LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Esomeprazole Orifarm
(esomeprazole magnesium)

SE/H/1979/01/DC

This module reflects the scientific discussion for the approval of Esomeprazole Orifarm. The procedure was finalised on 2021-01-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Esomeprazole Orifarm, 10 mg, Gastro-resistant granules for oral susp. in sachet.

The active substance is esomeprazole magnesium. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Esomeprazole Orifarm, 10 mg, gastro-resistant granules for oral suspension in sachet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orifarm Generics A/S, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Nexium, 20 mg, gastro-resistant tablet, authorised in Sweden since 2000, with AstraZeneca as marketing authorisation holder.

The reference product used in the bioequivalence study is Nexium, 10mg, gastro-resistant granules for oral suspension in sachet, from DE with AstraZeneca as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of esomeprazole magnesium are well known. As esomeprazole magnesium is a widely used, well-known active substance, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Esomeprazole Orifarm is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Esomeprazole Orifarm from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics

To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing esomeprazole with the reference product Nexium.

Pharmacokinetic properties of the active substance
Absorption: Esomeprazole is acid labile and is administered orally as enteric-coated granules. In vivo conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Elimination: The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing.

Methods
This was a single-dose, two-way crossover study conducted in 56 healthy volunteers, comparing esomeprazole, 10 mg, gastro-resistant granules for oral suspension with Nexium, 10 mg, gastro-resistant granules for oral suspension under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 20 hours post-dose. Plasma concentrations of esomeprazole were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 2018-12-27 and 2019-01-30.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters, corrected (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for esomeprazole, n=55.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1259.27 ± 806.23**	**1268.76 ± 813.48**	**434.42 ± 175.75**	**2.25 (1.25-4.00)**
Reference	**1187.71 ± 723.79**	**1211.73 ± 725.40^**	**393.58 ± 152.85**	**2.00 (0.75-4.00)**
***Ratio (90% CI)**	**106.76 (100.38-113.56)**	**105.68 (99.56-112.18)**	**110.21 (102.10-118.96)**	**-**

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

**calculated based on ln-transformed data*
^indicates N=54. As the subject no.37 was not exhibit a log linear relationship in the terminal elimination phase in the concentration versus time profile in the treatment of reference (R).

For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %.

Methods
This was a single-dose, two-way, four-period, full-replicate crossover study conducted in 50 healthy volunteers, comparing esomeprazole, 10 mg, gastro-resistant granules for oral suspension with Nexium, 10 mg, gastro-resistant granules for oral suspension under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of esomeprazole were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 2018-12-26 and 2019-02-26.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for esomeprazole, n=94.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$^ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1001.48 ± 679.77**	**1021.24 ± 685.23**	**231.33 ± 108.67**	**4.50 (1.00-6.50)**
Reference	**1070.69 ± 721.11**	**1085.74 ± 735.26**	**234.53 ± 110.74**	**4.50 (1.00-8.00)**
***Ratio (90% CI)**	**92.77 (88.03-97.75)**	**92.66 (87.98-97.58)**	**98.33 (91.69-105.46)**	**-**

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

**calculated based on ln-transformed data*
^Indicates N=93, Subject no. 05 for test (T1) and subject no.40 for reference (R1) did not exhibit log linear relationship in the terminal elimination pharse as R^2 value was found to be less than 0.8, i.e. 0.7985 and 0.6535.

For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %.

Discussion and overall conclusion

The bioequivalence studies and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence studies, esomeprazole can be considered bioequivalent with Nexium.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Esomeprazole Orifarm.

Safety specification

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Summary of the RMP

The submitted updated Risk Management Plan, version 1.1 signed 10.08.2020 is updated in line with the revised GVP module V. All important identified and potential risks are well-known and are monitored by routine pharmacovigilance only. No additional risk mitigation measures apply. The RMP is acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

Content
The applicant has proposed a bridging to a user test carried out on the product Nexium 10 mg gastro-resistant granules for oral suspension, sachet. The user test of the Nexium 10 mg gastro-resistant granules for oral suspension, sachet leaflet was assessed and accepted in SE/H/0211/004.

Layout
The applicant has proposed a bridging to a user test carried out on the product Kaliumklorid Orifarm 750 mg prolonged-release tablets. The user test of the Kaliumklorid Orifarm 750 mg prolonged-release tablets was assessed and accepted in DK/H/2347/001.

A comparison between the parent PL and the daughter PL (including lay-out) together with a critical discussion hereof has been provided.

The proposed bridging regarding content and layout is considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Esomeprazole Orifarm, is found adequate. There are no objections to approval of product name, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Esomeprazole Orifarm, 10 mg, Gastro-resistant granules for oral susp. in sachet was positively finalised on 2021-01-18.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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