COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Pantoprazol Ametas 20 mg and 40 mg gastro-resistant tablets (pantoprazole sodium sesquihydrate)

NL/H/5056/001-002/DC

Date: 23 September 2022

This module reflects the scientific discussion for the approval of Pantoprazol Ametas 20 mg and 40 mg gastro-resistant tablets. The procedure was finalised on 28 April 2022. 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 Ametas 20 mg and 40 mg gastro-resistant tablets from Ametas medical GmbH.

Pantoprazol Ametas 20 mg is indicated in:

- *adults and adolescents 12 years of age and above for*
  - symptomatic gastro-oesophageal reflux disease
  - long-term management and prevention of relapse in reflux oesophagitis
- *adults for*
  - prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment.

Pantoprazol Ametas 40 mg is indicated in:

- *adults and adolescents 12 years of age and above for*
  - reflux oesophagitis
- *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 hypersecretory conditions.

Comprehensive descriptions of the indications and posology are given in the SmPCs.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Pantozol 20 mg and 40 mg gastro-resistant tablets (NL License RVG 23513 and 18300 respectively), which have been registered in the Netherlands by Takeda Nederland B.V. since 1995 via mutual recognition procedures (AT/H/0588/002/DC for 40 mg and DE/H/0268/001/DC for 20 mg). In addition, reference is made to pantoprazole authorisations in the individual member states all belonging to the same Global Marketing Authorisation. The reference products have been included in a pantoprazole Article 30 referral (EMEA/H/A-30/1002).

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

Pantoprazol Ametas 20 mg tablets are elliptical, biconvex light yellow and enteric-coated (gastro-resistant). Each tablet contains as active substance pantoprazole sodium sesquihydrate, equivalent to 20 mg pantoprazole.
Pantoprazol Ametas 40 mg tablets are elliptical, biconvex dark yellow and enteric-coated. Each tablet contains as active substance pantoprazole sodium sesquihydrate, equivalent to 40 mg pantoprazole.

Each strength of tablets is packed in aluminium/aluminium blister packs.

The excipients for both tablet strengths are:

- *Core* - mannitol (E421), anhydrous sodium carbonate (E500), sodium starch glycolate (Type A), basic butylated methacrylate copolymer and calcium stearate (E470A);
- *Sub-coating* - hypromellose (E464), titanium dioxide (E171), talc (E553B), macrogol 400 and sodium lauryl sulfate (E487);
- *Enteric coating* - methacrylic acid-ethyl acrylate copolymer dispersion, propylene glycol (E477), yellow iron oxide (E172), titanium dioxide (E171) and talc (E553B).

The excipients and packaging are usual for this type of dosage form. The two tablet strengths are fully dose proportional.

II.2 Drug Substance

The active substance is pantoprazole sodium sesquihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is very soluble in water and in ethanol (96 %), has a chiral sulphur in its chemical structure and exhibits optical isomerism. The substance is produced as a racemate: it has equal left- and right-handed isomers. It does not exhibit polymorphisms.

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. In addition to the monograph requirements, the MAH adopted tests and limits for residual solvents and microbiological quality. A description of the methods used and the validation reports of the in-house methods have been provided. Batch analytical data demonstrating compliance with this specification have been provided for three 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 products are an established pharmaceutical form and their development is adequately described in accordance with the relevant European guidelines. Several development studies have been performed related to the choice and quantity of the excipients and the choice of the manufacturing process.

The MAH provided dissolution data of validation batches from two manufacturing sites. In general, the pharmaceutical development of the products has been adequately performed.

Manufacturing process
The manufacturing process consists of dry mixing, sifting, blending, wet granulation and sifting. The granulates are dried, sifted and blended with calcium stearate. These steps are followed by compression, film-sub coating, enteric coating and packing. The manufacturing process is considered a non-standard process, and it has been described in sufficient detail.
Process validation data were presented for the three batches of common blend, and two batches per strength (20 mg and 40 mg) manufactured from this blend. These validation data led to approval of one site for each product strength.

Control of excipients
The excipients comply with Ph. Eur. monographs and in-house requirements. An exception is iron oxide yellow, which is not described in the Ph. Eur. Reference to the United States Pharmacopeia and the National Formulary is made. This is 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, identification, uniformity of dosage units by content uniformity, disintegration, assay, related substances, residual

solvents and microbiological quality. The release and shelf-life limits are identical. The proposed dissolution limit is in line with Ph. Eur. section 2.9.3 ("Dissolution test for solid dosage forms", method A) and with the dissolution data of the bio-batches. The proposed specifications are acceptable and the analytical methods have been adequately described and validated. Batch analytical data from several batches for each strength demonstrated compliance with the specification.

Stability of drug product

Stability data have been provided for drug product batches of both strengths. The photostability study is acceptable, demonstrating the product is photostable. Based on the submitted data, a shelf life was granted of 3 years for the 40 mg strength and 4 years for the 20 mg strength. No special storage conditions are required.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The finished products do not contain any excipients of human or animal origin, 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 Ametas has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished products.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Pantoprazol Ametas is intended for generic substitution, it 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

These products are generic formulations of Pantozol 20 mg and 40 mg gastro-resistant tablets which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. 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 four bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Pantoprazol Ametas 40 mg, gastro-resistant tablets (Ametas medical GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Pantozol 40 mg gastro-resistant tablets (Takeda, Nederland). On request of the MEB, an additional bioequivalence study was performed for Pantoprazol Ametas 20 mg gastro-resistant tablets (Ametas medical GmbH, Germany) versus Pantozol 20 mg gastro-resistant tablets (Takeda Nederland). In accordance with the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1), a single dose study under fasting conditions is required for all strengths as this is a monolithic formulation. As per the guideline, one single dose bioequivalence study at the highest/most sensitive strength conducted in fed state is acceptable. The formulas and preparation of the bioequivalence batches are identical to the formulas proposed for marketing.

Bioequivalence studies

Study 1 – Fasting, single-dose, 40 mg

Design

An open label, randomised, comparative, single dose, two-way crossover bioequivalence study was carried out under fasted conditions in 50 healthy male subjects, aged 19 - 55 years. Each subject received a single dose (40 mg) of both the test and reference gastro-resistant pantoprazole formulations with 240 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. For each subject there were two dosing periods, separated by a washout period of 14 days. Blood samples were collected pre-dose and at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 7, 8, 10 and 12 hours after administration of the products.

Analytical/statistical methods

The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable. Doubts were raised about the robustness of the analytical method concerning the analysis of subject samples. Based on reanalysis of several samples, it was concluded that the results indicated sufficient reproducibility. Overall, the lack of the incurred sample reanalysis (ISR) data has been sufficiently addressed and the analytical method is considered acceptable for analysis of the plasma samples.

Results

One subject was withdrawn prior check-in of Period II due to an adverse event (AE). One subject withdrew from the study prior check-in of Period II. This resulted in 48 subjects completing the study entirely, who were eligible for pharmacokinetic analysis.

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

Treatment N=48	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	5579 ± 3926	6122 ± 5959	3310 ± 831	2.3 (1.0 – 5.0)	1.3 ± 1.2
Reference	5408 ± 4232	5958 ± 6333	2939 ± 848	2.3 (1.0 - 6.0)	1.4 ± 1.2
***Ratio (90% CI)**	1.05 (0.99 - 1.12)	1.05 (0.99 – 1.11)	1.14 (1.04 - 1.25)	--	--
CV (%)	17.9	17.4	26.3	--	--

$AUC_{0-\infty}$ 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
CV coefficient of variation
***** ln-transformed values

Study 2 – Fed, single-dose, 40 mg

An open label, randomised, single dose, two-way crossover bioequivalence study was carried out under fed conditions in 180 healthy male subjects, aged 18 - 55 years. Each subject received a single dose (40 mg) of both the test and reference pantoprazole formulations. For each subject there were 2 dosing periods, separated by a washout period of 14 days. The design of the study was acceptable, and the test and reference products were acceptable. However, the absorption of pantoprazole is usually delayed under fed conditions and was reported to be highly variable due to its extremely rapid absorption. This led to several concentration-time profiles being missed or not adequately covered. As a result, some subjects displayed only a few measurable plasma concentrations of pantoprazole over the 26-hour sampling period. Therefore, an extra study with 40 mg tablets under fed conditions (study 3) was carried out with a better sampling scheme.

Study 3 – Fed, single-dose, 40 mg

Design

An open label, randomised, single dose, two sequence, two treatment, two-way crossover bioequivalence study was carried out under fed conditions in 80 healthy male subjects, aged 18 - 34 years. Each subject received a single dose (40 mg) of both the test and reference pantoprazole formulations. The tablets were orally administered with 240 ml water, 30 min after start of the intake of a high fat, high caloric breakfast. For each subject there were 2 dosing periods, separated by a washout period of 7 days. Blood samples were collected pre-dose and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24 hours after administration of the products. The design of the study was acceptable.

Analytical/statistical methods

The analytical method is validated and a validation report is provided. The method proved to be sensitive, accurate and precise for the determination of pantoprazole in plasma. Doubts were raised concerning the reproducibility of the analysis due to the effect on the analysis caused by all other components of the sample except the specific compound (also called the matrix effect). Additional data was provided showing that the matrix effect was within criteria, and it was noted that incurred sample reanalysis data from study 4 showed good reproducibility as well. The long-term stability data covered the storage period of the plasma samples (36 days). The applied statistical method by the MAH was acceptable.

Results

One subject withdrew prior check-in of Period II. One subject was withdrawn in Period II due to an AE (vomiting). Two subjects were withdrawn as they were not dosed as per randomisation scheme. This resulted in 76 subjects completing the study entirely, who were eligible for pharmacokinetic analysis. One subject had detectable plasma concentrations only at time points 22, 23 and 24h and no complete C-t curve could be obtained, so exclusion of this subject was considered acceptable.

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

Treatment N=75	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	9165 ± 8518	10318 ± 10777	2932 ± 1106	7.5 (3.0 – 20.0)	2.5 ± 2.6
Reference	10007 ± 9072	11944 ± 13290	2988 ± 1024	7.0 (3.0 - 22.0)	2.9 ± 3.6
***Ratio (90% CI)**	0.93 (0.87 – 0.99)	0.92 (0.86 – 0.97)	0.95 (0.87 - 1.05)	--	--
CV (%)	24.9	22.7	36.1	--	--

$AUC_{0-\infty}$	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
CV	coefficient of variation
*****	ln-transformed values

Study 4 – Fasting, single-dose, 20 mg

Design

An open label, randomised, single dose, two-way crossover bioequivalence study was carried out under fasting conditions in 50 healthy male subjects, aged 18 - 45 years. Each subject received a single dose (20 mg) of one of the both the test and reference pantoprazole formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was continued for 4 h after dosing. For each subject there were 2 dosing periods, separated by a washout period of 5 days. Blood samples were collected pre-dose and at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 10, 12 and 16 hours after administration of the products. The design of the study was acceptable.

Analytical/statistical methods

The analytical method was validated and a validation report is provided. The method was proved to be sensitive, accurate and precise for the determination of pantoprazole in plasma. The long-term stability data are covering the storage period of the plasma samples (14 days). Incurred sample reanalysis showed good reproducibility. The methods used in this study for the pharmacokinetic calculations and statistical evaluation were considered acceptable.

Results

One subject withdrew his consent from the study in Period I. Two subjects were withdrawn prior check-in of Period II due to late arrival and not meeting protocol requirements regarding fasting and housing. One subject was withdrawn in Period II due to an AE. This resulted in 46 subjects completing the study entirely, who were eligible for pharmacokinetic analysis. A pre-dose concentration (<5% of C_{max}) was observed in Period I for one subject. No clear reason could be identified for this and it was agreed that it would not impact the study outcome.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pantoprazole under fasting conditions.

Treatment N=46	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	5926 ± 4089	6529 ± 5438	2226 ± 495	2.3 (0.5 – 5.0)	2.3 ± 1.8
Reference	6149 ± 4351	6718 ± 5697	2235 ± 555	2.3 (0.5 – 4.7)	2.2 ± 1.6
***Ratio (90% CI)**	0.97 (0.91 - 1.04)	0.98 (0.91 – 1.05)	1.01 (0.95 - 1.06)	--	--
CV (%)	20.0	20.4	16.1	--	--

$AUC_{0-\infty}$ 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
CV coefficient of variation
* ln-transformed values

Overall conclusion on the bioequivalence studies

In studies 1, 3 and 4, 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. Study 2 was not used in the assessment due to the limited number of measurable plasma concentrations as a result of the sample schedule combined with fast absorption of the product under fed conditions.

In study 1, the CI for C_{max} was right on the 1.25 limit; it was noted that sample mistake preparation and thus reproducibility could have had an impact. Study 3 provided additional incurred sample reanalysis (ISR) data, supporting reproducibility, and study 4 ISR data showed good reproducibility. Overall, the ISR data in study 1 have been sufficiently addressed and the analytical methods of the studies were accepted.

Based on studies 1, 3 and 4, Pantoprazol Ametas 20 mg gastro-resistant tablets (Actavis), is considered bioequivalent with Pantozol 20 mg gastro-resistant tablets and Pantoprazol Ametas 40 mg, gastro-resistant tablets (Actavis), is considered bioequivalent with Pantozol 40 mg gastro-resistant tablets.

The MEB has been assured that the bioequivalence studies used in the assessment have 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 Ametas.

Table 4. 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 products Pantozol 20 mg and 40 mg gastro-resistant tablets. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profiles of the products are similar to the pharmacokinetic profile of these reference products. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

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 for the content making reference to Pantoprazol Beximco 20 mg and 40 mg gastro-resistant tablets (UK/H/2769/002/DC), and a bridging report for the layout making reference to Pantoprazole 20 mg gastro-resistant tablets (UK/H/2769/002/DC). The bridging reports submitted by the MAH have been found acceptable; bridging is justified for both content and layout of the leaflet. The package leaflets of Pantoprazole Ametas meet the criteria set out in Art 59(3) of Directive 2001/83/EC.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pantoprazol Ametas 20 mg and 40 mg gastro-resistant tablets have a proven chemical-pharmaceutical quality and are generic forms of Pantozol 20 mg and 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 Ametas 20 mg and 40 mg gastro-resistant tablets with the reference product, and have therefore granted a marketing authorisation. The decentralized procedure was finalised with a positive outcome on 28 April 2022.

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