Public Assessment Report

Scientific discussion

Bepraz 10 mg and 20 mg, gastro-resistant tablets (rabeprazole sodium)

NL/H/2976/001-002/MR

Date: 26 May 2014

This module reflects the scientific discussion for the approval of Bepraz 10 mg and 20 mg gastro-resistant tablets. The procedure was finalised on 9 January 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 Bepraz 10 mg and 20 mg, gastro-resistant tablets from PharmaSwiss Česká republika s.r.o.

The product is indicated for:

- Active duodenal ulcer
- Active benign gastric ulcer
- Symptomatic erosive or ulcerative gastro-oesophageal reflux disease (GORD).
- Gastro-oesophageal reflux disease long-term management (GORD maintenance)
- Symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GORD)
- Zollinger-Ellison syndrome
- In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* in patients with peptic ulcer disease. See section 4.2 of the approved SmPC.

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 product Pariet gastro-resistant tablets 10 mg and 20 mg which has been registered in Denmark since 26 November 1998 (original product). In the Netherlands Pariet 10 mg and 20 mg gastro-resistant tablets (NL license RVG 23210-23211) have been registered by Janssen-Cilag B.V. since 8 December 1998.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Bepraz 10 mg contains as active substance 10 mg rabeprazole sodium, equivalent to 9.42 mg rabeprazole. It is a pink, film-coated, biconvex, round tablet of 5.35 mm diameter.

Bepraz 20 mg contains as active substance 20 mg rabeprazole sodium, equivalent to 18.85 mg rabeprazole. It is a yellow, film-coated, biconvex, round tablet of 7.30 mm diameter.

The gastro-resistant tablets are packed in aluminium/aluminium blisters.

The excipients are:
*Tablet core* – mannitol, heavy magnesium oxide, hydroxypropyl cellulose, magnesium stearate.
*Intermediate layer* – ethylcellulose, heavy magnesium oxide
*Film-coating* – hypromellos phtalate, dibutyl sebacate, titanium dioxide (E171), talc; yellow iron oxide (E172) – 20 mg only; red iron oxide (E172) – 10 mg only.

The tablet cores are dose proportional for 10 and 20 mg tablets. For the intermediate and enteric coating the amount of excipients was recalculated, taking into account the surface area of the tablets, so that both strengths are proportional.

II.2 Drug Substance

The active substance is rabeprazole, present as rabeprazole sodium, an established active substance however not described in any the European, British or US Pharmacopoeia (Ph.Eur., BP, USP, respectively). It is a white to slightly yellow powder which is freely soluble in water and ethanol.
Rabeprazole sodium is a racemic mixture of two optical isomers. The drug substance is manufactured as amorphous solid.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process consists of six steps. No class 1 organic solvents are used. A heavy metal catalyst is used in the synthesis. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for six full-scale batches stored at 25°C/60% RH (up to 36 months) of which three batches were also stored at 40°C/75% RH (6 months). At accelerated conditions some trends were observed. Based on the data provided, a retest period of 36 months could be granted with the applicable storage condition “Store in the original package in order to protect from light and moisture”.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified. The main development studies that were performed concerned the solubility of the drug substance and the compatibility with the excipients and the performance of comparative dissolution studies at different pH values. Similarity in dissolution between the different strengths of test batches and between the reference and test batches used in the bioequivalence studies has been demonstrated in accordance with the requirements of the Guideline on the investigation of bioequivalence. Bioequivalence studies were performed with the highest strength of drug product. The batches used in the bioequivalence studies are of sufficient batch size and were manufactured according to the finalized formulation and manufacturing process. The pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process mainly consists of mixing the excipients, wet granulation and drying, compression, intermediate coating and final coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches per strength.

Control of excipients
The excipients comply with the Ph.Eur. or USP-NF. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, average weight, loss on drying, identification, uniformity of dosage units, assay, gastric resistance, dissolution, related substances, residual solvents and microbiological quality. Except for related substances the release and shelf-life limits are identical. The drug product specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided three pilot-scale batches per strength stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The tablets were stored in Al-Al blisters. A significant increase of related substances is observed after 6 months storage at accelerated conditions. At long-term and intermediate conditions some trends are observed, but all parameters remain within the specified limits. The drug product was demonstrated to be light sensitive. The granted shelf-life is 3 years with storage conditions ‘Do not store above 30°C’ and ‘Store in the original package in order to protect from moisture and light’.

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

No excipients of human or animal origin are used in the manufacture of the drug product. Magnesium stearate is of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Bepraz 10 mg and 20 mg 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 Bepraz gastro-resistant tablets are 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 Pariet, which is available on the European market. Reference is made to 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

Rabeprazole 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

In accordance with the Note for Guidance on Modified Release Oral and Transdermal Dosage Forms (CPMP/EWP/280/96), for gastro-resistant or enteric products bioequivalence should be demonstrated not only in a single dose study in fasted conditions, but also in a single dose study under fed conditions.
The MAH therefore conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Rabeprazolnatrium Chemo Iberica 20 mg (Chemo Iberica S.A., Spain) is compared with the pharmacokinetic profile of the reference product Pariet 20 mg gastro-resistant tablets (Janssen-Cilag) under fasted and fed conditions. The reference product in the study under fasted conditions was obtained from Spain, the product used in the fed study from Germany.

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. 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 this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Biowaiver
The 10 mg tablet is dose-proportional with the 20 mg tablet regarding the core. The enteric coated layer is based upon surface area. The tablets are manufactured by the same manufacturing process. In addition, rabeprazole shows linear pharmacokinetics and comparative dissolution data were provided with supporting similarity factors. Extrapolation of the 20 mg study results was sufficiently justified. A biowaiver has been granted for the lower strength.

Bioequivalence studies

Study under fasted conditions (20 mg)

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 46 healthy subjects (21 females/25 males), aged 18-43 years. Each subject received a single dose (20 mg) of one of the 2 rabeprazole sodium formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 1 day.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 8, 12 and 16 hours after administration of the products.

The study design is considered adequate.

Results
All 46 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\_max (median, range)) of rabeprazole under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_0-t</th>
<th>AUC_0-\infty</th>
<th>C_max</th>
<th>t_max</th>
<th>t_1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>764 ± 299</td>
<td>770 ± 299</td>
<td>444 ± 163</td>
<td>3.3 (1.5 – 5.67)</td>
<td>1.4 ± 0.6</td>
</tr>
<tr>
<td>Reference</td>
<td>749 ± 336</td>
<td>754 ± 336</td>
<td>469 ± 197</td>
<td>3.2 (1.5 – 8.0)</td>
<td>1.3 ± 0.5</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.06 (0.96-1.16)</td>
<td>--</td>
<td>0.99 (0.85-1.15)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV (%)</td>
<td>27.2</td>
<td>42.5</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

AUC\_0-t area under the plasma concentration-time curve from time zero to infinity
AUC\_0-\infty 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

Study under fed conditions (20 mg)

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 80 healthy subjects (42 females/38 males), aged 18-44 years. Each subject received a single dose (20 mg) of one of the 2 rabeprazole sodium formulations. The tablet was orally administered with 240 ml water, 30 min after start of serving a standardized continental breakfast. The breakfast consisted of 2 croissants, 1 cereal bar, 20 g butter, 200 ml orange juice and 200 ml whole milk. The total amount of calories was 800. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.33, 5.67, 6, 6.33, 6.67, 7, 7.33, 7.67, 8, 8.33, 8.67, 9, 9.33, 9.67, 10, 11, 12, and 16 hours after administration of the products.

The study design is considered adequate.

Results
All 80 subjects completed the study and were eligible for pharmacokinetic analysis.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=80</th>
<th>AUC\textsubscript{0-t}</th>
<th>AUC\textsubscript{0-∞}</th>
<th>C\textsubscript{max}</th>
<th>t\text{max}</th>
<th>t\text{1/2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>756 ± 385</td>
<td>773 ± 383</td>
<td>515 ± 213</td>
<td>5.67 (2.0 – 9.33)</td>
<td>1.7 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>756 ± 447</td>
<td>792 ± 443</td>
<td>533 ± 227</td>
<td>5.33 (3.0 – 16.0)</td>
<td>1.7 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>0.99 (0.92-1.06)</td>
<td>--</td>
<td>0.92 (0.83-1.02)</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>CV (%)</td>
<td>26.7</td>
<td>--</td>
<td>38.7</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

AUC\textsubscript{0-∞} area under the plasma concentration-time curve from time zero to infinity
AUC\textsubscript{0-t} area under the plasma concentration-time curve from time zero to t hours
C\textsubscript{max} maximum plasma concentration
t\text{max} time for maximum concentration
t\text{1/2} half-life

*ln-transformed values

Conclusion on bioequivalence studies
The 90% confidence intervals calculated for AUC\textsubscript{0-t} and C\textsubscript{max} are within the bioequivalence acceptance range of 0.80–1.25. Based on the submitted bioequivalence studies Bepraz 20 mg is considered bioequivalent with Pariet 20 mg gastro-resistant tablets under both fasted and fed conditions.

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).

The results of the two studies with the 20 mg formulation can be extrapolated to the 10 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Risk Management Plan

The MAH provided a commitment to submit a Risk Management Plan (RMP) through a type II variation after finalization of the mutual recognition procedure. This is acceptable, as an RMP was not yet required at the time of application. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient at this point.

IV.4 Discussion on the clinical aspects
For this authorisation, reference is made to the clinical studies and experience with the innovator product Pariet gastro-resistant tablets. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study 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. The applicant submitted the results of the user consultation of the patient leaflet of Rabeprazole Liconsa approved during DK/H/1513/01-02/DC, together with a bridging report for the patient leaflet of Rabeprazol Chemo Iberica (NL/H/2072-2073/001-002), which is identical to the PL of Bepraz. The bridging report submitted has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bepraz 10 mg and 20 mg, gastro-resistant tablets have a proven chemical-pharmaceutical quality and are generic forms of Pariet 10 mg and 20 mg gastro-resistant tablets. Pariet is a well-known medicinal product with an established favourable efficacy and safety profile.

The status of supply is ‘prescription only’.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors. The marketing authorization for Bepraz 10 mg and 20 mg was granted in the Netherlands on 1 March 2013.

The concerned member state, on the basis of the data submitted, mutually recognized the Dutch assessment for marketing authorization and considered essential similarity with the reference product demonstrated. There was no discussion in the CMD(h). The mutual recognition procedure was finalised with a positive outcome on 9 January 2014.

The following post-approval commitment has been made during the procedure:
- The MAH committed to submit a Risk Management Plan (RMP) through a type II variation.
<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached</th>
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