COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Omzar 20 mg and 40 mg gastro-resistant tablets

(esomeprazole)

NL License RVG 125034 & 125036

Date: 29 December 2020

This module reflects the scientific discussion for the approval of Omzar 20 mg and 40 mg gastro-resistant tablets. The procedure was finalised at 23 July 2020. 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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Omzar 20 mg and 40 mg gastro-resistant tablets, from Maddox Pharma Swiss B.V.

The product is indicated for in adults for:

- Gastroesophageal Reflux Disease (GERD)
  - treatment of erosive reflux esophagitis
  - long-term management of patients with healed esophagitis to prevent relapse
  - symptomatic treatment of gastroesophageal reflux disease (GERD)
- In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* and
  - healing of *Helicobacter pylori* associated duodenal ulcer
  - prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.
- Patients requiring continued NSAID therapy
  - healing of gastric ulcers associated with NSAID therapy.
  - prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.
- Prolonged treatment after i.v. induced prevention of rebleeding of peptic ulcers.
- Treatment of Zollinger Ellison Syndrome

The product is indicated in adolescents from the age of 12 years for:

- Gastroesophageal Reflux Disease
  - treatment of erosive reflux esophagitis
  - long-term management of patients with healed esophagitis to prevent relapse
  - symptomatic treatment of gastroesophageal reflux disease (GERD)

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

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

This national procedure concerns a generic application claiming essential similarity with the innovator product Nexium 20 mg and 40 mg, gastro-resistant tablets which has been registered in Sweden by AstraZeneca AB since 10 March 2000 (original product). In the Netherlands, Nexium 20 mg and 40 mg gastro-resistant tablets (NL License RVG 25387-25388) have been registered since 15 August 2000 by MRP SE/H/0211/001-002. In addition, reference is made to Nexium authorisations in the individual member states (reference product).

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

II. QUALITY ASPECTS

II.1 Introduction

Omzar 20 mg is a light pink, oval, biconvex, film-coated, gastro-resistant tablet. Each tablet contains 21,75 mg esomeprazole magnesium dihydrate (equivalent to 20 mg esomeprazole base).
Omzar 40 mg is a pink, oval, biconvex, film-coated, gastro-resistant tablet. Each tablet contains 43,50 mg esomeprazole magnesium dihydrate (equivalent to 40 mg esomeprazole base).

The gastro-resistant tablets are packed in Al/Al (OPA/Al/PVC/Al) blisters.

The excipients are: methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30%, talc, triethyl citrate, hypromellose, sugar spheres, magnesium stearate, hydroxypropyl cellulose, glycerol monostearate, polysorbate 80, microcrystalline cellulose, povidone, crospovidone, sodium stearyl fumarate and Opadry film-coatings consisting of hypromellose, titanium dioxide, iron oxide red and iron oxide yellow.

The tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is esomeprazole magnesium dihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a white or slightly coloured powder and slightly hygroscopic. It is slightly soluble in water, soluble in methanol and practically insoluble in heptane. The drug substance shows polymorphism and crystalline form B.

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
Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised. The manufacturing process is acceptable.

Quality control of drug substance

The drug substance specification of the MAH has been adopted from the drug substance specification of the ASMF holder, except for the tests for solubility, microbiological contamination, tests for specified microorganisms, vanadium content, as it was shown by the ASMF holder that control of these tests is not required. An additional test for particle size distribution has been included in the drug substance specification of the MAH. The active substance has been adequately characterised. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three full-scaled batches stored at 2 – 8°C (60 months), 25°C/60% RH (24 months) and 40°C/75%RH (4 months). Based on the data submitted, a retest period could be granted of 36 months when stored under the stated conditions.

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 performed were regarding the characterisation of the innovator product and optimisation of the formulation, the manufacturing process and dissolution method. The excipients used in the products are well known. The choices of the packaging and manufacturing process are justified. The 40 mg test batch used in the bioequivalence study was manufactured according to the finalised manufacturing process and composition. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process is an non-standard manufacturing process and has been validated according to relevant European guidelines. Process validation data on the product have been presented for batches for both strengths in accordance with the relevant European guidelines.

Control of excipients

The 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, identification (of esomeprazole, iron oxide and titanium dioxide), uniformity of dosage units, average weight, disintegration, assay, related substances, dissolution and microbiology. Except for related substances, the release and shelf-life specifications are identical. Non-routine testing is applied for identification of iron oxide and titanium dioxide and microbiology and considered acceptable 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 four pilot scaled batches and at least two full scaled batches per tablet strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

The conditions used in the stability studies are according to the ICH stability guideline and the minimum requirement for the time period covered by data at submission has been met. Under accelerated (40°C/75% RH) and intermediate conditions (30°C/75% RH) several out of specification results are obtained for related substances. Compliance of the provided data with the proposed shelf-life specifications was demonstrated for the product stored for 36 months at long term conditions. Based on the provided stability data, the proposed shelf-life of 24 months and storage conditions 'Store below 25°C' can be granted.

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 MEB considers that Omzar 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 Omzar 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 Nexium 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 MEB agrees that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Esomeprazole 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 MEB agrees 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 Omzar 40 mg gastro-resistant tablets (Maddox Pharma Swiss B.V., NL) is compared with the pharmacokinetic profile of the reference product Nexium 40 mg, gastro-resistant tablets (AstraZeneca AB, Sweden).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH requested for a biowaiver for the 20 mg strength tablet as the following conditions are considered met:

a) the pharmaceutical products are manufactured by the same manufacturing process
b) the qualitative composition of the different strengths is the same
c) the composition of the strengths is quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule).

