COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Esomeprazol 10 mg Focus Care, gastro-resistant granules for oral suspension in sachet (esomeprazole magnesium)

NL License RVG: 127431

Date: 12 December 2022

This module reflects the scientific discussion for the approval of Esomeprazol 10 mg Focus Care, gastro-resistant granules for oral suspension in sachet. The marketing authorisation was granted on 13-January-2022. 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
EMA	European Medicines Agency
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
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 Esomeprazol 10 mg Focus Care, gastro-resistant granules for oral suspension in sachet, from Focus Care Pharmaceuticals B.V.

The product is indicated for:

Adults

- 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)
- Eradication of *Helicobacter pylori* in combination with appropriate antibiotics
  - therapeutic regimens 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.
- Follow-up treatment after intravenous treatment to prevent rebleeding of peptic ulcers.
- Treatment of Zollinger-Ellison Syndrome

Paediatric population

Adults and adolescents from the age of 12 years

- 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)
- Treatment of a duodenal ulcer caused by *Helicobacter pylori*, in combination with appropriate antibiotics

Children over 4 years of age

- Treatment of a duodenal ulcer caused by *Helicobacter pylori*, in combination with appropriate antibiotics

Children 1-11 years old

- Gastroesophageal Reflux Disease (GERD)
  - treatment of endoscopically proven erosive reflux esophagitis
  - symptomatic treatment of GERD

Esomeprazole 10 mg Focus Care gastro-resistant granules for oral suspension in sachet may also be used by patients having difficulty swallowing dispersed esomeprazole magnesium-containing gastro-resistant tablets.

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 10 mg Sachet, gastro-resistant granules for oral suspension (NL License RVG 101600) which has been registered in the Netherlands by Grunenthal B.V. since 13 June 2008 by the mutual recognition procedure SE/H/0211/004.

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

II. QUALITY ASPECTS

II.1 Introduction

Esomeprazol 10 mg Focus Care, contains light yellow, free flow granules consisting of off-white to cream esomeprazole pellets (enteric coated) and pale yellow inactive granules. Each sachet contains as active substance 10,353 mg esomeprazole magnesium, corresponding to 10 mg esomeprazole.

The drug product (granules) is packed in sachets laminated with three layers consisting of polyethylene terephthalate (PET), aluminium and low density polyethylene (LDPE) that protect the granules from moisture.

The excipients are: sugar spheres (sucrose and corn starch), ethyl cellulose (E462), magnesium stearate (E572), povidone K90, magnesium oxide (E530), copolymer of ethyl acrylate-methacrylic acid (1:1), triethyl citrate (E1505), glycerol monostearate 40-55 (E1516), polysorbate 80 (E433), talc (E553b), glucose monohydrate, xanthan gum (E415), crospovidone (type B) (E1202), yellow iron oxide (E172), hydroxypropyl cellulose (E463), citric acid monohydrate (E330) and anhydrous colloidal silica.

II.2 Drug Substance

The active substance is esomeprazole magnesium, amorphous, an established active substance. The amorphous form is not described in the European Pharmacopoeia (Ph.Eur.), only the trihydrate and dihydrate form. In the United States Pharmacopoeia (USP) a combined monograph is provided for the amorphous, dihydrate and trihydrate form. Esomeprazol magnesium is a white to pale cream coloured powder, hygroscopic and very slightly soluble in water, soluble in N,N-dimethyl formamide and slightly soluble in methanol. Omeprazole contains one chiral centre. Hence two isomers are possible (R & S). For this product, the S-isomer of omeprazole (esomeprazole) is manufactured and isolated as magnesium salt. Esomeprazole magnesium exhibits several polymorphic forms, the

manufacturing procedure used by ASMF holder consistently produces the amorphous form, this is controlled in 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 drug substance is produced through five steps. In the first two steps, the starting materials are mixed to obtain intermediate products through condensation and oxidation reactions. The third step is the resolution of S-isomer, followed by the last two steps used for the conversion to esomeprazole magnesium. For the used synthesis route, no metal catalysts are used. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. The active substance specification is in line with the ASMF. During the procedure the MAH was requested to include an additional routine test for a specific impurity. This test was included in the ASMF, acceptable limits were set and adequately validation of the method was performed. Batch analytical data demonstrating compliance with this specification have been provided for eight batches.

Stability of drug substance

Stability data on the active substance have been submitted for two full scale batches and three pilot scale batches stored at 2°C - 8°C (24 months) and at 25°C ±2°C/60% ±5% RH (6 months). For total impurities, an increasing trend is observed under accelerated conditions. No other clear trends have been observed. Based on these results, the proposed re-test period (as in the ASMF) of 24 months with the storage conditions store at 2-8°C, under nitrogen atmosphere, protect from light and moisture is acceptable.

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. Compatibility of the excipients with the drug substance was demonstrated. The pharmaceutical development is based on the similarity with reference product Nexium 10 mg Sachet. To test the similarity, a two-stage dissolution method consisting of an acidic phase followed by a buffer phase has been adequately developed according to the Ph.Eur. A comparative dissolution study between the proposed drug product and the reference product and an alcohol dose dumping study was provided.

Manufacturing process

The manufacturing process of the product consists of three stages for the production of the enteric coated pellets, the inactivation of the granules and the sachet filling. The manufacturing process has been validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation data on the product have been submitted for three full scaled batches. The validation was adequately performed.

Control of excipients

The excipients comply with Ph.Eur. requirements, except yellow ferric oxide which is tested as per specification complying to EU 231/2012. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, identification of esomeprazole (two methods), identification of ferric oxide, average net content of sachet, water, viscosity, pH, dissolution acid stage and buffer stage, uniformity of dosage units, organic impurities, R-isomer, assay of esomeprazole, residual solvents and microbial testing. The release and shelf life criteria are mostly the same, except for water, organic impurities and R-isomer. The drug product specification is acceptable. Furthermore, the analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full scaled batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided from three full scaled batches in accordance with applicable ICH stability guidelines. The batches were stored in the proposed sachets at 25°C ±2°C/60% ±5% RH (24 months), 30°C ±2°C/65% ±5% RH (12 months) and 40°C ±2°C/75% ±5% RH. The accelerated stability studies show a significant increase in several impurities and a decrease in assay, while the intermediate and long term stability studies only demonstrate a slight increase in impurities. All results are well within the stated shelf-life acceptance criteria. Photostability studies showed that the product is stable when exposed to light. Based on the submitted stability data, a shelf life of 24 months was granted with the storage conditions ‘do not store above 30°C’.

In-use stability studies were performed. The results show that the product remains stable for 30 minutes after suspending one sachet of the drug product in 15 mL water with a pH of 5.5, 7.0 and 8.5, and in syringes at room temperature followed by immediate gastric or nasogastric tube passage.

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

For the sugars spheres (manufactured using bone char as filtering aid), 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 MEB considers that Esomeprazol 10 mg Focus Care, has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of esomeprazole are well known. As the active substance is a widely used, it is a well-known active substance. Therefore, no further studies are required and the MAH provides none. An overview based on literature review is acceptable.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Esomeprazol 10 mg Focus Care 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 10 mg Sachet, 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 finds that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Esomeprazole 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 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 Esomeprazol 10 mg Focus Care, gastro-resistant granules for oral suspension in sachet (Focus Care Pharmaceuticals B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Nexium 10 mg Sachet, gastro-resistant granules for oral suspension, (Grunenthal B.V., the Netherlands). 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.

Bioequivalence studies

According to the SmPC, food consumption delays the absorption of esomeprazole. Therefore two bioequivalence studies were conducted, one under fasting conditions and one under fed conditions, to determine the clinically relevant effect of food on the bioavailability of esomeprazole magnesium.

Design Study 1, fasted conditions

A single-dose, open label, balanced, randomised, two-treatment, two-sequence, two-period, crossover oral bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 20-44 years. Each subject received a single dose (10 mg) of one of the two esomeprazole magnesium formulations. After an overnight fasting of at least 10 hours, subjects were dosed with a single oral dose (1 x sachet 10 mg) with 200 mL of drinking water at room temperature.

Blood samples were collected at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16 and 20 hours after administration of the products in each period.

The design of the study 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

One subject was absent in period II. Therefore, 55 subjects completed the study and were eligible for pharmacokinetic analysis. No serious adverse events were reported during the entire duration of the study. The pharmacokinetic results are described in Table 1.

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

Treatment N=55	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)
Test	1259 ± 806	1269 ± 813	434 ± 176	2.25 (1.25-4.00)	1.365 ± 0.6962
Reference	1188 ± 724	1212 ± 725	394 ± 153	2.00 (0.75-4.00)	1.364 ± 0.66
***Ratio (90% CI)**	1.07 (1.00 – 1.14)	1.06 (1.00 – 1.12)	1.10 (1.02 – 1.19)	--	--
CV (%)	19.5	18.8	24.3	--	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life

**ln-transformed values*

Design Study 2, fed conditions
A single-dose, open label, balanced, randomised, two-treatment, two-sequence, four-period, full replicate, crossover oral bioequivalence study was carried out under fed conditions in 50 healthy male subjects, aged 18-45 years. Each subject received a single dose (10 mg) of one of the two esomeprazole magnesium formulations. After an overnight fasting of at least ten hours (and exactly 30 minutes after providing a high fat, high calorie breakfast) subjects were dosed with a single oral dose (1 x sachet 10 mg) with 200 mL of drinking water at room temperature.

There were four dosing periods, each separated by a washout period of twelve days. Pre study, all subjects were provided with a 1054 Kcal dinner on the day of check-in during each period. On the day of doses, a high calorie, high fat breakfast was provided. The meal plan is shown in Table 2. The provided meal was completely consumed by all subjects in all periods, with the exception of five subjects (in period-IV) who had consumed more than 75% of lunch on the dosing day.

Table 2. Meal plan on day of doses.

Meal plan Day-1 (approx. 2895 kcal)		
Meal type	**Approx. calories**	**Schedule time (hr)**
Breakfast	966	30 minutes prior to dosing
Lunch	849	4 post-dose
Snacks	228	8 post-dose
Dinner	852	13 post-dose

Blood samples were collected at 0.25, 0.50, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 14, 16, 18, 20 and 24 hours after administration of the products in each period.

The design of the study 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
Three subjects were absent in period II and III. Therefore, 47 subjects completed the study and were eligible for pharmacokinetic analysis. No serious adverse events were reported during the entire duration of the study. The pharmacokinetic results are described in Table 3.

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

Treatment N=47	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	1001 ± 680	1021 ± 685	231 ± 109	4.50 (1.00-6.50)	1.77 ± 0.93
Reference	1071 ± 721	1086 ± 735	235 ± 111	4.50 (1.00-8.00)	1.77 ± 0.90
***Ratio (90% CI)**	0.93 (0.88 – 0.98)	0.93 (0.88 – 0.98)	0.98 (0.92 -1.05)	--	--
CV (%)	22.4	22.1	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

**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 studies Esomeprazol 10 mg Focus Care is considered bioequivalent with Nexium 10 mg Sachet.

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 Esomeprazol 10 mg Focus Care.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are not applicable.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Nexium 10 mg Sachet. 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 innovator Nexium 10 mg Sachet, gastro-resistant granules for oral suspension for the text content. For font and text size, an in-house design is used. 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

Esomeprazol 10 mg Focus Care, gastro-resistant granules for oral suspension in sachet has a proven chemical-pharmaceutical quality and is a generic form of Nexium 10 mg Sachet, gastro-resistant granules for oral suspension. 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 Esomeprazol 10 mg Focus Care with the reference product, and have therefore granted a marketing authorisation. Esomeprazol 10 mg Focus Care was authorised in the Netherlands on 13 January 2022.

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
B.II.b.2.c.2	Replacement or addition of a manufacturer responsible for importation and/or batch release: - Including batch control/testing.	Yes	11-05-2022	Approved	N/A
Art. 61(3)	Changing the labelling and package leaflet: - Bringing outer text and mock-up of carton in line with the PIL and SmPC.	Yes	21-06-2022	Approved	N/A
B.II.b.2.a	Change to importer, batch release arrangements and quality control testing of the finished product: - Replacement or addition of a site where batch control/testing takes place.	No	25-9-22	Approved	N/A