COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Omeprazol Sandoz 10 mg, 20 mg and 40 mg gastro-resistant capsules, hard

(omeprazole)

NL/H/4047/001-003/DC

Date: 16 November 2018

This module reflects the scientific discussion for the approval of Omeprazol Sandoz 10 mg, 20 mg, and 40 mg gastro-resistant capsules, hard. The procedure was finalised at 26 April 2018. 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 Sandoz 10 mg, 20 mg, and 40 mg gastro-resistant capsules, hard, from Sandoz B.V.

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 oesophagitis
- Long-term management of patients with healed reflux oesophagitis
- Treatment of symptomatic gastro-oesophageal reflux disease
- Treatment of Zollinger-Ellison syndrome

Paediatric population

Children over 1 year of age and ≥10 kg

- Treatment of reflux oesophagitis
- Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease

Children over 4 years of age 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 product Losec 10 mg, 20 mg, and 40 mg gastro-resistant capsules, hard (NL License RVG 16745, 12438, 14905) which have been registered in The Netherlands by AstraZeneca B.V. since 15 February 1994, 9 November 1988, and 14 June 1991 through procedure NL/H/2081/001-003.

The concerned member states (CMS) involved in this procedure were Denmark, Spain (only the 10 mg strength), Bulgaria (only the 20 mg strength), Iceland, Norway, and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Omeprazol Sandoz is a hard gastro-resistant capsule in three strengths:

- 10 mg strength: light brown cap, light brown body, containing almost white to light brown pellets.
- 20 mg strength: white cap, white body, containing almost white to light brown pellets.
- 40 mg strength: white cap, light brown body, containing almost white to light brown pellets.

Each gastro-resistant tablet contains 10 mg, 20 mg or 40 mg omeprazole.

The product is packed in OPA/Al/PVC-Al blisters and HDPE bottles with inserted desiccant (silica gel capsule) PP screw cap with or without a child resistant closure.

The excipients are:
Capsule contents - sugar spheres (sucrose and maize starch), hypromellose, sodium laurilsulfate, magnesium oxide heavy, povidone, talc, methacrylic acid - ethyl acrylate copolymer 1:1, and triethyl citrate.
Capsule shell - 10 mg and 40 mg strength: gelatine, water, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172), may also contain: black iron oxide (E172). 20 mg strength: gelatine, water, titanium dioxide (E171).

The three capsules fillings are dose proportional.

II.2 Drug Substance

The active substance is omeprazole, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white powder and is very slightly soluble in water. The drug substance exhibits polymorphism.

The CEP procedure is used by three manufacturers 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 general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

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

Quality control of drug substance
The active substance specification is considered adequate to control the quality. It is in line with the requirements in the CEPs, with additional requirements for particle size. Batch analytical data demonstrating compliance with this specification have been provided for two batches of each manufacturer.

Stability of drug substance
The active substance is stable for three to five years when stored under the stated conditions. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

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 excipients and packaging are usual for this type of dosage form. Pharmaceutical development has been adequately performed.

Three bioequivalence studies have been submitted comparing the highest strength of the test product with Losec 40 mg gastro-resistant hard capsules. For the lower strengths a biowaiver has been requested. Comparable dissolution profiles have been shown at three different pHs.

Manufacturing process
Sugar spheres are coated with the active substance coating, followed by protective coating and finally enteric coating. Coated pellets are dried. Magnesium stearate is added to the pellets prior to the end of drying. Pellets are sieved and filled in hard gelatin capsules. 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 the Ph.Eur. 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 appearance of the capsules and their contents, uniformity of dosage units, loss on drying, identity, assay, dissolution, related substances and microbial quality. The acceptance limits for loss on drying and related

substances differ at release and shelf-life. The specification is 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 three batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided on three full scaled batches for each strength stored at 25°C/60% RH (24 months), 30°C/65% 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 the proposed packaging. Photostability studies were performed in accordance with ICH recommendations showing that the product is stable when exposed to light. At 40°C/75% RH the colour and appearance of the pellets does not conform. The proposed shelf-life of two years is justified. The storage condition 'Do not store above 25°C. Store in the original packaging in order to protect from moisture' is acceptable.
Stability data has been provided demonstrating that the product remains stable for 100 days following first opening of the container, when stored at or below 25°C in the original packaging.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have 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 Omeprazol Sandoz 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 Sandoz 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 three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Omeprazol Sandoz 40 mg gastro-resistant capsules, hard (Sandoz B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Losec 40 mg gastro-resistant capsules (AstraZeneca UK Ltd, United Kingdom):

