IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Pantoprazole Teva Pharma 40 mg gastro-resistant tablets
Pantoprazole sodium sesquihydrate
PA0749/144/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

The applicant submits the necessary information in accordance with the abridged process under section 10.1.a (iii) of European Directive 2001/83/EC.

These applications are abridged based on the demonstration of essential similarity between Pantoprazole 20 mg & 40 mg gastro-resistant tablets manufactured by Laboratorios Belmac S.A. (Spain) and the reference product developed and manufactured by the originator Altana Pharma AG as licenced and marketed throughout Europe, for example under the following product names: Pantecta 20 mg & Pantecta 40 mg gastro resistant tablets - Spain; Protium 20 mg & Protium 40 mg gastro resistant tablets- United Kingdom; and Eupantol 20 mg, comprimé gastro-résistant- France.

II. QUALITY ASPECTS

II.1 Introduction

This application is for Pantoprazole Pharmascope 20mg and 40mg gastro-resistant tablets contained either in Alu/Alu blisters or in a HDPE container.

II.2 2.2 Drug Substance

Active substance

The active substance is pantoprazole sodium sesquihydrate, an established active substance described in the European Pharmacopoeia. The active substance is manufactured by Natco Pharma Limited in accordance with the principles of GMP. The manufacturing process from the starting materials and the control of the active substance have been described adequately.
The active substance specifications and analytical methods applied by Natco and Belmac are considered adequate to control the quality as they meet current pharmacopoeial requirements for pantoprazole sodium sesquihydrate Ph.Eur. Batch analytical data demonstrating compliance with this specification has been provided, along with stability data to support the applied retest period.

II.3 Medicinal Product

Drug product

P.1 Composition of the medicinal product

The tablets contain the active substance Pantoprazole sodium sesquihydrate and the excipients Disodium phosphate anhydrous, Mannitol, Microcrystalline cellulose,Croscarmellose sodium, Magnesium stearate (vegetable) ,Hypromellose, Triethylcitrate, Sodium starch glycolate (Type A), Methacrylic acid-Ethylacrylate co-polymer (1:1), Triethylcitrate, Yellow iron oxide.

P.2 Pharmaceutical development

The product is an established pharmaceutical form and its development has been adequately described in accordance with the relevant EU guidelines.

P.3. Manufacture of the product

The manufacturing process and controls have been described. The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.
The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated. A further validation protocol has also been provided for the validation of the first three industrial scale batches of each tablet strength.

P.4 Excipients

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets and the tests and control limits are considered appropriate for this type of gastro-resistant product.
The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material
The product is presented as Alu/Alu blisters or HDPE containers
Evidence has been provided that these packaging types complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product
Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines which demonstrates a shelf life of at 'Do not store above 30°C' when packaged in Alu/Alu blisters, and a shelf life of 2 years with 'No special storage conditions' when packaged in HDPE containers.

Adventitious Agent Safety
Compliance with the Note For Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products has been satisfactorily demonstrated

II.4 Discussion on chemical, pharmaceutical and biological aspects
The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Pantoprazole Pharmascope 20mg and 40mg gastro-resistant tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pantoprazole is a widely clinically used, well known active substance. No further non-clinical studies were submitted or deemed to be required. The company provided a comprehensive non-clinical bibliographic overview and an expert provided a sufficiently detailed review of all relevant non-clinical data. There were considered to be no non-clinical concerns.

IV. CLINICAL ASPECTS

IV.1 Introduction

The applicant submits the necessary information in accordance with the abridged process under section 10.1.a (iii) of European Directive 2001/83/EC.

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IV.2 Pharmacokinetics
General pharmacokinetics
Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single oral dose. On average, the maximum serum concentrations are 1−1.5 µg/ml at about 2.0−2.5 hours post-administration, and these values remain constant after multiple administration. Volume of distribution is about 0.15 l/kg and clearance is about 0.1 l/h/kg.

Terminal half-life is about 1 h. There were a few cases of subjects with delayed elimination. Because of the specific binding of pantoprazole to the proton pumps of the parietal cell the elimination halflife does not correlate with the much longer duration of action (inhibition of acid secretion).