Therefore, a biowaiver has been granted.

Bioequivalence studies

Bioequivalence study I – single dose, full replicate under fasting conditions

Design

A randomised, open label, two treatment, four period, two sequence, single dose, crossover, fully replicate, bioequivalence study was carried out under fasted conditions in 64 healthy male subjects, aged 19-42 years. Each subject received a single dose (40 mg) of one of the 2 esomeprazole formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 4 dosing periods, separated by a washout period of 6 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.3, 1.7, 2, 2.3, 2.7, 3, 3.5, 4, 5, 6, 8, 10, 12, 16 and 20 hours after administration of the products.

The design of the study is acceptable. The wash-out period and sampling period are considered long enough.

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
There were four drop-outs as they did not check in for the second or third period and three subjects were withdrawn (due to protocol non-compliance, testing positive for tetrahydrocannabinol and an adverse event). A total of 61 subjects completed at least two study periods and were eligible for pharmacokinetic analysis.

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

Treatment	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test				
T1 (N=61)	6.2 ± 3.3	6.3 ± 3.4	1.8 ± 0.6	2.7 (1.3-5.0)
T2 (N=57)	6.8 ± 3.4	6.9 ± 3.5	1.9 ± 0.6	2.0 (1.0-5.0)
Reference				
T1 (N=61)	6.1 ± 3.3	6.2 ± 3.3	1.9 ± 0.7	2.3 (1.3-5.0)
T2 (N=57)	6.8 ± 3.4	6.9 ± 3.4	2.1 ± 0.6	2.0 (1.3-5.0)
***Ratio**	1.01	--	0.91	--
(90% CI)	(0.97-1.04)		(0.88-0.95)	
CV (%)				
Test	15.0	14.8	16.0	--
Reference	18.3	18.1	17.4	
All	16.7	16.5	16.7	

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Bioequivalence study II – single dose, full replicate under fed conditions
Design
A randomised, open label, two treatment, four period, two sequence, single dose, crossover, fully replicate, bioequivalence study was carried out under fasted conditions in 64 healthy male subjects, aged 19-43 years. Each subject received a single dose (40 mg) of one of the 2

esomeprazole formulations. The tablet was orally administered with 240 ml water 30 minutes after a high calorie, high fat breakfast (consisting of bread, masala eggs, hash brown potatoes and milk). There were 4 dosing periods, separated by a washout period of 4 days.

Blood samples were collected pre-dose and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 12, 16 and 20 hours after administration of the products.

The design of the study is acceptable. The constituents and the calorie intake from the high fat meal is acceptable. The wash-out period and sampling period are considered long enough.

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
There was one drop-out as the subject did not check in for the third period and three subjects were withdrawn (due to an adverse event, alcohol consumption and reduced haemoglobin). A total of 60 subjects completed at least two study periods and were eligible for pharmacokinetic analysis.

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

Treatment **N=**	**AUC_{0-t}** **(ng.h/ml)**	**$AUC_{0-\infty}$** **(ng.h/ml)**	**C_{max}** **(ng/ml)**	**t_{max}** **(h)**
Test **T1 (N=61)** **T2 (N=57)**	 4.8 ± 3.5 5.1 ± 3.2	 4.9 ± 3.6 5.2 ± 3.3	 1.0 ± 0.6 1.1 ± 0.5	 6.0 (2.0-9.0) 5.5 (2.0-9.0)
Reference **T1 (N=61)** **T2 (N=57)**	 4.5 ± 3.2 4.9 ± 3.2	 4.5 ± 3.2 4.9 ± 3.2	 1.1 ± 0.6 1.1 ± 0.6	 5.5 (3.0-8.0) 5.5 (2.5-8.0)
***Ratio** **(90% CI)**	1.09 (1.02-1.17)	--	0.98 (0.91-1.06)	--
CV (%) **Test** **Reference** **All**	 26.2 37.0 32.0	 24.6 34.8 30.1	 28.5 42.3 36.0	 --

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Conclusion on 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 Omzar is considered bioequivalent with Nexium.

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).

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 Omzar.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	– Agranulocytosis – Hypersensitivity reactions – Hypomagnesaemia – Depression – Hepatic reactions – Severe cutaneous adverse reactions – Interstitial nephritis – Fracture of the hip, wrist or spine – Gastrointestinal infections – Interactions with: ▪ Warfarin or other coumarin derivatives ▪ Phenytoin ▪ Atazanavir ▪ Nelfinavir ▪ Digoxin ▪ Methotrexate ▪ Tacrolimus ▪ Clopidogrel
Important potential risks	– Convulsion/seizure – Pneumonia
Missing information	– Use in pregnant and lactating women – Use in patients with renal impairment

The MEB agrees 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 Nexium. 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 user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Nexium 20 mg and 40 mg gastro-resistant tablets (content) and Etorixan 30 mg, 60 mg, 90 mg and 120 mg, film-coated tablets (layout). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Omzar 20 mg and 40 mg gastro-resistant tablets have a proven chemical-pharmaceutical quality and are generic forms of Nexium 20 mg and 40 mg, gastro-resistant tablets. Nexium 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.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Omzar with the reference product, and has therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 23 July 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse