COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Pantoprazol ARX 40 mg gastro-resistant tablets

(pantoprazole)

NL/H/4641/002/DC

Date: 26 May 2020

This module reflects the scientific discussion for the approval of Pantoprazol ARX 40 mg gastro-resistant tablets. The procedure was finalised at 26 February 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 ARX 40 mg gastro-resistant tablets, from Amarox Limited.

The product is indicated for use in adults and adolescents 12 years of age and above for:

- Reflux oesophagitis.

The product is indicated in adults for:

- Eradication of *Helicobacter pylori* (*H. pylori*) in combination with appropriate antibiotic therapy in patients with *H. pylori* associated ulcers.
- 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 gastro-resistant tablets (NL License RVG 18300), which has been registered in the Netherlands by Takeda Nederland bv since 1995 through a mutual recognition procedure (AT/H/0588/002). In addition, reference is made to pantoprazole authorisations in the individual member states all belonging to the same Global Marketing Authorisation (EMEA/H/A-30/1002).

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

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

Withdrawal of the 20 mg strength
Initially the application included another strength: Pantoprazol ARX 20 mg gastro-resistant tablets. Bioequivalence was not demonstrated with the reference product and therefore this strength was considered not approvable. The company MAH withdrew Pantoprazol ARX 20 mg gastro-resistant tablets from the application before finalisation of the procedure.

II. QUALITY ASPECTS

II.1 Introduction

Pantoprazol ARX is a yellow to pale yellow, oval, biconvex gastro-resistant tablet imprinted with "H126" on one side with black ink and plain on the other side. Each gastro-resistant tablet contains pantoprazole sodium sesquihydrate, equivalent to 40 mg pantoprazole.

The gastro-resistant tablets are packed in PVC/Al/OPA-Al blister packs and/or HDPE container pack with child resistant white opaque polypropylene plastic caps.

The excipients are:
Core - lactose monohydrate, hydroxypropylcellulose, calcium stearate, sodium carbonate and sodium laurilsulfate
Coating - hypromellose, yellow iron oxide (E 172), propylene glycol, titanium dioxide (E 171), methacrylic acid-ethyl acrylate copolymer (1:1), triethyl citrate and polysorbate 80
Printing ink – shellac, black iron oxide (E172) and propylene glycol

II.2 Drug Substance

The active substance is pantoprazole, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is white or almost white and is freely soluble in water and in ethanol (96%), practically insoluble in n-hexane. Pantoprazole sodium exhibits polymorphism; the pantoprazole sodium sesquihydrate crystalline form-I is consistently produced.

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 requirements for residual solvents. In addition, the MAH also included particle size and microbiological examination in

the specification. Batch analytical data demonstrating compliance with this specification have been provided for three production scaled batches.

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. The choices of the packaging and manufacturing process are justified in relation to the innovator. The manufacture and composition of the bio-batches used in bioavailability/bioequivalence studies is identical to the marketed product. The discriminatory capabilities of the proposed dissolution method have been adequately demonstrated. The pharmaceutical development of the product has generally been adequately performed.

Manufacturing process
The manufacturing process involves dry granulation, direct compression and enteric coating and has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full-scaled batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur. requirements with some additional tests. The 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, identity, average weight, water content, dissolution, uniformity of dosage units, related substances, assay, microbiological examination and identification of the colourants. The release and shelf-life requirements/limits are identical with exception of the water content. 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 production scaled 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 production scaled batches stored at 25°C/60% RH (up to 36 months) and 30°/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 proposed packaging. Photostability data on 2

production scaled batches have been submitted in line with ICH guidelines. The drug product is not light sensitive. On basis of the data submitted, a shelf life was granted of 2 years when stored below 30°.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate has been produced from milk that has been sourced from healthy cows in the same conditions as milk collected for human consumption. It is produced without the use of other ruminant material than calf rennet, according to the description as published in Public Statement EMEA/CPMP/571/02 of 27 February 2002.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Pantoprazol ARX 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 ARX 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.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Pantoprazol ARX 40 mg gastro-resistant tablets (Amarox Limited, UK) is compared with the pharmacokinetic profile of the reference product Pantoprazole Takeda 40 mg (Takeda, Germany), one under fasting conditions and one under fed conditions.

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

The design of the studies is acceptable and in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence. The washout period is sufficient (terminal half-time of approximately 1 hour). The sampling scheme covered 36 hours, which seems to be sufficient to estimate pharmacokinetic parameters of interest.

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

Bioequivalence studies
Bioequivalence study I – 40 mg, under fasted conditions
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 18-45 years. Each subject received a single dose (40 mg) of one of the 2 pantoprazole formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected within 1.00 hours prior to dosing and at 0.50, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 20.00, 24.00 and 36.00 hours after administration of the products.

Results

One subject withdrew on his own accord and two subjects did not return to the facility before the second period. Therefore, a total of 41 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=41	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	16302 ± 12862	17235 ± 14970	3933 ± 919	3.0 (2.0 – 6.0)
Reference	16786 ± 13546	17806 ± 15780	4131 ± 1194	2.7 (1.7 – 6.0)
***Ratio (90% CI)**	0.99 (0.94 – 1.03)	0.98 (0.94 – 1.03)	0.97 (0.91 – 1.04)	--
CV (%)	13.01	12.99	17.44	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Bioequivalence study II – 40 mg, fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 48 healthy male subjects, aged 18-45 years. Each subject received a single dose (40 mg) of one of the 2 pantoprazole formulations. The tablet was orally administered with 240 ml water 30 minutes of a high fat high calorie breakfast (consisting of fried chicken, Bombay toast, French fries and milk). There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected within 1.00 hours prior to dosing and at 0.50, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 20.00, 24.00 and 36.00 hours after administration of the products.

Results

One subject did not return to the facility before the second period. Therefore, a total of 47 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}	t_{max}

N=47	(ng.h/ml)	(ng.h/ml)	(ng/ml)	(h)
Test	14384 ± 11841	15094 ± 13337	3477 ± 1025	5.5 (2.0 – 22.0)
Reference	14203 ± 11620	14940 ± 13258	3536 ± 1000	5.0 (3.0 – 14.0)
***Ratio (90% CI)**	1.00 (0.96 – 1.05)	1.00 (0.96 – 1.05)	0.98 (0.90 – 1.06)	--
CV (%)	12.35	12.55	22.76	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Pantoprazol ARX is considered bioequivalent with Pantoprazole Takeda.

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).

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 ARX.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

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. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the

product is similar to the pharmacokinetic profile of this reference product. 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 Pantoprazol 20 mg, 40 mg (UK NAP, PL 01656/0024-31) for the content and to Levetiracetam Hetero 750 mg (PT/H/0515/001-004/DC) for the lay-out and design. 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 ARX 40 mg gastro-resistant tablets has a proven chemical-pharmaceutical quality and is a generic form of Pantozol 40 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 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 ARX with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 February 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