CBG MEB

Public Assessment Report

Scientific discussion

Omeprazol Mylan OTC 10 mg and 20 mg gastro-resistant tablets

(omeprazole magnesium)

NL/H/3095/001-002/DC

Date: 14 April 2016

This module reflects the scientific discussion for the approval of Omeprazol Mylan OTC 10 mg and 20 mg gastro-resistant tablets. The procedure was finalised on 1 July 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Omeprazol Mylan OTC 10 mg and 20 mg gastro-resistant tablets, from Mylan B.V.

The product is indicated for the treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.
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 product in The Netherlands, Losecosan 10 and 20 mg gastro-resistant tablets registered by Bayer B.V. since 28 February 2000 (NL License RVG 25212, 25213).

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

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

II. QUALITY ASPECTS

II.1 Introduction

Omeprazol Mylan OTC is a gastro-resistant tablet in two strengths:
- 10 mg - a yellow, film-coated, oblong, biconvex tablet (approximately 6.8 mm x 13.2 mm) debossed with 'M' on one side of the tablet and 'OM1' on the other side
- 20 mg - a yellow, film-coated, oblong, biconvex tablet (approximately 9.5 mm x 16.5 mm) debossed with 'M' on one side of the tablet and 'OM2' on the other side

Each gastro-resistant tablet contains 10 mg or 20 mg omeprazole (as omeprazole magnesium).

The gastro-resistant tablets are packed in white HDPE bottles with opaque polypropylene (PP) cap with aluminium induction sealing liner wad along with a desiccant, or in OPA/aluminum/PVC/aluminum blister packs.

The excipients are:
- Sugar spheres (Maize starch, Sucrose)
- Crospovidone
- Hydroxypropylcellulose
- Polysorbate 80
- Mannitol
- Povidone
- Talc
- Macrogol
- Methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30 percent (containing methacrylic acid-ethyl acrylate, sodium laurilsulfate, polysorbate)
- Triethyl citrate
- Glycerol monostearate
- Titanium dioxide (E171)
- Sodium hydroxide (for pH adjustment)
- Magnesium stearate
- Silicified microcrystalline cellulose
- Silica, colloidal anhydrous
- Hydrogenated vegetable oil
- Hypromellose
- Iron oxide yellow (E172)

The different tablet strengths are fully dose proportional with regard to the enteric-coated pellets content. The 10 mg and 20 mg tablets are manufactured fully dose proportional also with regard to the final tablet blend.

II.2 Drug Substance

The active substance is omeprazole magnesium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Omeprazole magnesium is very slightly soluble in water. The used omeprazole magnesium has the amorphous form. The solid state form of the drug substance is not considered relevant for the drug product as the drug substance is dissolved during the drug product manufacturing process.

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 synthesis of omeprazole magnesium consists of one step from the starting material omeprazole. No class 1 organic solvents or heavy metal catalysts are used. The starting material omeprazole is the subject of a CEP. 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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches.

Stability of drug substance
Stability data on the active substance have been provided for several full scaled batches stored at 2-8°C (36 months) and 25°/60% RH (6 months). Except for a slight increase of total impurities at accelerated conditions, no trends or changes were observed for any of the tested parameters. The proposed retest period of 36 months and storage conditions 'Store at 2-8°C' and 'Store in an airtight container, protected from light' are justified.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies were the characterisation of the reference product, optimization of the tablet composition and performance of *in vitro* dissolution studies.

A bioequivalence study has been performed with the 20 mg strength versus the respective reference product strength. The 20 mg test batch used in the bioequivalence study was manufactured according to the finalized composition and manufacturing process. Sufficient comparative dissolution data between the test and reference product have been provided.

For the 10 mg tablets a biowaiver was justified. The biowaiver is based on the bioequivalence study with the 20 mg product. Both batches comply with the general biowaiver criteria and it has been sufficiently demonstrated that dissolution of the 10 mg batch is similar to that of the 20 mg bioequivalence study test batch under the relevant dissolution conditions (0.1N HCl, pH 4.5 and pH 6.8). The 10 mg and 20 mg tablets are fully dose proportional tablets and are manufactured using the same manufacturing process.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the process are the layering of a drug substance dispersion on sugar spheres, after which a first and a second sub-coating are applied. Then two enteric coatings are applied followed by two seal coatings. The final enteric coated pellets are then blended with the extragranular tablet components and the tablets are compressed and film-coated. The final enteric coated pellets are the same for both product strengths. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches per strength.

Control of excipients
Except for the film-coating material, all excipients comply with relevant compendial monographs. The film-coating material is tested according to in-house specifications. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identity, dissolution, uniformity of dosage units, assay, related substances, water, residual solvents and microbial quality. Except for assay, related substances and water content, the release and shelf-life requirements are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the products has been provided on three full scaled batches per strength stored at 25°C/60% RH (18 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 HDPE bottles and OPA/Al/PVC-Al blisters. At accelerated conditions an increase in impurities and a decrease in assay were seen. At long-term conditions only an increase in impurities was observed. No trends or changes were seen in any of the other tested parameters. As part of the stability study the MAH demonstrated that tablet hardness remains acceptable throughout the drug product's shelf-life. The product is not sensitive to light. The proposed shelf-life of 2 years with storage conditions 'Do not store above 25°C' and 'Store in the original package in order to protect from moisture' are justified.

For the HDPE bottle pack the MAH has performed an adequate in-use stability study. Testing was done with two batches of 10 mg that were packed in 100's count HDPE bottles 25°C/60% RH (100 days). The pack was opened once every day for about 2 minutes and the condition of the patient withdrawing 1 tablet was simulated. No relevant changes were seen.
An in-use shelf life is included in the SmPC: 'After opening, use within 100 days'.

