CBG MEB

Public Assessment Report

Scientific discussion

Pantoprazol Aurobindo 20 mg and 40 mg, gastro-resistant tablets

(pantoprazole)

NL/H/2944/001-002/MR

Date: 8 December 2014

This module reflects the scientific discussion for the approval of Pantoprazol Aurobindo 20 mg and 40 mg, gastro-resistant tablets. The procedure was finalised on 17 June 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Pantoprazol Aurobindo 20 mg and 40 mg, gastro-resistant tablets from Aurobindo Pharma B.V.

The 20 mg product is indicated for:
Adults and adolescents 12 years of age and above
- Symptomatic gastro-oesophageal reflux disease.
- Long-term management and prevention of relapse in reflux oesophagitis.

Adults
- 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.

The 40 mg product is indicated for:
Adults and adolescents 12 years of age and above
- Reflux oesophagitis.

Adults
- 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 indications and posology is given in the SmPC.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Pantoprazole Altana 20 and 40 mg, gastro-resistant tablets which are registered in Portugal by Nycomed. The Dutch innovator is Pantozol 40 mg and 20 mg gastro-resistant tablets (NL License RVG 18300 and 23513), which have been registered by Takeda Nederland bv since 1995 and 1998, respectively. The innovator product is registered throughout Europe under different trade names, such as Protium, Inipomp, Pantoloc and Pantozol.

The concerned member states (CMS) involved in this procedure were Bulgaria, Cyprus, Germany, Denmark, France, Italy, Malta, Poland, Romania, Spain, Sweden and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Pantoprazol Aurobindo 20 mg are yellow colored, enteric coated, oval biconvex tablets with “PT20” printed on one side with brown ink.
Pantoprazol Aurobindo 40 mg are yellow colored, enteric coated, oval biconvex tablets with “PT40” printed on one side with brown ink.

The gastro-resistant tablets are packed in Polyamide/Aluminium/PVC-Aluminium blisters.

The excipients are: mannitol, crospovidone type B, sodium carbonate anhydrous, hydroxypropyl cellulose, calcium stearate, hypromellose, iron oxide (black, red and yellow), methacrylic acid-ethyl acrylate copolymer (1:1), triethyl citrate, propylene glycol, shellac and concentrated ammonia solution.

The two strengths are dose proportional.

II.2 Drug Substance

The active substance is pantoprazole (as 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. Pantoprazole sodium exists in two polymorphic forms, as monohydrate and as sesquihydrate. The CEP holder consistently produces the sesquihydrate form. Pantoprazole has a chiral atom therefore two possible enantiomers exist. The manufacturer produces a racemic mixture

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 European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification has been composed from the specifications from the drug substance manufacturer and the Ph.Eur. The specification is acceptable and in line with the various European guidelines and the Ph.Eur. Batch analytical data from three batches have been provided, demonstrating compliance with the specification.

Stability of drug substance
The retest period is 48 months 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 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 and 40 mg that would be essentially similar to the reference product Protium®.
Both Pantoprazol Aurobindo 20 mg and 40 mg were used in the 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 MAH sufficiently demonstrated that the test and reference product have similar dissolution profiles. Comparison between the two strengths of the test product also demonstrated similarity. For both strengths bioequivalence under fed and fasted conditions has been shown.

Manufacturing process
The manufacturing process consists of dry granulation followed by compression and film-coating (seal coating and enteric coating). The product is manufactured using conventional manufacturing techniques. Process validation has been performed on three pilot-scale batches. It has been 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 are specified according to the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification of pantoprazole and colorants, average weight, uniformity of weight, water content, disintegration time, dissolution, uniformity of dosage units by content uniformity, assay, related substances and microbial limits. The release and shelf-life specifications are identical. The analytical methods have been adequately described and validated. Batch analytical data of both strengths have been provided demonstrating compliance with the release specification.

