CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Rabeprazol KRKA 10 mg and 20 mg gastro-resistant tablets
Krka d.d. Novo mesto, Solvenia

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/1787/001- 002/DC
Registration number in the Netherlands: RVG 105588-9

14 October 2010

Pharmacotherapeutic group:	propton 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:	14 September 2010
Concerned Member States:	Decentral procedure with AT, BG, CY, CZ, DE, DK, EE, ES, HU, IT, LT, LV, PL, PT, RO, SI, SK
Application type/legal basis:	Directive 2001/83/EC, Article10 (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 Rabeprazol KRKA 10 mg and 20 mg gastro-resistant tablets, from Krka d.d. Novo mesto. The date of authorisation was on 14 September 2010 in the Netherlands. The product is indicated for treatment of:

- 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 (NL license RVG 23210-1) which has been registered in the Netherlands by Janssen-cilag since 1998 (original product). In addition, reference is made to Pariet authorisations in the individual member states (reference product). In some member states reference is made to the European reference product, Pariet gastro-resistant tablets registered in the UK.

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 UK. 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. This generic product can be used instead of its 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 not described in any pharmacopoeia*. The active substance is freely soluble in water, soluble in ethanol and methanol. As the drug substance is dissolved during manufacture of the drug product, a difference in polymorphic form can be accepted. The S-atom in rabeprazole is chiral. The drug substance is present as a racemic mixture, and the R isomer is the active form.

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/EMEA 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.

Manufacture
The active substance from two different manufacturers is made by similar synthetic routes. By one manufacturer a heavy metal catalyst is used. The solvents used in the process have been adequately described. No class 1 solvents are used. In general, the active substance has been adequately characterized and adequate specifications have been laid down for the starting materials, solvents and reagents.

Specification of drug substance
The drug substance specification is has been established in-house by the DMF-holders and 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 pilot-scale batches and three production-scale batches from one site and for 5 production-scale batches from another site.

Stability of drug substance
Stability data on the active substance have been provided for three pilot-scale batches from one site, stored at 25°C/60%RH (12 months) and 40°C/75%RH (6 months) and for three production scale batches from another site, stored at 2-8°C (up to 60 months) and 25°C/60%RH (6 months). The batches were adequately stored. For the API of both DMF-holders no clear trends could be observed up to the claimed retest periods. For one batch from one specific site material manufactured in 2002, OOS values for unknown impurity were found after 48 and 60 months of storage.
The claimed retest period of 24 months for one site can be granted and the storage conditions '*store in the original container to protect from light and moisture*' are acceptable. For another site a retest period of 36 months can be granted for the drug substance preserved in tight closed containers and stored at 2-8°C, protected from moisture.
The MAH has committed to provide stability data up to the claimed retest period of 24 months.

Medicinal Product

Composition
Rabeprazol KRKA 10 mg are orange-pink, biconvex, round, gastro-resistant tablets with bevelled edges. Each gastro-resistant tablet contains 10 mg rabeprazole sodium, equivalent to 9.42 mg rabeprazole.
Rabeprazol KRKA 20 mg are slightly brownish yellow, biconvex, round gastro-resistant tablets. Each gastro-resistant tablet contains 20 mg rabeprazole sodium, equivalent to 18.85 mg rabeprazole.

The excipients are:
Tablet core: mannitol (E421, magnesium oxide, light (E530), hydroxypropylcellulose (E463), low-substituted hydroxypropylcellulose (E463), magnesium stearate (E572).
Film-coating: ethylcellulose (E462), light magnesium oxide (E530), hypromellose phthalate, diacetylated monoglycerides (E472a), talc (E553b), titanium dioxide (E171), red iron oxide (E172) 20 mg only
yellow iron oxide (E172) – 20 mg only
Red iron oxide (E172) – 10 mg only

The tablets are dose proportional with respect to the core excipients only. This is acceptable as the amount of coating excipients are based on the thickness of the gastro-resistant coating and the ratio of the coating excipients remains constant.
The gastro-resistant tablets are packed in blisters of OPA/Al/PVC film and aluminium foil. The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The dissolution method is acceptable and the medium with pH 9.0 borate buffer is justified, although it is outside the physiological pH range, as the drug substance is prone to degrade in media below pH 9. A gradual degradation was observed at pH 6.8 and 7.4. Comparative dissolution profiles have been provided at different pH for both strength of the proposed and innovator product. Similarity factors have been provided at pH 9.0 only, but the waiver for the 10 mg strength was cancelled and *in-vivo* bioequivalence study results have been provided for this strength. The manufacturing process and composition of the biobatches are the same as described. Equivalence of the reference products with the product from the Dutch market will be demonstrated as soon as available.

Manufacturing process
The drug product is manufactured via standard wet granulation process using ethanol as granulation fluid due to the instability of the active substance in water. The tablets are manufactured by dry mixing of active substance and excipients. The mixture is then compressed, film-coated (undercoating and gastro-resistant coating) and packed. Process validation data on the product has been presented for two pilot-scale, one lab-scale and two production-scale batches of each strength. The manufacturing process has been adequately validated.

