

Public Assessment Report

Scientific discussion

**Prenome 10 mg, 20 mg and 40 mg
gastro-resistant capsules, hard
(omeprazole)**

NL/H/2940/001-003/DC

Date: 11 February 2015

This module reflects the scientific discussion for the approval of Prenome 10 mg, 20 mg and 40 mg, gastro-resistant capsules, hard. The procedure was finalised on 3 June 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 Prenome 10 mg, 20 mg and 40 mg gastro-resistant capsules, hard from Distriquimica S.A.

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

Children aged over 1 year and ≥ 10 kg

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

Children aged over 4 years and adolescents

- 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 SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Losec 10, 20 and 40 gastro-resistant capsules (NL License RVG 16745, 12438 and 14905) which have been registered in the Netherlands by AstraZeneca B.V. since 9 November 1988 (20 mg), 14 June 1991 (40 mg) and 15 February 1994 (10 mg), respectively.

The concerned member states (CMS) involved in this procedure were Belgium, Poland and Romania.

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

II. QUALITY ASPECTS

II.1 Introduction

Prenome 10 mg, 20 mg and 40 mg are opaque white hard gelatine capsules containing spherical pellets. The strengths are distinguishable by size.

The capsules are packed in white HDPE bottles or Al/Al blisters.

The excipients are:

Capsule content – sugar spheres (sucrose and maize starch), hypromellose (E-464), talc (E-553b), titanium dioxide (E-171), disodium phosphate dihydrate (E-339 ii), sodium lauryl sulphate, p-olysorbate 80, methacrylic acid-ethyl acrylate copolymer, triethyl citrate (E-1505)

Capsule shell – gelatine, titanium dioxide (E-171)

The different strengths are fully dose proportional.

II.2 Drug Substance

The active substance is omeprazole, an established active substance described in the European Pharmacopoeia. It is a white or almost white powder which is very slightly soluble in water. The drug substance is a racemic mixture of two enantiomers. It exhibits polymorphism and both sources of the drug substance manufacture the same polymorphic form, which is form C.

For one manufacturer the Active Substance Master File (ASMF) procedure is used. 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.

The CEP procedure is used for the other supplier of 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 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

For the first supplier the manufacturing process consists of three synthetic steps and a purification step. The proposed starting materials are acceptable. The active substance has been adequately characterised.

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

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. with additional requirements residual solvents and particle size. 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 production batches from each supplier.

Stability of drug substance

Stability data on the active substance obtained from the first manufacturer have been provided for three production batches stored at 2-8°C (24 months), 25°C/60% RH (6 months) and 40°C/75% RH (1 month). Based on the stability data provided the proposed re-test period of 2 years when stored in a tight container in a refrigerator protected from moisture.

The active substance obtained from the second supplier is stable for 4 years when stored at a temperature between 2°C and 8°C. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 main development studies formulation development, dissolution studies and manufacturing process development. A more enhanced quality by design approach was applied to the formulation and manufacturing process development. Bioequivalence studies were performed with the 40 mg drug product. The batch used in the bioequivalence study is of sufficient size, has the same composition and is manufactured in the same way as the future commercial batches. Dissolution profiles of three production scale batches of each strength have been provided and were found to be

similar to the bioequivalence batch and within the three batches. Based on the comparative dissolution profiles versus the reference product, a biowaiver of strength was granted for the 10 mg and 20 mg capsule. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process is divided into the following steps: film coating sugar spheres in 3 layers, sieving, encapsulation and packaging. 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 of each strength.

Control of excipients

The excipients comply with their respective Ph.Eur. monographs. These specifications are acceptable; functionality related characteristics are included.

Quality control of drug product

The product specification includes tests for appearance, water content, dissolution, identification, assay, related substances, uniformity of dosage units, titanium dioxide and microbial quality. The release and shelf life limits are identical with the exception of water content, assay and related substances. 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 three full-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided three full-scale batches of 10 mg, 20 mg and 40 mg capsules stored at 25°C/60% RH (12 months), 30°/65% RH (12 months), 30°/75% 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 batches were stored in Al/Al blister, HDPE bottle 7 count and HDPE bottle 100 count. The drug product seems more stable in the HDPE bottle. In the blister slight increases in water content, decreases in assay and increases in related substances were observed. Assay and related substances were out of specification at accelerated conditions. In the HDPE bottle decreases in water content and slight increases in related substances were observed. Results of photostability studies showed that no differences were detected between the results obtained in the dark control and samples exposed to light.