- Single dose replicate crossover comparative bioavailability study of omeprazole 40 mg gastro-resistant capsules in healthy male and female volunteers under fasting conditions.
- Single dose replicate crossover comparative bioavailability study of omeprazole 40 mg gastro-resistant capsules in healthy male and female volunteers under fed conditions.
- Single dose replicate crossover comparative bioavailability study of omeprazole 40 mg gastro-resistant capsules in healthy male and female volunteers under fed conditions.

A single dose bioequivalence study under fasting and fed conditions to support this application for a gastro-resistant formulation is considered sufficient. Due to the fact that bioequivalence could not be proven in the first study under fed conditions, the study was repeated including a larger number of subjects.

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 product.

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

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.

Biowaiver
The biowaiver for Omeprazol Sandoz 10 mg and 10 mg gastro-resistant capsules is acceptable, as the following criteria have been fulfilled:

- The pharmaceutical products are manufactured by the same manufacturing process
- The qualitative composition of the different strengths is the same
- The bioequivalence study has been conducted with the highest strength
- The compositions are dose proportional; the differences in capsule shells are not relevant.
- The MAH has adequately demonstrated similar dissolution profiles in pH 6.8 medium after 2 hours in pH 4.5 medium for the additional 10 mg and 20 mg strengths versus the BE study test batch. Similarity in dissolution was adequately demonstrated by proper f2-calculation on at least one batch of the 10 mg and 20 mg additional strengths. An additional confirmation of similarity for the other batches by multivariate analysis as well as a visual comparison of the profiles and the calculation of f2-values is considered as supportive.

Single dose four period bioequivalence study with the 40 mg capsule under fasted conditions
Design
A single-dose, four-period, replicate crossover comparative bioequivalence study was carried out under fasted conditions in 60 healthy male (n=24)/female (n=36) subjects, aged 19-54 years. Each subject received a single dose (40 mg) of one of the 2 omeprazole formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were four dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10 and 12 hours after administration of the products.

The design of the study is acceptable. A replicate design was applied to widen the 90% CI for C_{max} based upon the observed intra-subject variability for the Reference formulation, if applicable.

Results
Four subjects did not complete the study (all four periods). Therefore, 56 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=112	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	2118 ± 1837	2226 ± 1912	1140 ± 605	2.0 (0.67 - 5.0)	1.0 ± 0.45
Reference	2197 ± 1983	2318 ± 2069	1095 ± 596	2.0 (0.67 - 5.0)	1.0 ± 0.54
***Ratio (90% CI)**	0.97 (0.94 - 1.00)	--	1.04 (0.98 - 1.09)	--	--
CV (%)	13.8	--	25.5	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Based on the pharmacokinetic parameters of omeprazole the Reference and Test are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for $AUC_{(0-t)}$ and C_{max} were inside the normal range of acceptability (0.80 – 1.25).

An additional statistical analysis was carried out including subjects whom had at least 1 treatment with Test and Reference, which is in accordance with EMAs Bioequivalence guideline. Including these subjects (three subjects) bioequivalence under fasted conditions could still be proven (see table below).

			90% confidence interval	
Parameter	Method*	Point estimate [%]	Lower limit [%]	Upper limit [%]
C_{max}	A	105.31	99.89	111.02
	B	105.24	99.83	110.94
$AUC_{0-tlast}$	A	98.22	95.25	101.29
	B	98.21	95.23	101.28
$AUC_{0-\infty}$	A	98.70	95.74	101.75
	B	98.69	95.72	101.74

*according to EMA Questions & Answers: Positions on Specific questions addressed to the pharmacokinetic working party (EMA/618604/2008 Rev. 9)

Single dose, four period bioequivalence study with the 40 mg capsule under fed conditions

Design

A single-dose, four-period, replicate crossover comparative bioequivalence study was carried out under fed conditions in 60 healthy male (n=30)/female (n=30) subjects, aged 18-55 years. Each subject received a single dose (40 mg) of one of the 2 omeprazole formulations. The tablet was orally administered with 240 ml water after intake of a high caloric and high fat meal. 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. There were four dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.33, 6.67, 7, 7.5, 8, 9, 10, 11, 12, 14, 16 and 24 hours after administration of the products.

