COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Esomeprazol SUN 20 mg and 40 mg, gastro-resistant hard capsules

(esomeprazole magnesium)

NL/H/4120/001-002/DC

Date: 5 September 2019

This module reflects the scientific discussion for the approval of Esomeprazol SUN 20 mg and 40 mg, gastro-resistant hard capsules. The procedure was finalised at 1 November 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 Esomeprazol SUN 20 mg and 40 mg, gastro-resistant hard capsules, from Sun Pharmaceutical Industries Europe 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 decentralised procedure concerns a hybrid 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 20mg and 40 mg (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 concerned member states (CMS) involved in this procedure were Germany, Italy, Romania, Sweden and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as the reference product has a different pharmaceutical form (gastro-resistant capsules versus gastro-resistant tablets).

II. QUALITY ASPECTS

II.1 Introduction

Esomeprazol SUN 20 mg is a hard gelatin capsule with a light pink opaque cap imprinted with 'E7' in black ink and a light pink opaque body, containing off-white to brownish coloured pellets. Each gastro-resistant capsule contains esomeprazole magnesium amorphous equivalent to 20 mg esomeprazole.

Esomeprazol SUN 40 mg is a hard gelatin capsule with a brick red opaque cap imprinted with 'E8' in black ink and a brick red opaque body, containing off-white to brownish coloured pellets. Each gastro-resistant capsule contains esomeprazole magnesium amorphous equivalent to 40 mg esomeprazole.

The capsules are packed in OPA/Al/PVC/Al blisters and OPA/Al/PE/desiccant/Al/PE blisters or HDPE bottles with screw cap and induction seal liner, containing silica gel.

The excipients are:
Capsule content - sugar spheres, hydroxypropyl cellulose (E463), hypromellose (E464), magnesium stearate (E470b), talc (E553 B), methacrylic acid – ethyl acrylate copolymer (1:1) 30% dispersion, sodium lauryl sulfate (E487), polysorbate 80 (E433), triethyl citrate (E1505) and glyceryl mono stearate 40-55.
Capsule shell - red iron oxide (E172), titanium dioxide (E171), gelatin (E441) and sodium lauryl sulfate (E487)
Ink - shellac (E 904), strong ammonia solution (E 527), black iron oxide (E 172) and potassium hydroxide (E 525).

II.2 Drug Substance

The active substance is esomeprazole magnesium (amorphous), an established active substance described in the United States Pharmacopeia (USP). The European Pharmacopoeia (Ph. Eur.) contains monographs for esomeprazole magnesium dihydrate and esomeprazole magnesium trihydrate. The active substance is a white to slightly coloured, amorphous powder and slightly soluble in water. The amorphous form and the absolute S-configuration are controlled by the drug substance specification.

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 manufacturing of amorphous esomeprazole magnesium is a two-step process. No class I solvent or heavy metal catalysts are used in the process. The active substance has been adequately characterised and the specifications for the starting materials, solvents and reagents are acceptable.

Quality control of drug substance

The active substance specification has been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the proposed drug substance specification have been provided for nine full scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for 6 full scaled batches stored at 5°C (12-18 months) and 20°C/60% RH (6 months). During the accelerated and long term stability studies all parameters remain stable and within the proposed acceptance limits. The proposed re-test period of 12 months and storage condition of 2° to 8° C, under the stated conditions is 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. Using design of experiments the quantities of various excipients were optimised. Two bioequivalence studies have been performed, under fasting and fed conditions. The bioequivalence batch was manufactured by the same process with a very similar composition, only the colour and imprinting of the capsule shell differs, which is not expected to be of influence on the bioavailability. Dissolution studies in support of bioequivalence and a biowaiver for additional strength have been performed mimicking the fasted and fed states. The potential influence of alcohol on the release of the active substance has been investigated and is comparable with the reference product. The choices of the packaging and manufacturing process are adequately justified because they are common for this type of product. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consist of dispensing and shifting, layering, coating, lubrication and capsule filling. The process has been validated according to relevant European

guidelines. Process validation data on the product have been presented for three full scale batches of each strength in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with Ph. Eur. or EU 231/2012 requirements. 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, identification (active substance and color), uniformity of dosage units, loss on drying, dissolution, organic impurities, assay and microbial quality. 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 scaled batches 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 for three full scaled batches of both strengths stored at 25°C/60%RH (24 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 18 months when stored below 30°C in the original package in order to protect from moisture.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
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 Esomeprazol SUN 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 Esomeprazol SUN is intended for hybrid 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 hybrid 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 member states agreed 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 member states agreed that no further clinical studies are required.

