COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5963/001-002/DC

Date: 8 October 2025

This module reflects the scientific discussion for the approval of Pantoprazol Reddy 20 mg and 40 mg gastro-resistant tablets. The procedure was finalised on 10 December 2024. 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
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
NSAID	Non-Steroidal Anti-Inflammatory Drug
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
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 Reddy 20 mg and 40 mg gastro-resistant tablets, from Reddy Holding GmbH.

Pantoprazol Reddy 20 mg
The product is indicated for use 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.

The product is indicated for use in 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 Reddy 40 mg
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 hypersecretory conditions.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new products and the innovator products Pantozol 20 and 40 mg, gastro-resistant tablets. In the Netherlands, Pantozol 20 mg has been registered by Takeda Austria GmbH since 28 December 1998 by the procedure DE/H/0268/001 (NL RVG 23513). Pantozol 40 mg has been registered in the Netherlands (NL RVG 18300) by Takeda Nederland B.V. since 6 June 1995 by the procedure AT/H/0588/002.

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

II. QUALITY ASPECTS

II.1 Introduction

Pantoprazol Reddy 20 mg and 40 mg are gastro-resistant tablets.

Pantoprazol Reddy 20 mg are white to off white, round biconvex tablets, plain on both sides with an approximate diameter of 5.9 mm. Each tablet contains as active substance 20 mg of pantoprazole (as sodium sesquihydrate).
Pantoprazol Reddy 40 mg are light yellow to yellow, round biconvex tablets, plain on both sides with an approximate diameter of 7.9 mm. Each tablet contains as active substance 40 mg of pantoprazole (as sodium sesquihydrate).

The excipients are, for both strengths:
Tablet core: sodium carbonate, mannitol (E421), crospovidone, hydroxypropylcellulose, calcium stearate and talc.
Coating: hypromellose, titanium dioxide (E171), macrogol, methacrylic acid - ethyl acrylate copolymer (1:1), purified water, sodium laurilsulfate, triethyl citrate, talc and yellow iron oxide (E172).

The tablets are packed in - Alu blisters, made of a combination of oriented polyamide (OPA), aluminium (Alu) and polyvinyl chloride (PVC).

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 white or almost white and is freely soluble in water, methanol and ethanol (96%), practically insoluble in n-hexane. Due to the chiral sulfoxide, pantoprazole sodium exhibits optical activity.
For this product, polymorphic form-I is consistently produced. This is the same as the reference product.

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 in line with the Ph. Eur. and CEP, with additional in-house requirements for bulk density and microbial quality. The specification is acceptable.

Batch analytical data demonstrating compliance with this specification have been provided for four production scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three production scale batches in accordance with applicable European guidelines. Additional stability data are provided for three different batches. Based on the data submitted, a retest period could be granted of 24 months when stored under the stated conditions.

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-batch used in the bioequivalence (BE) studies is identical to the product initially intended for marketing. Therapeutic equivalence to the reference product could not be shown based on dissolution data, hence reference is made to the clinical BE studies.

Alcohol dose dumping studies were conducted in quality control (QC) medium, in line with relevant EMA guidance. No drug release was seen in pH 1.2 medium and in pH 6.8 medium no deviations in release are observed between the reference and test product in the presence of alcohol. A slight delay of the release of pantoprazole can be observed at higher ethanol concentrations, meaning that no dose dumping occurs. This is acceptable and no reformulation or warning in the SmPC is necessary.

Manufacturing process
The tablets are manufactured by milling of sodium carbonate, sifting of intragranular, granulation and drying, milling, sifting of extra granular, blending, compression, seal coating and enteric coating. The manufacturing process has been adequately validated according to relevant European guidelines.

Process validation data on the product has been presented for three production scale batches of both strengths, in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with Ph. Eur., USP or in-house requirements. 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, identity, assay, uniformity of

dosage units, dissolution, related substances, water content and microbiological examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

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.

Stability of drug product

Stability data on the product have been provided for three full scale batches stored at 25°C/ 60% RH (12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months. No specific storage conditions needed to be included in the SmPC or on the label.

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 Pantoprazol Reddy 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 Reddy is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was 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 was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further clinical studies are required, besides the four bioequivalence studies, which are discussed below. No biowaiver of strength is requested, as therapeutic equivalence of the two strengths is based on the BE studies.

IV.2 Pharmacokinetics

The MAH conducted four bioequivalence studies in which the pharmacokinetic profile of the test products Pantoprazol Reddy 20 mg and 40 mg gastro-resistant tablets (Reddy Holding GmbH, Germany) was compared with the pharmacokinetic profile of the reference products Pantozol 20 and 40 mg, gastro-resistant tablets (Takeda GmbH, Germany).

The choice of the reference products in the bioequivalence studies has been investigated by comparison of dissolution study results and composition. The dissolution results of the reference product versus test product were dissimilar, due to differences in formulation and differences in physical characteristics. According to the guideline of Bioequivalence, if the results of comparative *in vitro* dissolution of the bio batch do not reflect bioequivalence *in vivo* (as shown) the latter prevails.

Bioequivalence studies

Study 1: pantoprazole 20 mg under fasting 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 24-42 years. Each subject received a single dose (20 mg) of one of the two pantoprazole formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of at least three days.

Blood samples were collected pre-dose and at 0.33, 0.67, 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, 16 and 24 hours after administration of the products.

The design of the study is acceptable.

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
44 Subjects enrolled in the study. There were no drop-outs, all 44 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pantoprazole sodium sesquihydrate, 20 mg 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)**
Test	7552 ± 5079	8124 ± 5995	2070 ± 494	2.33 (1.33 – 5.00)
Reference	7856 ± 5624	8537 ± 6867	2117 ± 573	2.33 (1.00 – 4.33)
***Ratio (90% CI)**	0.98 (0.96 – 1.00)	0.98 (0.95 – 1.00)	0.98 (0.94 – 1.03)	

$AUC_{0-\infty}$	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 = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2: pantoprazole 20 mg under fed conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in X healthy male subjects, aged 20-42 years. Each subject received a single dose (20 mg) of one of the two pantoprazole formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours and subsequent consumption of a standardised high fat, high caloric breakfast of 924 kcal (of which 55% fat) 30 minutes before dosing. There were two dosing periods, separated by a washout period of at least three days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 20 and 24 hours after administration of the products.

The design of the study is acceptable.

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
44 Subjects enrolled in the study. There were no drop-outs, all 44 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pantoprazole sodium sesquihydrate, 20 mg under fed conditions.

Treatment N=44	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ [1] (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	6418 ± 5318	7767 ± 7629	1550 ± 507.4	7.0 (2.5 – 20)
Reference	7047 ± 5971	7786 ± 77514	1652 ± 560	5.5 (2.5 – 11)
***Ratio (90% CI)**	0.94 (0.87-1.02)	1.00 (0.94-1.07)	0.95 (0.86-1.06)	

$AUC_{0-\infty}$	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 = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

[1] **n= 39. Four subjects did not exhibit a terminal log-linear phase in concentration versus time profile and were excluded from estimation of $AUC_{0-\infty}$ parameter**

Study 3: pantoprazole 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 19-42 years. Each subject received a single dose (40 mg) of one of the two pantoprazole formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of at least three days.

Blood samples were collected pre-dose and at 0.33, 0.67, 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, 16 and 24 hours after administration of the products.

The design of the study is acceptable.

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
44 Subjects enrolled in the study. There were no drop-outs, all 44 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pantoprazole sodium sesquihydrate, 40 mg 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)**
Test	12823 ± 10362	13985 ± 12929	3946 ± 901	3.0 (1.67 – 4.67)
Reference	13155 ± 11016	14360 ± 13740	3676 ± 984	2.67 (1.67 – 6.00)
***Ratio (90% CI)**	1.00 (0.95 – 1.04)	1.00 (0.95 – 1.04)	1.12 (1.01 – 1.24)	

$AUC_{0-\infty}$	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 = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 4: pantoprazole 40 mg under fed conditions
Design
A single-dose, randomised, four-period, two-treatment, two-sequence, replicate design crossover bioequivalence study was carried out under fed conditions in 44 healthy male subjects, aged 21-43 years. Each subject received a single dose (40 mg) of one of the two pantoprazole formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours and subsequent consumption of a standardised high fat, high caloric breakfast of 924 kcal (of which 55% fat) 30 minutes before dosing. There were X dosing periods, separated by a washout period of at least three days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 20 and 24 hours after administration of the products.

The design of the study is acceptable.

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
44 Subjects enrolled in the study. One subject was withdrawn from the study due to non-compliance of dose administration during period I. Therefore, 43 subjects were eligible for pharmacokinetic analysis.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pantoprazole sodium sesquihydrate, 40 mg 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)
Test administered first time	12774 ± 10094	14735 ± 13785	3284 ± 1087	6.0 (2.0 – 14.0)
Test administered second time	14347 ± 10770	16325 ± 14571	3380 ± 1037	7.0 (3.0 – 14.0)
Reference administered first time	12704 ± 10534	14676 ± 13997	3350 ± 1337	5.5 (2.0 – 24)
Reference administered second time	14671 ± 10783	17006 ± 14672	3369 ± 1141	6.0 (2.5 – 14.0)
*Ratio (90% CI)	0.99 (0.96 – 1.03)	0.99 (0.96 – 1.02)	1.00 (0.95 – 1.06)	

$AUC_{0-\infty}$	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 = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**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 studies Pantoprazol Reddy 20 mg and 40 mg is considered bioequivalent with Pantozol 20 mg and 40 mg. Concomitant intake of food has no influence on bioavailability.

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 Reddy. At the time of approval, the most recent version of the RMP was version 0.1 dated 8 November 2023.

Table 5. 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. The MAH demonstrated through bioequivalence studies 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. For the design and lay-out, the report is making reference to the PL of Sitagliptin/Metformin 50 mg/850 mg and 50 mg/1000 mg film-coated tablets, approved through decentralised procedure AT/H/1183/001-002/DC. For the content, reference is made to the PL of Protium 20 mg/40 mg gastro-resistant tablets, approved through decentralised procedure DE/H/0268/001-002/DC.
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 Reddy 20 mg and 40 mg gastro-resistant tablets have a proven chemical-pharmaceutical quality and are generic forms of Pantozol 20 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 Reddy with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 December 2024.

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
-	-	-	-	-	-