LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Omeprazol Evolan
(omeprazole)

Asp no: 2016-2235

This module reflects the scientific discussion for the approval of Omeprazol Evolan. The procedure was finalised on 2018-09-17. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Evolan Pharma AB has applied for a marketing authorisation for Omeprazol Evolan, 20 mg, Gastro-resistant capsule, hard. The active substance is omeprazole.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

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

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

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The applicant submitted two bioequivalence studies with the 40 mg strength, one in the fasted (Study OMEP-2429-14) and one in the fed state (Study OMEP-2430-14) in the original application.
The quality system was however not acceptable for the site Micro Therapeutics Research Labs Pvt. and the bioequivalence studies OMEP-2429-14 and OMEP-2430-14 could not be approvable and new studies was requested.

Two new studies have been submitted with the 40 mg strength, one in the fed state (0102-17) and one in the fasted state (0103-17). Omeprazol Evolan is a delayed-release formulation for which single-dose bioequivalence studies under both fasting and fed conditions are adequate and in accordance with guideline recommendations.

Study 0102-17

Methods

This was a single-dose, four-way, two-treatment crossover study conducted in 66 healthy volunteers, comparing Omeprazole, 40 mg, delayed-release capsule with Losec, 40 mg, hard gastro-resistant capsule under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of omeprazole 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 17th November and 1st December 2017.

Results

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

Table 1. Study 0102-17 (40 mg fed). Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for omeprazole, n=63.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test[a)]	**1584 ± 1567**	**1630 ± 1585**[c)]	**548 ± 367**	**5.33 (3.00- 12.0)**
Reference[b)]	**1896 ± 1889**	**2001 ± 1925**[d)]	**538 ± 354**	**5.37 (1.05- 14.0)**
***Ratio (90% CI)**	**84.8 (80.54-89.39)**	**82.7 (78.76-86.90)**	**104.9 (96.43-114.18)**	**-**

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*
a) N=123 observations, b) N=124 observations, c) N=120 observations, d) N=117 observations

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

Study 0103-17

Methods

This was a single-dose, two-way crossover study conducted in 66 healthy volunteers, comparing Omeprazole, 40 mg, delayed-release capsule with Losec, 40 mg, hard gastro-resistant capsule under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of omeprazole 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 27th November and 3rd December 2017.

Results

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

Table 2. Study 0103-17 (40 mg fasted). Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for omeprazole, n=63.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**2534 ± 2622**	**2551 ± 2632**	**1082 ± 672**	**2.00 (1.00- 5.00)**
Reference	**2740 ± 2931**	**2754 ± 2940**	**1097 ± 640**	**2.00 (0.50- 5.00)**
***Ratio (90% CI)**	**95.1 (91.46 - 98.92)**	**95.4 (91.73 - 99.15)**	**95.8 (89.60 - 102.41)**	**-**

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*

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

The applied strength is 20 mg and the bioequivalence studies are performed with a higher strength, 40 mg. A biowaiver was sought for the applied strength of 20 mg.

Discussion and overall conclusion

The bioequivalence studies and its statistical evaluation were in general 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/CPMP/EWP/280/96 Corr1). The bioanalytical methods were adequately validated.

Bioequivalence was demonstrated for all parameters in study 0103-17 and for AUC_{0-t} and C_{max} in study 0102-17. For $AUC_{0-\infty}$ in study 0102-17, the confidence interval fell just outside the acceptance limits.

The applicant made a content correction based on that the test and reference products used in the studies differed more than 5% in content of omeprazole and states that bioequivalence was demonstrated. The content correction was not pre-specified in the study protocols and is hence not acceptable for calculation of bioequivalence in this application.

However, the non-bioequivalence was seen for $AUC_{0-\infty}$ in the fed study. Considering that the parameter $AUC_{0-\infty}$ is not as critical parameter as C_{max} and AUC_{0-t} for an enterocoated capsule and that the lower boundary was just outside the acceptance limits this could be acceptable. In addition, a study in the fasted state is in general most sensitive in showing differences in formulations and bioequivalence was demonstrated for all PK parameters in the fasted study. The non-bioequivalence for $AUC_{0-\infty}$ in the fed study is hence considered acceptable in this case. Taken together, bioequivalence between Omeprazole, 40 mg, delayed-release capsule and Losec, 40 mg, hard gastro-resistant capsule has been sufficiently assured based on the submitted studies 0102-17 in the fed state and 0103-17 in the fasted state.

The applied strength is 20 mg and the bioequivalence studies are performed with a higher strength, 40 mg. Absence of studies with the 20 mg strength is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of omeprazole is linear between 10 mg and 40 mg.

Based on the submitted bioequivalence studies 0102-17 and 0103-17 , Omeprazol Evolan, gastro-resistant capsule is considered bioequivalent with Losec, gastro-resistant capsule.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plans

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 Evolan.

Safety specification
The Applicant has submitted a RMP with the following proposed safety concerns:

Summary table of safety concerns as approved in RMP

Important identified risks	Drug interactions Hypomagnesemia Fracture of hip, wrist and spine Gastrointestinal infections Severe cutanous reactions
Important potential risks	None
Missing information	None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The RMP is approved.

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.

IV.4 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 Omeprazol Actavis 20 mg hard gastro-resistant capsules, SE/H/754/01-03/MR. The bridging report submitted by the applicant has been found acceptable.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the hybrid product, Omeprazol Evolan, is found adequate. There are no objections to approval of Omeprazol Evolan, 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/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

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

N/A

VI. APPROVAL

Omeprazol Evolan, 20 mg, Gastro-resistant capsule, hard, was approved in the national procedure on 2018-09-17.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	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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