Microbiological attributes
The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product, since some excipients may tend to support microbial growth. Limits for microbiological attributes are set in current Ph.Eur. 5.1.4. This is acceptable for this type of dosage form. The MAH committed to provide results of microbiological testing at the end of storage of the drug product at intermediate storage condition.

Excipients
The excipients comply with their Ph.Eur.* or USP/NF* monographs. These specifications are acceptable. The iron oxides are in accordance with Directive 2008/128/EC

Quality control of drug product
The product specification includes tests for appearance, disintegration, identification (HPLC, TLC, colorants), uniformity of dosage units, related substances, gastro-resistance, dissolution, assay, ethanol content and microbiological purity. The release and shelf-life limits differ only on the limits of the sulphone impurity and total impurities. The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production site have been provided on the six validation batches, demonstrating compliance with the release specification. All impurity limits will be reevaluated at the end of the stability study.

Stability tests on the finished product
Stability data on the product has been provided for the six validation batches stored at 25°C/60%RH (12 months), 30°C/65%RH (12 months) and 40°C/75%RH (6 months) and an additional batch stored at these conditions up to 18 months. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in OPA/Al/PVC-Al blisters. The tablets are stable at long-term and intermediate conditions, but show out of specification results after 3 months of accelerated storage for related substances. Therefore, a maximum extrapolation of 3 months can be allowed in line with the *Guideline on the Evaluation of stability data (ICH Q1E)*. Only one batch is stored for 18 months and only for the 20 mg strength, while at least three pilot-scale batches should be used to support a claimed shelf-life. The stability data support a shelf-life of 15 months. The storage conditions '*do not store above 30°C in original packaging in order to protect from moisture and light*' can be accepted.
The MAH has committed to continue the stability study up to 60 months and place additional production batches on long-term stability through the proposed shelf-life and accelerated stability testing for 6 months. As this is considered to be GMP, results should be held available at the manufacturing site.
The MAH has committed to provide stability data up to the claimed shelf-life of 15 months.

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. Magnesium stearate and diacetylated monoglycerides are of vegetable origin.

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

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 Rabeprazol KRKA 20 mg gastro-resistant tablets (Krka d.d. Novo Mesto, Slovenia) is compared with the pharmacokinetic profile of the reference product Pariet 20 mg gastro-resistant tablets (Janssen-Cilag, UK) under fasted and fed conditions.

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 or with the EU reference product.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Study under fasted conditions (20 mg)
A single-dose, three-way, three-period, two sequence, semi-replicate cross-over bioequivalence study was carried out under fasted conditions in 54 healthy male subjects, aged 19-50 years. Each subject received a single dose (20 mg) of one of the 2 rabeprazole formulations. The tablet was orally administered in solid form with 180 ml water after an overnight fast. Fasting was continued for 5 hours after dosing There were 3 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12 and 14 hours after administration of the products.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Rabeprazole may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of rabeprazole. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with *CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.*

Results
All subjects completed the study entirely, and were included in the pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rabeprazole under fasted conditions.

Treatment N=54**	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	716 ± 350	724 ± 356	455 ± 177	3.67 (1.5 – 7.5)	1.4 ± 0.8
Reference	758 ± 366	765 ± 371	487 ± 167	3.33 (2.0 – 6.0)	1.3 ± 0.6
***Ratio (90% CI)**	0.96 (0.90 – 1.01)	0.96 (0.91 – 1.01)	0.93 (0.84 – 1.02)	---	---
CV (%)	18.5	18.0	31	---	---

$AUC_{0-\infty}$ 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*
*** For Reference and Test mean of the replicate; n=81*

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 (active substance) under fasted conditions, it can be concluded that Rabeprazol KRKA 20 mg gastro-resistant tablets and Pariet 20 mg gastro-resistant tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Study under fed conditions (20 mg)
A single-dose, three-way, three-period, two sequence, semi-replicate cross-over bioequivalence study was carried out under fasted conditions in 54 healthy male subjects, aged 19-50 years. Each subject received a single dose (20 mg) of one of the 2 rabeprazole formulations applying a semi-replicate design.

The tablets were administered in solid form with 240 ml water, 30 minutes after start of intake of a high fat breakfast. The breakfast consisted 2 slices of toast with butter (10 g), 2 eggs fried in butter, 2 strips of bacon (40 g), fried potatoes (120 g) and 240 ml of whole milk.
For each subject there were 3 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 17 and 18 hours after administration of the products.
The analytical method is adequately validated and 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
One subject withdrew after Period I for personal reasons. Fifty-three subjects completed the study entirely, and were included in the pharmacokinetic analysis. It appeared tha for 3 subjects pharmacokinetic profiles could not be adequately characterised for all three parts. In accordance with the protocol, the data for these 3 subjects were not included in the pharmacokinetic and statistical analysis.

