

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Omeprazol Krka 10 mg, 20 mg and 40 mg,
gastro-resistant capsules, hard
Krka d.d., Slovenia**

omeprazole

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/1749/001-003/MR
Registration number in the Netherlands: RVG 104537-104539**

10 March 2011

Pharmacotherapeutic group:	proton pump inhibitors
ATC code:	A02BC01
Route of administration:	oral
Therapeutic indication:	(prevention of relapse of) duodenal ulcers, gastric ulcers; Helicobacter pylori (H. pylori) eradication in peptic ulcer disease; (prevention of) NSAID-associated gastric and duodenal ulcers; reflux esophagitis; long-term management of healed reflux esophagitis; treatment of symptomatic gastro-esophageal reflux disease; treatment of Zollinger-Ellison syndrome. (see next page)
Prescription status:	prescription only
Date of first authorisation in NL:	3 April 2009
Concerned Member States:	Mutual recognition procedure with PL
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 Omeprazol Krka 10 mg, 20 mg and 40 mg, gastro-resistant capsules, hard from Krka d.d. The date of authorisation was on 3 April 2009 in the Netherlands.

The product is indicated for:

Adults

- Treatment of duodenal ulcers
- Prevention of relapse of duodenal ulcers
- Treatment of gastric ulcers
- Prevention of relapse of gastric ulcers
- In combination with appropriate antibiotics, *Helicobacter pylori* (*H. pylori*) eradication in peptic ulcer disease
- Treatment of NSAID-associated gastric and duodenal ulcers
- Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk
- Treatment of reflux esophagitis
- Long-term management of patients with healed reflux esophagitis
- Treatment of symptomatic gastro-esophageal reflux disease
- Treatment of Zollinger-Ellison syndrome

Paediatric use

Children over 1 year of age and ≥ 10 kg

- Treatment of reflux esophagitis
- Symptomatic treatment of heartburn and acid regurgitation in gastro-esophageal reflux disease

Children and adolescents over 4 years of age

- In combination with antibiotics in treatment of duodenal ulcer caused by *H. pylori*

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

Omeprazole, a racemic mixture of two enantiomers, reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing. Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H⁺ K⁺-ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Mopral gastro-resistant capsules, which have been registered in France by Astra Zeneca since 15 April 1987. In the Netherlands, the innovator products Losec 10, 20 and 40, gastro-resistant capsules (NL License RVG 16745, 12438 and 14905) have been registered since 9 November 1988 (20 mg), 14 June 1991 (40 mg) and 15 February 1994 (10 mg), respectively. In addition, reference is made to Mopral and Losec authorisations in the individual member states.

The marketing authorisation is granted based on article 10(1) 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 in which the pharmacokinetic profile of the 20 mg product is compared with the pharmacokinetic profile of the reference products Mopral 20 mg gastro-resistant capsules, registered in Spain and France. 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. In addition, two food interaction studies were submitted. These generic products can be used instead of their reference products.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

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 these product types 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 omeprazole, an established active substance described in de European Pharmacopoeia (Ph.Eur.*). It is a white to almost white powder, which is slightly soluble in water, soluble in methylene chloride and sparingly soluble in ethanol. It shows polymorphism. Omeprazole is a mixture of two enantiomers.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance complies with the specifications as stated in the Ph. Eur., on the CEP and in the USP. These are therefore sufficiently justified. Additionally, the MAH has adequately justified the particle size/density parameters. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance

The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

* *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition

Omeprazol Krka 10 mg is an opaque yellow, size No. 3 capsule containing off-white to cream-white spherical microgranules.

Omeprazol Krka 20 mg is an opaque yellow, size No. 2 capsule containing off-white to cream-white spherical microgranules.

Omeprazol Krka 40 mg is an opaque blue and opaque white, size No. 0 capsule containing off-white to cream-white spherical microgranules.

The composition of the three strengths is proportional; the capsules contain the same pellets.

The capsules are packed in OPA-Al-PVC/Al blisters or HDPE bottles with silica gel desiccant contained in the polypropylene lid.

The excipients are:

Capsule content - sugar spheres (consisting of maize starch and sucrose), sodium laurilsulfate, anhydrous disodium phosphate, mannitol, hypromellose 6 cP, macrogol 6000, talc, polysorbate 80, titanium dioxide (E 171), methacrylic acid-ethylacrylate copolymer (1:1).

Capsule shell - gelatin, titanium dioxide (E 171), quinoline yellow (10/20 mg) (E 104), indigo carmine (E 132).