The design of the study is acceptable. A replicate design was applied to widen the 90% CI for C_{max} based upon the observed intra-subject variability for the Reference formulation, if applicable.

Results
Five subjects did not complete the study (all four periods). 57 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=114	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	1735 ± 1909	1788 ± 1969	547 ± 397	5.3 (3.0 - 12.0)	1.4 ± 0.98
Reference	1954 ± 1997	1977 ± 2066	569 ± 388	5.7 (3.5 - 14.0)	1.5 ± 1.1
***Ratio (90% CI)**	0.86 (0.7992 - 0.92)	--	0.93 (0.84 - 1.02)	--	--
CV (%)	32.0	--	32.6	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

The 90% confidence interval calculated for $AUC_{(0-t)}$ was outside the normal range of acceptability (0.80 - 1.25). For C_{max} bioequivalence could be proven within the normal range of acceptability, without widening the range, although a high intra-subject variability was shown for this parameter (i.e. 32.6%).

Different post-hoc methods showed bioequivalence for AUC_{0-t} and C_{max}. However it can be discussed whether a post-hoc analysis may be applied to show that the products are

bioequivalent. The MAH submitted an additional bioequivalence study under fed conditions (see below).

Single-dose, four period, bioequivalence study under fed conditions

Design

A single-dose, four-period, replicate crossover comparative bioequivalence study was carried out under fed conditions in 80 healthy male (n=35)/female (n=45) subjects, aged 19-55 years. Each subject received a single dose (40 mg) of one of the 2 omeprazole formulations. The tablet was orally administered with 240 ml water after intake of a high caloric and high fat meal. 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. There were four dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.33, 6.67, 7, 7.5, 8, 9, 10, 11, 12, 14, 16 and 24 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study under fasting to assess bioequivalence is considered adequate. As this is a gastro-resistant formulation, also a single dose bioequivalence study under fed condition is submitted, in accordance with EMAs Bioequivalence guideline. A replicate design was applied to widen the 90% CI for C_{max} based upon the observed intra-subject variability for the Reference formulation, if applicable.

Results

Eleven subjects did not complete the study (all four periods). However 72 subjects were included in the pharmacokinetic and statistical analysis. These subjects completed at least one period with the Test formulation and one period with the Reference formulation.

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

Treatment **N_{test} = 142** **N_{ref} = 141**	**AUC_{0-t}** **(ng.h/ml)**	**$AUC_{0-\infty}$** **(ng.h/ml)**	**C_{max}** **(ng/ml)**	**t_{max}** **(h)**	**$t_{1/2}$** **(h)**
Test	1304 ± 1189	1387 ± 1213	453 ± 361	5.3 (3.0 – 12.0)	1.5 ± 0.90
Reference	1458 ± 1283	1631 ± 1339	462 ± 349	5.3 (2.0 – 12.0)	1.6 ± 0.94
***Ratio** **(90% CI)**	0.86 (0.81 – 0.91)	--	0.93 (0.85 - 1.02)	--	--
CV (%)	27.9	--	46	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Based on the pharmacokinetic parameters of omeprazole the Reference and Test are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for $AUC_{(0-t)}$ and C_{max} were inside the normal range of acceptability (0.8000 - 1.2500).

Conclusion on bioequivalence studies:
Taking into account the overall data, bioequivalence is considered proven under fasting as well as under fed conditions.

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 Omeprazol Sandoz.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Severe hypomagnesaemia • Risk of hypersensitivity reaction • Risk of interaction with nelfinavir and atazanavir • Risk of the fractures of the hip, wrist or spine
Important potential risks	• Risk of decreased absorption of vitamin B12 • Risk of inhibition of CYP2C19 and potential interaction with remedies metabolised this way • Increased risk of gastrointestinal infections
Missing information	--

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 Losec. 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 the PL of Losec MUPS 10 mg, 20 mg, 40 mg gastro-resistant tablets (Astra Zeneca UK Limited). 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

Omeprazol Sandoz 10 mg, 20 mg, and 40 mg gastro-resistant capsules, hard, has a proven chemical-pharmaceutical quality and is a generic form of Losec 10 mg, 20 mg, and 40 mg 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 Omeprazol Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 April 2018.

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
NL/H/4047/002/E/001	20 mg strength registration in Bulgaria	--	9-11-2018	Approval	--