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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Omeprazol Mylan OTC has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Omeprazol Mylan OTC 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 Losecosan 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 magnesium 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

Bioequivalence study
The MAH submitted a bioequivalence study in which the test product Omeprazol Mylan OTC 20 mg gastro-resistant tablets (Mylan B.V., The Netherlands) is compared to reference product Mopralpro 20 mg gastro-resistant tablets (Bayer Sante Familiale, France).

Acceptability of the proposed 20 mg reference product for this application has been assessed, and was accepted as there is a licence agreement between the manufacturers of both reference products. Therefore Mopralpro and Losecosan can be considered to belong to the same global marketing authorization. In this respect it is also mentioned that the composition of both products is identical. The test batch used in the bioequivalence study was of production scale and was manufactured according to the finalized formulation and manufacturing process.

Biowaiver
A biowaiver was granted for the 10 mg product, based on the bioequivalence study conducted on the 20 mg strength. Both batches comply with the general biowaiver criteria and it has been sufficiently demonstrated that dissolution of the 10 mg batch is similar to that of the 20 mg bioequivalence study test batch under the relevant dissolution conditions (pH 4.5 and 6.8).

Study design
A single-dose, randomised, balanced, four-period, four treatment, two sequence, crossover bioequivalence study for the 20 mg formulation was carried out under fasted (Period I and II) and fed conditions (Period III and IV) in 48 healthy male subjects, aged 20-41 years. Each subject received a single dose (20 mg) of one of the 2 omeprazole formulations. The tablet was orally administered with 240 ml water. Depending on the period, the tablets were taken after a 10 hour fasting period or with a high-fat and high-calorie non-vegetarian breakfast 30 minutes prior to the dosing. Subjects consumed this meal completely within 30 minutes. For each subject there were 4 dosing periods, separated by a washout period of 7 days.

For the study under fasting conditions, blood samples were taken pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 14.00, 16.00, 20.00 and 24.00 hours after administration of the products.
For the study under fed conditions, blood samples were taken pre-dose and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 8.00, 9.00, 10.00, 12.00, 16.00, 24.00, 28.00, 32.00 and 36.00 hours after administration of the products.

The overall study design is acceptable considering the absorption rate and half-lives. The study was conducted under fasted and fed conditions as is required for products of this pharmaceutical class. Also the washout period is acceptable.

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
In the 20 mg formulation fasting study, three subjects were withdrawn due to an adverse event. Two subjects did not report for Period II. As such, 43 subjects completed the fasting study entirely, and were included in the analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 20 mg omeprazole under fasted conditions.

Treatment N=43	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**$t_{1/2}$** h	**t_{max}** h
Test	2756 ± 2837	2822 ± 2928	810 ± 416	1.6 ± 1.2	2.75 (1.25 – 5.00)
Reference	2675 ± 2734	2734 ± 2815	850 ± 410	1.6 ± 1.2	1.75 (1.00 – 6.00)
***Ratio (90% CI)**	1.03 (0.98-1.08)	1.03 (0.98-1.08)	0.95 (0.90-1.01)	--	--
CV (%)	13.2	12.6	17.1	--	--

$AUC_{0-\infty}$	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
$t_{1/2}$	half-life
t_{max}	time for maximum concentration
CV	coefficient of variation

**ln-transformed values*

The 43 subjects that completed the fasting part of the study, started the fed part of the 20 mg study. During the fed part, three subjects were excluded from the analysis. One subject did not report for Period III and two subjects did not report for Period III and IV. As such, 40 subjects completed the study under fed conditions entirely, and were included in the analysis.

Table 4 Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 20 mg omeprazole under fed conditions.

Treatment N=40	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**$t_{1/2}$** h	**t_{max}** h
Test	2249 ± 2517	2301 ± 2556	570 ± 354	1.7 ± 1.1	4.5 (2.5 – 6.5)
Reference	2195 ± 2469	2238 ± 2494	548 ± 321	1.7 ± 1.1	4.0 (2.0 – 9.0)
***Ratio (90% CI)**	1.05 (0.98-1.11)	1.05 (0.99-1.11)	1.07 (0.98-1.17)	--	--

CV (%)	16.5	15.8	25.1	--	--

$AUC_{0-\infty}$	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
$t_{1/2}$	half-life
t_{max}	time for maximum concentration
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Omeprazol Mylan OTC 20 mg gastro-resistant tablets is considered bioequivalent with Mopralpro 20 mg tablets under fasting and fed conditions.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Omeprazol Mylan OTC.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Gastrointestinal infections • Chronic treatment with PPIs decreases absorption of cyanocobalamine (vitamin B12) • Interaction with active substances with pH dependent absorption • Interaction with active substances metabolised by CYP2C19 • Interaction with active substances by unknown mechanism
Important potential risks	• Convulsion/seizure • Off-label use • Pneumonia • Increased risk of Clostridium difficile-associated diarrhea (CDAD) with PPIs • Decrease in absorption of iron (Iron deficiency)
Missing information	• Use in pregnant and lactating women • Use in patients in renal impairment

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Losecosan. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Omeprazol Mylan 10 mg and 20 mg gastro-resistant tablets, NL/H/3094/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Omeprazol Mylan OTC 10 mg and 20 mg gastro-resistant tablets have a proven chemical-pharmaceutical quality and are generic forms of Losecosan 10 mg and 20 mg gastro-resistant tablets. Losecosan 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, under both fasted and fed conditions.

The Member States agreed that the 20 mg reference product used in the bioequivalence study can be accepted based on the licence agreement between the manufacturers of both products.

The Board followed the advice of the assessors.

The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Omeprazol Mylan OTC gastro-resistant tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 1 July 2015.

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

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
SmPC sections have been updated	NL/H/3095/ 001-002/IB	IB	11-11-2015	11-12-2015	Approval	No