Based on the stability data the following shelf life and storage conditions can be granted:

- Blister: 18 months - Do not store above 30°C. Store in the original package in order to protect from moisture.
- HDPE bottle: 24 months – Does not require any special storage conditions. Keep the bottle tightly closed in order to protect from moisture.

Stability data has been provided demonstrating that the product remains stable for 100 days following first opening of the container, when stored at long term conditions. Given the proposed pack size, an in-use shelf life claim is not considered necessary in the SmPC.

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

The only substance of animal or human origin used in the manufacture of the drug product is gelatin. Certificates of suitability issued by the EDQM has been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Prenome 10 mg, 20 mg and 40 mg gastro-resistant capsules, hard have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to continue the stability study of the three submitted production scale batches through the proposed shelf life according to the stability protocol.
- The MAH committed to include a second batch of each strength towards the end of its shelf life in in-use stability studies.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Prenome is 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 Losec, 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

Omeprazole 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

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Prenome 40 mg (Distriquimica S.A., Spain) is compared with the pharmacokinetic profile of the reference product Losec® 40 mg gastro-resistant capsules (AstraZeneca, UK) under fasted and fed conditions as is required for products of this pharmaceutical class.

The choice of the reference product in the bioequivalence study has been justified by comparison of compositions of reference products.

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

Biowaiver

The 10 mg and 20 mg capsules are filled with the same enteric coated pellets as the 40 mg strength used in the bioequivalence studies. The dosage forms are fully dose-proportional. The capsules are manufactured by the same manufacturing process. In addition, omeprazole shows linear pharmacokinetics. The comparative dissolution profiles justify a biowaiver for the 10 mg and 20 mg capsules. Extrapolation of the results obtained for the 40 mg gastro-resistant capsule to the lower strengths is considered acceptable.

Bioequivalence study I – 40 mg capsule, fasted conditions

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, replicate crossover bioequivalence study was carried out under fasted conditions in 28 healthy subjects (9 males/19 females), aged 26-65 years. Each subject received a single dose (40 mg) of one of the 2 omeprazole formulations. The capsule was orally administered with 240 ml water after an overnight fast. For each subject there were 4 dosing periods (RTTR or TRTR; R = reference, T = test), separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 0.75, 1, 1.25, 1.5, 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.

The study design is considered adequate.

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.

Widening of the acceptance criteria was to be defined based upon the within-subject variability seen in the study using a scaled-average-bioequivalence approach, if applicable.

Results

One subject withdrew for personal reasons before dosing of period 4. Another subject withdrew consent for personal reasons before dosing of period 3 and received one single dose of Test and Reference, and one subject was withdrawn before dosing of period 4 for safety reasons (fractured left foot).

All 28 subjects were analysed and included in the pharmacokinetic and statistical analysis.

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

Treatment N=28	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	2561 ± 2458	2660 ± 2761	1254 ± 642	2.5 (1.0 – 4.5)	1.1 ± 0.6
Reference	2535 ± 2552	2599 ± 2818	1214 ± 617	2.25 (1.0 – 4.5)	1.0 ± 0.6
*Ratio (90% CI)	1.01 (0.98-1.05)	--	1.02 (0.95-1.09)	--	--
CV (%)	11.7	--	22	--	--
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*

Bioequivalence study II – 40 mg capsule, fed conditions

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, replicate crossover bioequivalence study was carried out under fed conditions in 44 healthy subjects (21 males/23 females), aged 19-71 years. Each subject received a single dose (40 mg) of one of the 2 omeprazole formulations. The capsule was orally administered 30 min after start of a high fat, high caloric breakfast with 240 ml water. The FDA standard meal was used; the meal was comprised of approximately 240 mL of whole milk, 2 large eggs, 4 ounces of hash brown potatoes (2 potato patties), 1 English muffin with approximately 4.5 g of butter and 2 strips of bacon.

For each subject there were 4 dosing periods (RTTR or TRTR; R = reference, T = test), separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 1.5, 3.0, 3.5, 4, 4.5, 5, 5.5, 6, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 13 and 14 hours after administration of the products.

The study design is considered adequate. A replicate design was chosen in order to obtain intra-subject variability of the reference formulation and therefore to have the possibility of using the scaling approach if the drug was judged to be highly variable. Although the Reference-to-Reference intra-subject CV was greater than 30% for C_{max} (30.5%), the scaling approach was not necessary as bioequivalence was proven.

