LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Pantoprazol Orion
(pantoprazole)

SE/H/1659/01-02/DC

This module reflects the scientific discussion for the approval of Pantoprazol Orion. The procedure was finalised on 2017-12-20. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Pantoprazol Orion 20 mg and 40 mg gastro-resistant tablet is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orion Corporation applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and FI as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Inipomp, 20 mg and 40 mg, gastro-resistant tablet, authorised in France since 1999 and 1995, respectively, with Takeda France SAS as marketing authorisation holder.

The reference product used in the bioequivalence study is Inipomp, 20 mg, gastro-resistant tablet from FR with Nycomed (nowadays part of Takeda) as marketing authorisation holder and Protium, 40 mg, gastro-resistant tablet from UK with Altana Pharma AG (Nowadays part of Takeda) as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The applicant has submitted four single-dose bioequivalence studies, two studies with the 20 mg strength (fasting and fed conditions) and two studies with the 40 mg strength (fasting and fed conditions). Pantoprazol Orion is a delayed release formulation for which single-dose bioequivalence studies under both fasting and fed conditions are adequate and in accordance with the guideline recommendations.

Study 147/09 (40 mg fasting):
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Pantoprazole, 40 mg, gastro-resistant tablet with Protium, 40 mg, gastro-resistant tablet under fasting conditions. The study was conducted at Trident Life Sciences Limited, Serilingampally Mandal, Hyderabad, India between 23rd July and 2nd August 2009. Blood samples were collected pre-dose and up to 24 hours post-dose. The study design is considered acceptable. Plasma concentrations of pantoprazole were determined with an adequately validated LC-MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Table 1. Study 147/09 40 mg fasted. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for pantoprazole, n=33.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	20342 ± 14250	22645 ± 17892	4511 ± 1077	3.33 (2.00-6.00)
Reference	20784 ± 13861	23208 ± 17733	4634 ± 870	3.00 (2.00-5.00)
*Ratio (90% CI)	94.89 (91.26-98.67)	94.71 (91.09-98.46)	95.65 (90.29-101.33)	-

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

**calculated based on ln-transformed data*

Study 255/09 (40 mg fed):
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 48 healthy volunteers, comparing Pantoprazole, 40 mg, gastro-resistant tablet with Protium, 40 mg, gastro-resistant tablet under fed conditions. The study was conducted at Trident Life Sciences Limited, Serilingampally Mandal, Hyderabad, India between 23rd June and 4th July 2009. Blood samples were collected pre-dose and up to 48 hours post-dose. The study design is considered acceptable. Plasma concentrations of pantoprazole were determined with an

adequately validated LC-MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Table 2. Study 255/09 40 mg fed. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for pantoprazole, n=45.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	13739 ± 12185	14146 ± 13154	3162 ± 859	7.50 (2.50-24.00)
Reference	14062 ± 12786	14500 ± 13907	3527 ± 832	5.67 (2.00-24.00)
*Ratio (90% CI)	98.09 93.76-102.63	98.10 93.75-102.64	88.25 83.34-93.46	-

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

**calculated based on ln-transformed data*

Study BA1109371-01 (20 mg fasting):
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Pantoprazole, 20 mg, gastro-resistant tablet with Inipomp, 20 mg, gastro-resistant tablet under fasting conditions. The study was conducted at BA Research India Ltd., Bodakdev, Ahmedabad, India between 19th and 28th November 2011. Blood samples were collected pre-dose and up to 24 hours post-dose. The study design is considered acceptable. Plasma concentrations of pantoprazole were determined with an adequately validated LC-MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Table 3. Study BA1109371-01, 20 mg fasted. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for pantoprazole, n=35.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	9049 ± 7909	10285 ± 9827	2511 ± 685	3.00 (1.67-6.00)
Reference	8995 ± 7882	10018 ± 9459	2449 ± 765	2.67 (1.33-5.00)
*Ratio (90% CI)	103.50 95.01-112.75	104.37 95.87-113.63	106.09 95.68-117.63	-

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

**calculated based on ln-transformed data*

Study BA1109372-01 (20 mg fed):
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 52 healthy volunteers, comparing Pantoprazole, 20 mg, gastro-resistant tablet with Inipomp, 20 mg, gastro-resistant tablet under fed conditions. The study was conducted at BA Research India Ltd., Bodakdev, Ahmedabad, India between 16th and 26th November 2011. Blood samples were collected pre-dose and up to 48 hours post-dose. The study design is considered acceptable. Plasma concentrations of pantoprazole were determined with an adequately validated LC-MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Table 4. Study BA1109372-01, 20 mg fed. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for pantoprazole, n=49.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	7576 ± 8398	7742 ± 8745	2179 ± 884	6.50 (2.00-20.00)
Reference	6959 ± 7933	7081 ± 8191	2197 ± 860	5.67 (3.00-20.00)
*Ratio (90% CI)	106.03 94.12-119.43	106.19 94.28-119.61	96.56 83.71-111.38	-

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

**calculated based on ln-transformed data*

Bioequivalence between the test and reference product has been adequately demonstrated.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 Orion.

Safety specification

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Masking the symptoms of malignant gastric tumour
	• Increased risk of gastrointestinal infections
	• Drug interaction of pantoprazole with drugs which have pH dependent absorption
	• Hypomagnesaemia
Important potential risks	• Increased risk of fractures
	• Use in patients with severe hepatic impairment
	• Subacute cutaneous lupus erythematosus (SCLE)
Missing information	• Use during pregnancy and breastfeeding
	• Use in children below 12 years of age
	• Long term use

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed/ approved in RMP

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Summary of the RMP

The RMP is approved. The RMP has been updated in accordance with the Guideline on GVP, Module V-Risk management systems (Rev 2) for Generic products.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Beximco, assessed and accepted in the decentralized procedure NL/H/275/001-002. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Pantoprazol Orion, is found adequate. There are no objections to approval of Pantoprazol Orion, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.

The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Pantoprazol Orion 20 mg and 40 mg gastro-resistant tablet was positively finalised on 2017-12-20.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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