For this hybrid 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 Esomeprazol SUN 40 mg gastro-resistant hard capsules (Sun Pharmaceutical Industries Europe B.V., NL) is compared with the pharmacokinetic profile of the reference product Nexium 20 mg and 40 mg, gastro-resistant tablets (AstraZeneca AB, Sweden) under fasted and fed conditions.

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

Bioequivalence studies were performed only with the 40 mg test product and the MAH applies for a waiver of the 20 mg tablets. Pharmacokinetics increase more than dose proportional, so the use of the highest strength in the bioequivalence studies is acceptable.
Both strengths of drug product are manufactured by the same process and are dose proportional. For the manufacture of the 20 mg and 40 mg strengths the same enteric-coated pellets are used. This implies that the thickness of the enteric coating is similar for both strengths (mg/cm2).
In addition, comparative dissolution studies demonstrate that the dissolution profiles of the 20 mg test product are similar to the 40 mg test product used in the bioequivalence studies, at pH 6.8 after 2h in 0.1N HCL media and at pH 6.8 after 2h in pH 4.5 media.
The justification is considered acceptable, specifically as it concerns formulations containing the same pellets. As such, no difference in dissolution is expected.

Bioequivalence studies

The designs of the studies are acceptable. A study under fasting and fed conditions is considered acceptable to determine bioequivalence between the test and reference product.

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.

Bioequivalence study I - 40 mg single dose under fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 20-44 years. Each subject received a single dose (40 mg) of one of the 2 esomeprazole formulations. The dose was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 10, 12, 14, 16 and 18 hours after administration of the products.

Results

Three subjects were withdrawn from the study due to adverse events (vomiting and fever) and a protocol violation (positive for benzodiazepine). Therefore, 37 subjects completed the study 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 N=37	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)

Test	6460 ± 2803	6501 ± 3124	2156 ± 619	2.25 (1.0 – 4.67)
Reference	6258 ± 2803	6298 ± 2820	2238 ± 604	2.0 (1.0 – 4.33)
***Ratio (90% CI)**	1.01 (0.94 – 1.09)	--	0.96 (0.90 – 1.01)	--
CV (%)	18.3	--	15.3	--

$AUC_{0-\infty}$ 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 - 40 mg single dose under fed conditions

Design

A single-dose, two-period, randomised, four-way replicate, crossover bioequivalence study was carried out under fed conditions in 48 healthy male subjects, aged 18-43 years. Each subject received a single dose (40 mg) of both of the 2 esomeprazole formulations, test and reference product, twice. The dose was orally administered with 240 ml water 30 minutes after the start of a high-fat, high calorie breakfast (consisting of an egg and cheese McMuffin, chicken McNuggets, hash brown potatoes, full cream milk and butter). There were 2 dosing periods, separated by a washout period of 7-9 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6.33, 6.67, 7, 7.33, 7.67, 8, 8.5, 9, 10, 12, 16, 20, 24 and 36 hours after administration of the products.

Results

A total of six subjects were withdrawn from the study. Four subjects were withdrawn due to failure to comply with the requirements of the study (unable to consume study breakfast, found positive for cannabinoids or alcohol), one subject due to an adverse event and one subject dropped out for personal reasons. Therefore, 44 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=44	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test (T1)	4163.6016 ± 2849.41924	4397.1799 ± 2836.67779	949.90 ± 461.551	5.667 (3.333 – 12.017)
Test (T2)	3981.2056 ± 2526.86521	4231.2562 ± 2495.21140	920.28 ± 433.683	5.333 (3.667 – 10.017)
Reference (R1)	4279.8752 ± 3089.61817	4343.6157 ± 3117.45353	1044.86 ± 549.876	4.667 (2.333 – 6.333)

Reference (R2)	4087.5929 ± 2963.54489	4147.2369 ± 2995.38396	1027.88 ± 526.186	4.667 (2.000 – 6.333)
***Ratio (90% CI)**	0.99 (0.91 – 1.09)	--	0.90 (0.80 – 1.00)	--
CV (%)	38.0	--	46.3	--

$AUC_{0-\infty}$ 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

**In-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 Esomeprazol SUN 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 Esomeprazol SUN.

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

Important identified risks	- Agranulocytosis - Hypersensitivity reactions - Hypomagnesaemia - Depression - Hepatic reactions - Severe cutaneous 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 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 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

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Esomeprazol SUN 20 mg and 40 mg, gastro-resistant hard capsules have a proven chemical-pharmaceutical quality and are hybrid 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.

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 Esomeprazol SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 1 November 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