablets. The studied parameters remained within the specified limits and there appeared to be no significant changes in time. An in-use stability study was performed on one batch wherein the container was opened and closed daily for three months. After 33 months of in-use testing no changes were observed.
Also for the bulk stability testing no changes were observed in the studied parameters over a six month period. The following shelf life and storage conditions were granted: 36 months packed in a HDPE bottle and 48 months for the Al/Al blister without special storage condition.

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. Calcium stearate and lecithin are from vegetable origin.

II.2 Non-clinical aspects

This product is a generic formulation of Pantozol, 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.

For this generic application, the MAH has submitted 2 bioequivalence studies in which the pharmacokinetic profile of the test product Pantogerolan 20 mg (M.R. Pharma GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Pantozol 20 mg gastro-resistant tablets (Altana Pharma/Nycomed, Germany). One study was conducted under fasted conditions, the other under fed conditions.

The choice of the reference product
The choice of the reference products in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study I – 20 mg, fasted
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male subjects, aged 18-41 years. Each subject received a single dose (20 mg) of one of the 2 pantoprazole formulations. The tablet was orally administered with 200 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 1, 1.5, 2, 2.5, 3.33, 3.66, 4, 4.33, 4.66, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 16, and 24 hours after administration of the products.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All 44 subjects completed the study and were included in the pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pantoprazole under fasted conditions.

Treatment N=44	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	3003 ± 2646	3120 ± 3041	1362 ± 410	2.0(1.5 – 4.0)	1.8 ± 1.4

Reference	2859 ± 2493	3000 ± 2933	1257 ± 480	2.0 (1.0 – 4.33)	2.3 ± 2.4
***Ratio (90% CI)**	1.06 (0.99-1.13)	1.05 (0.98-1.13)	1.12 (1.02-1.24)	--	--
CV (%)	19.1	19.1	27.6	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. Based on the pharmacokinetic parameters of pantoprazole under fasted conditions, it can be concluded that Pantogerolan 20 mg and Pantozol 20 mg gastro-resistant tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study II –20 mg, fed

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 44 healthy subjects (24 males/20 females), aged 18-43 years. Each subject received a single dose (20 mg) of one of the 2 pantoprazole formulations within 30 min of the start of intake of a high fat breakfast (1 buttered slice of bread, 1 egg, 1 slice of bacon (25 g), 125 g French fries, and 250 ml whole milk; total calories 945, of which 478 cal from fat (about 50%)). The tablets were administered in solid form with 200 ml low carbonated water. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 1, 1.5, 2, 2.5, 3.33, 3.66, 4, 4.33, 4.66, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 16, and 24 hours after administration of the products.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One subject dropped out for personal reasons. Pharmacokinetic analysis was carried out on 43 subjects.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pantoprazole under fed conditions.

Treatment N=43	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1997 ± 1112	2117 ± 1070	1201 ± 511	4.67 (2.0 – 24.0)	1.1 ± 0.3
Reference	1982 ± 945	2092 ± 890	1290 ± 487	4.33 (1.0 – 24.0)	1.2 ± 0.3
***Ratio (90% CI)**	1.03 (0.97-1.10)	1.02 (0.95-1.08)	1.10 (1.01-1.19)	--	--
CV (%)	17.7	16.7	22.4	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity				
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours				
C_{max}	maximum plasma concentration				
t_{max}	time for maximum concentration				
$t_{1/2}$	half-life				

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. Based on the pharmacokinetic parameters of pantoprazole under fed conditions, it can be concluded that Pantogerolan 20 mg and Pantozol 20 mg gastro-resistant tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

From the literature it is known that food interacts with the absorption of pantoprazole. Therefore bioequivalence studies have been conducted under fasted and fed conditions, in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence. The interaction is such that no influence on clinical efficacy can be espected; pantoprazole may be taken without reference to food intake.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Control. The product information will remain similar with the centrally authorised reference product.

Readability test

The package leaflet has not been evaluated via a user consultation study. Instead a bridging report was provided. The wording of the Pantozol Control PIL has been adopted literally. The MAH sufficiently demonstrated that the lay-out of the 'daughter PIL' is similar to that of the 'parent PIL'.
Sufficient evidence for successful user testing of the Pantozol Control PIL has been provided and therefore a separate user test is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Pantogerolan 20 mg, gastro-resistant tablets has a proven chemical-pharmaceutical quality and is a generic form of Pantozol 20 mg gastro-resistant tablets. Pantozol is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other pantoprazole containing products.

The legal status of supply for Pantogerolan 20 mg, gastro-resistant tablets is non-prescription. This is in accordance with the reference product Pantoloc Control 20 mg, which has been approved through the centralised procedure. Further information can be found in the EPAR of Pantoloc Control (Doc.Ref.: EMEA/374696/2009).

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 Pantogerolan 20 mg, gastro-resistant tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 17 November 2010. Pantogerolan 20 mg, gastro-resistant tablets was authorised in the Netherlands on 28 March 2011.

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 November 2010 to August 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 17 November 2015.

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

Quality - active substance

- The MAH committed to provide batch analytical data from three consecutive batches of drug substance from one of the suppliers.

Quality - medicinal product

- The MAH committed to perform post-approval stability studies on manufacturing-scale batches.
- The MAH committed to maintain the product information in accordance with the centrally authorised product Pantozol Control.

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