Pharmacokinetics do not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

Pantoprazole's serum protein binding is about 98%. The substance is almost exclusively metabolized in the liver. Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole, the rest is excreted with the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 h) is not much longer than that of pantoprazole.

Bioavailability
Pantoprazole is completely absorbed after oral administration. The absolute bioavailability from the tablet was found to be about 77%. Concomitant intake of food had no influence on AUC, maximum serum concentration and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

Characteristics in patients/special groups of subjects
No dose reduction is requested when pantoprazole is administered to patients with restricted kidney function (incl. dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole can be dialyzed. Although the main metabolite has a moderately delayed half-life (2–3h), excretion is still rapid and thus accumulation does not occur. However, the daily dose of 40 mg pantoprazole should not be exceeded in patients with impaired renal function.

Although for patients with liver cirrhosis (classes A and B according to *Child*) the half-life values increased to between 3 and 6 h and the AUC values increased by a factor of 3–5, the maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.
A slight increase in AUC and Cmax in elderly volunteers compared with younger counterparts is also not clinically relevant.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Proton pump inhibitors
ATC code: A02BC02
Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific action on the proton pumps of the parietal cells.

Pantoprazole is converted to its active form in the acidic channel of the parietal cells where it inhibits the H+, K+-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved in 2 weeks. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, the substance can affect hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is administered orally or intravenously.

The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the normal upper limit. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia). However, according to the studies conducted so far (see section 5.3), the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids can be ruled out for humans.

An influence of a long term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid and liver enzymes according to results in animal studies.

IV.4 Clinical efficacy

In order to demonstrate bioequivalence of the drug product Pantoprazole Belmac and the reference products, two bioequivalence studies were carried out.

1: Bioequivalence study on two pantoprazole formulations (gastro-resistant tablets) at a single oral dose of 40 mg, in healthy volunteers.

2: Bioequivalence study on two pantoprazole formulations (gastro-resistant tablets) at a single oral dose of 40 mg, after breakfast, in healthy volunteers.

The trials were conducted as described in the Guidelines CPMP/EWP/QWP/1401/98 (Note for Guidance on the Investigation of Bioavailability and Bioequivalence) and CPMP/EWP/280 (Note for Guidance on Modified Release Oral and Transdermal Dosage forms.

The studies were conducted in accordance with the principles of Good Clinical Practice, ICH Guidelines, WHO recommendations and the Declaration of Helsinki. Prior to study initiation Ethics Committee approval was obtained and the volunteers signed the Informed Consent form, after receiving full explanations of study requirements.

Pharmacokinetics parameters for AUC0-infinity and C Max were similar following both formulations at both fasting and fed conditions however there were several outliers in the fed study as the sampling time was only for 15 hours. Therefore an additional fed study was undertaken

3: A Single-Dose, Comparative Bioavailability Study of Two Formulations of Pantoprazole 40 mg Gastro-Resistant Tablets under Fed Conditions

The 90% confidence intervals of the relative mean plasma pantoprazole AUCt and AUCinf of the test to reference products are within the 80.00-125.00% range.

The 90% confidence interval of the relative mean plasma pantoprazole Cmax of the test to reference products was in the extended range 75-133%.

In individual patients, it was demonstrated that AUC (not Cmax) correlates with the degree of acid suppression, which is known to correlate with the relief of acid-related symptoms [Hatlebakk, 1996; Thomson, 1997], and that there is no temporal association between the peak plasma concentration and the maximum acid suppression caused by proton pump inhibitors.

Therefore, it is believed that the observed difference in the Cmax parameters between the test and reference drug products has no clinical significance.

IV.5 Clinical safety

The new pantoprazole was tolerated well and there was no significant safety issue identified with the test pantroprazole versus the reference pantoprazole.

IV.6 Discussion on the clinical aspects

As this was a generic application and bioequivalence was shown in both a fasting and fed state no additional clinical studies are necessary.

The applicant submits the necessary information in accordance with the abridged process under section 10.1.a (iii) of European Directive 2001/83/EC.

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Pharmacovigilance System

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided

Risk Management Plan

An EU-RMP was not considered necessary at this time – routine pharmacovigilance was deemed sufficient.

V. OVERALL CONCLUSIONS

Overall the benefit/risk was deemed to be positive and marketing authorisation was granted.

VI. REVISION DATE

December 2010