CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Prabexol 10 mg and 20 mg gastro-resistant tablets Chemo Iberica S.A., Spain

rabeprazole (as sodium)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2073/001-002/DC
Registration number in the Netherlands: RVG 107937, 107942

21 September 2011

Pharmacotherapeutic group:	proton pump inhibitors
ATC code:	A02BC04
Route of administration:	oral
Therapeutic indication:	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.
Prescription status:	prescription only
Date of authorisation in NL:	13 July 2011
Concerned Member States:	Decentralised procedure with CZ, DE, ES, HU, SI, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Prabexol 10 mg and 20 mg gastro-resistant tablets from Chemo Iberica S.A. The date of authorisation was on 13 July 2011 in the Netherlands.

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 SPC.

A comprehensive description of the indications and posology is given in the SPC.

Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonist properties, but suppress gastric acid secretion by the specific inhibition of the H+/K+-ATPase enzyme (the acid or proton pump) The effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa. As a weak base, rabeprazole is rapidly absorbed following all doses and is concentrated in the acid environment of the parietal cells. Rabeprazole is converted to the active sulphenamide form through protonation and it subsequently reacts with the available cysteines on the proton pump.

This decentralised 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 by Janssen-cilag since 26 November 1998 (original product). In addition, reference is made to Pariet authorisations in the individual member states (reference product). For CZ, SI and SK reference is made to a European reference product, Pariet 10 mg and 20 mg gastro-resistant tablets (NL license RVG 23210-23211) registered in the Netherlands.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies (one under fasted conditions and one under fed conditions) in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Pariet 20 mg gastro-resistant tablets, registered in the Spain and Germany, respectively. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active 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.*). 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".

** Ph.Eur., BP and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively*.

Medicinal Product

Composition
Prabexol 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 5.35mm diameter.
Prabexol 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 7.30mm 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.

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 some trends are observed, but all parameters remain within the specified limits. 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.2 Non-clinical aspects

This product is a generic formulation of Pariet, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of rabeprazole released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Rabeprazole is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Prabexol 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.

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.

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
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.

Treatment N=46	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	764 ± 299	770 ± 299	444 ± 163	3.3 (1.5 – 5.67)	1.4 ± 0.6
Reference	749 ± 336	754 ± 336	469 ± 197	3.2 (1.5 – 8.0)	1.3 ± 0.5
***Ratio (90%**	1.06 (0.96-1.16)	--	0.99 (0.85-1.15)	--	--

CI)					
CV (%)	27.2		42.5	--	--

$AUC_{0-\infty}$ 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*

The 90% confidence intervals calculated for AUC_{0-t} 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 rabeprazole under fasted conditions, it can be concluded that Prabexol 20 mg and Pariet 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.

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.

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

All 80 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.

Treatment N=80	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	756 ± 385	773 ± 383	515 ± 213	5.67 (2.0 – 9.33)	1.7 ± 0.5
Reference	756 ± 447	792 ± 443	533 ± 227	5.33 (3.0 – 16.0)	1.7 ± 0.8
***Ratio (90% CI)**	0.99 (0.92-1.06)	--	0.92 (0.83-1.02)	--	--
CV (%)	26.7	--	38.7	--	--

$AUC_{0-\infty}$	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*

The 90% confidence intervals calculated for AUC_{0-t} 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 rabeprazole under fed conditions, it can be concluded that Prabexol 20 mg and Pariet 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

Extrapolation to 10 mg strength
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.

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).

Risk management plan
Rabeprazole was first approved in 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of rabeprazole can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Pariet (UK/H/0248/001-002).

Readability test
The package leaflet has not been evaluated via a user consultation study. A bridging report was provided with reference to the successfully user tested PIL for a pantoprazole product. The lay-out like dimensions and columns is similar with this text. Although differences are noted with regard to the content, the PIL could be approved. It is in accordance with previously approved and user-friendly rabeprazole PILs. A waiver for user testing has been granted.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Prabexol 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.

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

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 Prabexol 10 mg and 20 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 15 June 2011. Prabexol 10 mg and 20 mg gastro-resistant tablets were authorised in the Netherlands on 13 July 2011.

The date for the first renewal will be: 15 June 2014.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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