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.

Widening of the acceptance criteria was to be defined based upon the within-subject variability seen in the study using a scaled-average-bioequivalence approach, if applicable.

Results

One subject withdrew for personal reasons before dosing of period 4. Another subject withdrew consent for personal reasons before dosing of period 2 and received only one single dose of the reference product. A third subject was withdrawn before dosing of period 2 for safety reasons (accidental injury) and received only one single dose of test product. One of the subjects was withdrawn before dosing of period 2 due to emesis, however returned for period 3 and 4 and received one single oral dose of the reference formulation in periods 1 and 3 and one single oral dose of the test in period 4. Forty-two subjects were analyzed and included in the pharmacokinetic and statistical analysis.

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

Treatment N=42	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	1706 \pm 1697	1777 \pm 1926	539 \pm 370	7.5 (3.0 – 9.0)	1.1 \pm 0.4
Reference	1691 \pm 1612	1809 \pm 1883	482 \pm 317 617	6.5 (3.0 – 11.0)	1.1 \pm 0.5
*Ratio (90% CI)	1.00 (0.94-1.05)	--	1.11 (1.02-1.20)	--	--
CV (%)	22.3	--	33.3	--	--
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*

Conclusion on the two bioequivalence studies:

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80–1.25. Based on the submitted bioequivalence studies Prenome 40 mg is considered bioequivalent with Losec[®] 40 mg gastro-resistant capsules under both fasted and fed conditions.

In the fasted study scaling was not applied, as the observed intra-subject variability was below 30%. Although in the study under fed condition the reference-to-reference intra-subject CV was greater than 30% for C_{max} (30.5%) s, the scaling approach was not necessary to assess bioequivalence since the average bioequivalence criteria for the C_{max} parameter were all within the 80.00 to 125.00% acceptance range.

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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Prenome gastro-resistant capsules.

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • Hypersensitivity to omeprazole, substituted benzimidazoles or to any of the excipients. • Possible increase risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors, especially if used in high doses and over long durations (>1 year). • Class effects of proton-pump inhibitors on magnesium blood levels in long-term users has been reported in patients treated for at least three months, and in most cases for a year. • Concomitant administration with active substances with pH dependent absorption: atazanavir, nelfinavir, digoxina. • Use in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on longterm therapy. • Concomitant use with saquinavir, tacrolimus and methotrexate. • Interference with laboratory test for neuroendocrine tumours. • Interaction with clopidogrel (reduced clopidogrel effects) • Omeprazole may delay diagnose of malignancy due to alleviation of symptoms
Important potential risks	<ul style="list-style-type: none"> • Gastric glandular cysts (or development of fundic gland polyps) have been reported in a somewhat increased frequency during long-term treatment. • Slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter. • Severe vision disorders • Congenital cardiac malformations • Rhabdomyolysis
Important missing information	<ul style="list-style-type: none"> • Off label in children with chronic illnesses. • Use in patients with hepatic impaired function.

No additional pharmacovigilance activity is warranted. Currently the signal 'increase risk of pneumonia' is being examined (EMA/CHMP/PhVWP/182855/20122). The MAH committed to include the relevant recommendations in the RMP, once the final conclusions are available.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Losec. 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 bridging report is considered appropriate for the Prenome gastro-resistant capsules, hard package leaflet (daughter PL) and Losec gastro-resistant capsules package leaflet (parent PL) as both medicinal products have the same active moiety, administration route and strength, and both refer to solid oral pharmaceutical forms.

Regarding design and layout, PL for Prenome has been designed in line with the company's style. The design used for the daughter leaflet has been tested previously in other readability tests.

The comparison between layout of the leaflets shows that there are no differences in the relevant aspects, such as PIL dimensions, print colour, paper weight, style and layout of critical safety sections, while headings and sub-headings are similar, due to the update of QRD templates. The only difference found is font size and font type, both font styles are considered similar and do not interfere with the readability.

Following an evaluation of these points, it can be concluded that none of the differences between the Prenome and Losec gastro-resistant capsules PLs are significant. Therefore, a specific readability test is not considered necessary. The bridging report is considered sufficient.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Prenome 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 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 Prenome 10 mg, 20 mg and 40 mg gastro-resistant capsules, hard with the reference product, and have therefore granted a marketing authorisation. The decentralized procedure was finalised with a positive outcome on 3 June 2014.

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