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

Treatment N=53**	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	718 ± 308	726 ± 315	481 ± 136	7.0 (3.0 – 9.5)	1.5 ± 0.8
Reference	699 ± 322	706 ± 329	501 ± 149	7.0 (2.0 – 9.5)	1.3 ± 0.6
***Ratio (90% CI)**	1.02 (0.97 – 1.06)	1.02 (0.97 – 1.06)	0.98 (0.92 – 1.04)	---	---
CV (%)	13.7	13.6	20.3	---	---

$AUC_{0-\infty}$ 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*
*** For Reference and Test mean of the replicate; n=77*

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 rabeprazole under fed conditions, it can be concluded that Rabeprazol KRKA 20 mg gastro-resistant tablets and Pariet 20 mg gastro-resistant tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Initially, the MAH applied for a biowaiver to extrapolate the results obtained with the 20 mg tablets to the 10 mg tablets. The MAH however did not fulfil several criteria for a biowaiver, and therefore submitted an additional BE study carried out with the 10 mg gastro-resistant tablet under fasted conditions. See below. The 10 mg strength of the product under consideration was compared to Pariet 10 mg gastro-resistant tablets (Eisai, Germany).

Study under fasting conditions (10 mg)
A single-dose, three-way, three-period, two sequence, semi-replicate cross-over bioequivalence study was carried out under fasted conditions in 54 healthy male subjects, aged 19-52 years. Each subject received a single dose (10 mg) of one of the 2 rabeprazole formulations applying a semi-replicate design. The tablets were administered in solid form with 180 ml water after an overnight fast. Fasting was continued for 5 hrs after dosing. For each subject there were 3 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12 and 14 hours after administration of the products.
The analytical method is adequately validated and 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
One subject was withdrawn because of undercurrent illness during washout period. Fifty-three subjects completed the study entirely, and were included in the analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rabeprazole under fed conditions.

Treatment N=53	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test**	341 ± 138	345 ± 140	213 ± 77	3.0 (1.0 – 5.5)	1.5 ± 0.8
Reference***	342 ± 153	345 ± 155	231 ± 88	3.33 (1.5 – 6.5)	1.3 ± 0.6
***Ratio (90% CI)**	1.00 (0.94 – 1.05)	1.00 (0.95 – 1.05)	0.92 (0.84 – 1.02)	---	---
CV (%)	18.9	18.3	41.9	---	---

$AUC_{0-\infty}$ 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*
*** Test: n=79*
**** Reference: n=80*

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 rabeprazole under fasted conditions, it can be concluded that Rabeprazol KRKA 10 mg gastro-resistant tablets and Pariet 10 mg gastro-resistant tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The MEB has been assured that the bioequivalence study has 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 MAH committed to update the SPC and PIL in accordance with changes in the product information of the innovator (UK/H/0248/001-002).

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.
The MAH stated that a new readability test is not required, and proposed to bridge the patient leaflet with the user test performed for Pantoprazole Krka 20 mg and 40 mg, gastro-resistant tablets.

The MAH provided the User test Assessment report as was performed with the patient leaflet for Pantoprazol KRKA. This was previously assessed and agreed in procudure UK/H/0946/001-002/DC.
The member states agree with the MAH that bridging is possible for these products. Both medicinal products belong to the same therapeutic class and have the same pharmaceutical form. In addition, Rabeprazol KRKA has a similar therapeutic profile as Pantoprazole. The comparison of the information of both product was provided with the application and can be accepted.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Rabeprazol KRKA 10 mg and 20 mg gastro-resistant tablets have a proven chemical-pharmaceutical quality and are generic forms of Pariet 10 mg 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, package leaflet and labelling are in the agreed templates. The MAH committed to update the SPC and PIL in accordance with changes in the product information of the innovator (UK/H/0248/001-002).

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 Rabeprazol KRKA 10 mg and 20 mg gastro-resistant tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 2 July 2010. Rabeprazol KRKA 10 mg and 20 mg gastro-resistant tablets are authorised in the Netherlands on 14 September 2010.

The first PSUR will cover the period from July 2010 to July 2013, after which the PSUR submission cycle will be 3 years.

The date for the first renewal will be: 1 July 2015.

The following post-approval commitments have been made during the procedure:

Quality - active substance
- The MAH has committed to provide stability data up to the claimed retest period of 24 months.

Quality - medicinal product
- The MAH has committed to continue the stability study up to 60 months and place additional production batches on long-term stability through the proposed shelf-life and accelerated stability testing for 6 months. As this is considered to be GMP, results should be held available at the manufacturing site.
- The MAH has committed to provide stability data up to the claimed shelf-life of 15 months.
- The has committed to demonstrate the equivalence with the Dutch reference product when the results will be available.
- The MAH confirmed that results of microbiological testing at the end of storage of the drug product at intermediate storage condition will be provided.
- All impurity limits will be re-evaluated at the end of the stability study.

SPC
- The MAH committed to update the SPC and PIL in accordance with changes in the product information of the innovator (UK/H/0248/001-002).

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