Stability of drug product
Three production-scale 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 Al/Al blisters. Six months accelerated and 24 months long term data are available. The studied parameters remained within the specified limits and there appeared to be no significant changes in time. The proposed shelf-life of 24 months packed in the Al/Al blister without special storage conditions can be granted.

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 Aurobindo 20 mg and 40 mg, gastro-resistant tablets 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 Aurobindo 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 Pantoprazole Altana, which is available on the European market. Reference is made tot 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 four bioequivalence studies, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test products Pantoprazol Aurobindo 20 mg and 40 mg (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference products Inipomp 20 mg tablets (Nycomed, France) and Protium 40 mg tablets (Altana Pharma, Germany). Both strengths were studied under fasted and fed conditions.

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

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

Bioequivalence studies

Bioequivalence study I – 20 mg , fasted conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 22-43 years. Each subject received a single dose (20 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. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of at least 7 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, 6, 7, 8, 9, 10, 12, 16, 20 and 24 hours after administration of the products.

The single-dose, crossover study to assess bioequivalence is considered adequate.

Results
One subject was withdrawn because of protocol violation. The remaining 35 subjects completed the study entirely and were included in the pharmacokinetic and statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of pantoprazole under fasted conditions.

Treatment N=35	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	9049 ± 7909	10285 ± 9827	2511 ± 685	2.9 ± 1.0	3.8 ± 3.9
Reference	8995 ± 7882	10018 ± 9459	2449 ± 765	2.7 ± 1.0	3.4 ± 3.3
***Ratio (90% CI)**	1.04 (0.95 – 1.13)	1.04 (0.96 – 1.14)	1.06 (0.96 - 1.18)	--	--
CV (%)	21.4	21.2	25.9	--	--

$AUC_{0-\infty}$ 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*

Bioequivalence study II – 20 mg , fed conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 52 healthy male subjects, aged 19-44 years. Each subject received a single dose (20 mg) of one of the 2 pantoprazole formulations 30 min after intake of a high fat, high caloric breakfast. The tablet was orally administered with 240 ml water. There were 2 dosing periods, separated by a washout period of at least 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 11, 12, 14, 16, 18, 20, 22, 24, 28, 32, 36 and 48 hours after administration of the products.

This single dose, crossover study to assess bioequivalence is considered adequate.

Results
Three subjects were withdrawn during Period I because of vomiting. The remaining 49 subjects completed the study entirely and were included in the pharmacokinetic and statistical analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of pantoprazole under fed conditions.

Treatment N=49	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	7576 ± 8398	7742 ± 8745	2179 ± 884	8.4 ± 3.9	2.6 ± 2.8
Reference	6959 ± 7933	7081 ± 8191	2197 ± 860	7.2 ± 3.4	2.5 ± 2.7
***Ratio (90% CI)**	1.06 (0.94-1.19)	1.06 (0.94-1.20)	0.97 (0.84-1.11)	--	--
CV (%)	36.2	36.2	44.1	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Conclusion on bioequivalence studies I and II
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 and fed conditions, it can be concluded that Pantoprazol Aurobindo 20 mg and Inipomp 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 III – 40 mg, fasted conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 18-35 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. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of at least 8 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, 6, 7, 8, 9, 10, 12, 16, 20 and 24 hours after administration of the products.

This single dose, crossover study to assess bioequivalence is considered adequate.

Results
One subject withdrew for personal reasons in Period I, one subject did not show up for Period II and one subject was withdrawn due to protocol violation (consumption of coffee). Data of 33 subjects were analysed.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of pantoprazole under fasted conditions.

Treatment N=33	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	20342 ± 14250	22645 ± 17892	4511 ± 1077	3.5 ± 1.0	4.0 ± 2.7
Reference	20784 ± 13861	23208 ± 17733	4634 ± 870	3.2 ± 0.9	4.2 ± 2.8
***Ratio (90% CI)**	0.95 (0.91 - 0.99)	0.95 (0.91 - 0.98)	0.96 (0.90 - 1.01)	--	--
CV (%)	9.4	9.3	13.9	--	--

$AUC_{0-\infty}$ 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*

Bioequivalence study IV – 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 18-32 years. Each subject received a single dose (40 mg) of one of the 2 pantoprazole formulations within 30 min after the start of serving a high fat breakfast. The tablet was orally administered with 240 ml water. There were 2 dosing periods, separated by a washout period of at least 8 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 11, 12, 14, 16, 18, 20, 22, 24, 28, 32, 36 and 48 hours after administration of the products.

This single dose, crossover study to assess bioequivalence is considered adequate.

Results

One subject withdrew for personal reasons in Period I and two subjects did not show up for Period II. Two subjects received diclofenac for headache at day 1 and one subject had diarrhoea at day 2 and received oral rehydration salt and lactic acid bacillus. One subject vomited in the evening of day 1. Forty-five subjects completed the study entirely. No impact is expected from the co-medication, diarrhoea or vomiting.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of pantoprazole under fed conditions.

Treatment N=45	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	13739 ± 12185	14146 ± 13154	3162 ± 859	8.2 ± 4.5	3.4 ± 3.0
Reference	14062 ± 12786	14500 ± 13907	3527 ± 832	7.0 ± 3.7	3.4 ± 3.1
***Ratio (90% CI)**	0.98 (0.94-1.03)	0.98 (0.94-1.03)	0.88 (0.83-0.93)	--	--
CV (%)	12.8	12.8	16.3	--	--

$AUC_{0-\infty}$	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

**ln-transformed values*

Conclusion on bioequivalence studies III and IV

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 and fed conditions, it can be concluded that Pantoprazol Aurobindo 40 mg and Protium 40 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.

The MEB has been assured that the bioequivalence studies 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 Aurobindo.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Drug interaction between PPIs and clopidogrel • Chronic treatment with PPIs and hypomagnesaemia • Increased risk of fractures of the hip, wrist, and spine with the long term use of PPIs. • Chronic treatment with PPIs decreases absorption of cyanocobalamine (vitamin B12) • Visual disturbances • Microscopic colitis
Important potential risks	• Increased risk of Clostridium difficile–associated diarrhoea (CDAD) with PPIs • Chronic use of PPIs and the risk of pneumonia • Congenital cardiac malformation following in utero exposure. • Decrease in absorption of iron • Off-label use • Interactions with: - Warfarin or other coumarine derivatives

	- Phenytoin - Atazanavir - Nelfinavir - Digoxin - Methotrexate - Tacrolimus - Clopidogrel
Missing information	• Use in pregnancy and during lactation • Use in patients with renal impairment

The member states agree that routine pharmacovigilance activities are sufficient and that no additional risk minimisation measures are required.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Pantoprazol Aurobindo 20 mg and 40 mg, gastro-resistant tablets. No new clinical studies were conducted. 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 bridging statement has been submitted, based on a readability test for Omeprazol Aurobindo 10, 20 and 40 mg, as approved in the procedure MT/H/0120/001-003. Furthermore, the package leaflet (PL) has been brought in line with the Art.30 referral wording for Protium 20 and 40 mg.
Additionally, the bridging statement contains evidence that the lay-out of the leaflets of Pantoprazol Aurobindo 20 and 40 mg equals the lay-out of the tested and approved PL. The bridging report for design and layout is provided with the already approved user tested leaflet. The bridging report is accepted; no separate user testing is required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pantoprazol Aurobindo 20 and 40 mg, gastro-resistant tablets have a proven chemical-pharmaceutical quality and are generic forms of Pantoprazole Altana 20 and 40 mg, gastro-resistant tablets. Pantoprazole Altana 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. Pantoprazol Aurobindo 20 mg and 40 mg, gastro-resistant tablets were authorised in the Netherlands on 17 June 2011.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Pantoprazol Aurobindo with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 17 June 2014.

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