Pharmaceutical development

The development of the product has been extensively described, including the choice of excipients, a physico-chemical study of each chosen component as well as their compatibility, study of loading and coating suspensions and treatment of the parameters and processing conditions relevant for the process.

The drug product is formulated as a hard gelatin capsule containing twice coated pellets: the outer coating is a gastro-resistant layer; the inner coating contains the active substance.

For both bioequivalence studies comparative dissolution profiles between the test and reference capsules were presented. Dissolution was rapid for both formulations. The choice of the reference product used in the bioequivalence studies has been sufficiently justified.

The pharmaceutical development has been adequately performed and explained.

Manufacturing process

Sugar spheres are coated with an omeprazole suspension, which in turn are coated by a gastro-resistant layer. These pellets are filled into hard gelatin capsules. The process has been adequately described. Separate validation studies were performed to show that the procedures of pellet coating (twice) and of capsule filling are capable of yielding reliably and consistently a product of the designated quality. Validation included three maximum-scale batches of pellets. All pellet batches were filled into various capsule strengths, so that all strengths were covered and each line was validated.

Control of excipients

All the excipients used to make the pellets comply with Ph. Eur. monographs. A separate specification is applied for the gelatin capsules. These specifications are acceptable.

Quality control of drug product

The drug product specification includes tests and requirements for appearance, content uniformity, uniformity of mass, identification, water content, disintegration time, assay, gastro resistance, dissolution rate, related substances, appearance of the pellets and microbiological purity. The methods used have been adequately described and validated. Batch analysis data have been provided for all three pellet-production lines and all three capsule strengths. These data showed compliance with the release specifications.

Stability of drug product

Stability data have been obtained during storage at 25°C/60%RH, 30°/65%RH and 40°C/75%RH. The capsules were packed in Alu-Alu blisters or in HDPE-bottles. Stability data has been included for pilot

batches as well as up-scaled batches. A slight increase of water content and an increase in some impurities are observed in all batches tested.

In view of the results the proposed shelf life (3 years) and storage conditions (store below 30°C) could be granted for both packaging materials.

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

For all excipients there statements were provided that no TSE or other transmissible agents can be present in the products. The empty capsules are made of gelatin. The risk of TSE is covered by CEPs for each of the sources of gelatin used by the manufacturer.

II.2 Non-clinical aspects

This product is a generic formulation of Mopral gastro-resistant capules, 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 omeprazole 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

Omeprazole 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 Omeprazol Krka 20 mg (KRKA d.d., Slovenia) is compared with the pharmacokinetic profile of the reference product Mopral 20 mg gastro-resistant capsules. One study was conducted at single and multiple-dose under fasted conditions with the reference product Mopral 20 mg capsules (Astra Zeneca, Spain), and the other study at single-dose under fed conditions with reference Mopral 20 mg (Astra, France).

The choice of the reference product

The choice of the reference product in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products in different member states. In Bioequivalence study I the test product was also compared to the innovator product Losec from the Australian market. As it concerns a non-European reference product, the results were not assessed.

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

Bioequivalence study I – single/multiple dose, fasted conditions

Design

A single-dose and multiple-dose, randomised, three-period, three-treatment, three-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 18-45 years. Each subject received a single dose (20 mg) once daily for 5 days of one of the 3 omeprazole formulations. The capsule was orally administered with 240 ml water. At day 1 and 5, capsules were taken after a 10 hour fasting period. There were 3 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at day 1 and 5, pre-dose and at 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 6, 8, 10, and 12 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 36 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of omeprazole under fasted conditions at day 1.

Treatment N=36	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	545 ± 441	559 ± 453	327 ± 183	2.0 ± 1.1	0.8 ± 0.3
Reference	527 ± 439	540 ± 451	278 ± 131	2.3 ± 1.3	0.8 ± 0.3
*Ratio (90% CI)	1.02 (0.95-1.09)	1.02 (0.95-1.09)	1.12 (1.01 - 1.25)	--	--
CV (%)	17.5	17.0	26.9	--	--
AUC_{0-∞} 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					

**In-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of omeprazole under fasted conditions at day 5.

Treatment N=36	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	937 ± 799	967 ± 853	479 ± 260	2.3 ± 1.3	1.0 ± 0.6
Reference	974 ± 786	997 ± 816	486 ± 243	1.5 ± 1.6	0.9 ± 0.5
*Ratio (90% CI)	0.96 (0.90-1.02)	0.96 (0.90-1.02)	0.96 (0.86 - 1.07)	--	--
CV (%)	15.1	15.0	27.0	--	--
AUC_{0-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 omeprazole under fasted conditions, it can be concluded that Omeprazol Krka 20 mg and Mopral 20 mg, gastro-resistant capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study II – single dose, fed conditions

Design

A single-dose, block randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy subjects (15 males/21 females), aged 21-41 years. Each subject received a single dose (20 mg) of one of the 2 omeprazole formulations. The capsule was orally administered with 200 ml of water following a standard breakfast (2 croissants, 1 cereal bar, 20 g of butter, 200 ml orange juice, and 200 ml whole milk). There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 1, 2, 2.5, 3, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.25, 6.5, 7, 7.5, 8, 10, and 12 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 36 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=36	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	654 \pm 769	681 \pm 863	318 \pm 200	3.75 (1.0 - 6.25)	0.8 \pm 0.5
Reference	665 \pm 762	687 \pm 841	300 \pm 197	3.0 (1.0 - 6.5)	0.8 \pm 0.5
*Ratio (90% CI)	0.92 (0.83-1.09)	0.92 (0.83-1.01)	1.04 (0.88 - 1.22)	--	--
CV (%)	24.4	24.0	42.3	--	--
AUC_{0-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 omeprazole under fed conditions, it can be concluded that Omeprazol Krka 20 mg and Mopral 20 mg, gastro-resistant capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Food effect

Results from an earlier food-effect study with 30 volunteers were also included in this dossier. This study demonstrated that the omeprazol 20 mg test capsules and the reference Mopral 20 mg capsules are bioequivalent only with respect to the extent of absorption under fed conditions, but not with respect to the rate of absorption, with 90% CI for the C_{max} 0.70-0.99. In contrast, study II demonstrated bioequivalence for C_{max} as well. The reason for the different outcome of these two studies is not readily available, although the higher power of bioequivalence study II may contribute to this difference.

Overall, the combined data of bioequivalence studies I and II sufficiently demonstrate bioequivalence under fasted and fed conditions, and therefore omeprazol 10 mg, 20 mg and 40 mg capsules are considered acceptable for registration.

Extrapolation to other strengths

The 10 mg and 40 mg capsules are dose-proportional with the 20 mg capsule. Omeprazole pharmacokinetics is considered linear up to a dose of 40 mg. Therefore, no bioequivalence studies are needed for these strengths, as the results obtained for the 20 mg capsule can be extrapolated to the 10 mg and 40 mg capsule.

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

Omeprazole was first approved in 1987, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of omeprazole can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation 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

In an article 30 referral (EMA/H/A-30/1001), two harmonised SPCs and package leaflets were decided on, for the prescription only and OTC status. The MAH conformed the SPC to the harmonised 'prescription only' texts.

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. Fourteen subjects (7 females, 7 males; age 25-60 years) were interviewed by means of an in-depth interview. All subjects had experience with the illness. As the outcome of the readability test suggested only minor changes to the PIL, i.e. alphabetic order of subsection "taking other medicines", a second readability test was not conducted. To include a table with indications and dosage was suggested by the respondents in order to easily get an overview and quickly find the right doses in section "How to take Omeprazol 10/20/40 mg capsules". It was suggested by the respondents that in section 2 "Before you take Omeprazol 10/20/40 mg capsules; subsection "important information about some of the ingredients of Omeprazol 10/20/40 mg capsules", would be placed directly under subsection "Do not take Omeprazol 10/20/40 mg capsules" as this information was found to be most important.

These suggestions were applied in the current PIL. There was no need for a second test as no major changes were applied to the leaflet.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Omeprazol Krka 10 mg, 20 mg and 40 mg, gastro-resistant capsules, hard have a proven chemical-pharmaceutical quality and are generic forms of Losec 10, 20 and 40, gastro-resistant capsules. Losec 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. Omeprazol Krka 10 mg, 20 mg and 40 mg, gastro-resistant capsules, hard is authorised in the Netherlands on 3 April 2009.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Omeprazol Krka 10 mg, 20 mg and 40 mg, gastro-resistant capsules, hard with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 15 March 2010.

A European harmonised birth date has been allocated (15 April 1987) and subsequently the first data lock point for omeprazole is April 2012. The first PSUR will cover the period from March 2010 to April 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 17 March 2015.

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

Quality - medicinal product

- The MAH committed to analyse the next three manufactured batches of omeprazole 10, 20 and 40 mg capsules using the BP methods for dissolution, related substances and assay.
- The MAH committed to analyse, using the BP methods for dissolution, related substances and assay, omeprazole 10, 20 and 40 mg capsules at time 0 and at time = shelf life for all new batches placed on stability annually as directed by GMP.

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 _{1/2}	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