LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Zemograc
(omeprazole)

SE/H/2270/01-03/DC

This module reflects the scientific discussion for the approval of Zemograc. The procedure was finalised on 2023-06-14. 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 Zemograc, 10 mg, 20 mg, 40 mg, Gastro-resistant capsule, hard.

The active substance is omeprazole. 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 Zemograc, 10 mg, 20 mg, 40 mg, Gastro-resistant capsule, hard, is a hybrid application submitted according to Article 10(3) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and FI, NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Mopral 20 mg, Gastro-resistant capsule, hard, authorised in FR since 1987, with AstraZeneca France as marketing authorisation holder.

The reference product used in the bioequivalence studies is Losec 40 mg hard gastro-resistant capsules from UK with AstraZeneca UK Ltd as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS DE: Losec 10/20/40 mg, Gastro-resistant tablet authorised in SE since 1997, with AstraZeneca AB as marketing authorisation holder.
The justification to use this product is based on RMS's own files.

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

Pharmacology/Pharmacokinetics/Toxicology

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

This hybrid application concerns a new formulation of omeprazole forming a new impurity, i.e. omeprazole carboxylate. A number of toxicological studies have been performed in order to qualify the impurity.

Toxicology
Applicant has submitted new reports in order to qualify the impurity Omeprazole carboxylate. An Aim's test was performed on the impurity Omeprazole Carboxylate at an exposure dose range of 0.066 – 5.375 mg/plate in the presence and absence of S9. Omeprazole Carboxylate was considered to be non-mutagenic in the experiment.

In addition, Omeprazole Carboxylate did not induce structural and/or numerical chromosomal damage in human lymphocytes and is thus considered to be non-mutagenic with respect to clastogenicity and/or aneugenicity in the in vitro mammalian cell micronucleus test. However, it should be mentioned that in the experiment with metabolic activation, a statistically significant enhancement ($p = 0.0126$) of cells with micronuclei was noted at the highest concentration of 0.75 mM. The corresponding frequency of micronucleated cells were within the historical control limits of the negative control and no dose-response relationship could be observed. Therefore the increase was regarded as not biologically relevant.

An in vivo 13 week toxicity study was performed on Sprague Dawley rats using Omeprazole with or without 1% of the impurity. In both groups, a relationship between the test items and increased levels of cholesterol and triglycerides (only for high dose group) cannot be discarded nor the increased kidney weight (relative to body weight) and liver absolute and relative to body weight. However, no increase in toxicity was attributed to 1% impurity.

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

Conclusions on studies:
The active substance is a generic substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, omeprazole is not expected to pose a risk to the environment.

There are no objections to approval of Zemograc, from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
Three bioequivalence studies were submitted with the 40 mg strength, two in the fed state (0102-17 and 0209-18) and one in the fasted state (0103-17). Omeprazole LF 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.

The applied strengths are 10 mg, 20 mg and 40 mg and the bioequivalence studies are performed with the highest strength, 40 mg. A biowaiver was sought for the additional strengths of 10 mg and 20 mg.

Pharmacokinetic properties of the active substance
Absorption: Omeprazole has an oral bioavailability of 40%. After repeated once-daily administration, the bioavailability increases to about 60%. Following an oral dose of omeprazole maximal plasma concentrations occur at approximately 1-2 hours.

Concomitant intake of food has no influence on the bioavailability.

Linearity: The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulfone).
The AUC of omeprazole increased proportionally with dose following single doses of 10 to 40 mg.

Elimination: The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once-daily dosing.

Study 0102-17
Methods
This was a single-dose, four-way, two-treatment crossover study conducted in 66 healthy volunteers, comparing Omeprazole, 40 mg, gastro-resistant 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 a 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, gastro-resistant 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 a 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%.

Study 0209-18
Methods
This was a single-dose, four-way, two-treatment crossover study conducted in 64 healthy volunteers, comparing Omeprazole, 40 mg, gastro-resistant 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 a 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 15th April and 29th April 2018.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 3 below.

Table 3. Study 0209-18 (40 mg fed). Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for omeprazole, n=61.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**2177 ± 2191**	**2242 ± 2216[a)]**	**747 ± 491**	**5.67 (2.50- 14.0)**
Reference	**2108 ± 2059**	**2183 ± 2095[b)]**	**647 ± 415**	**5.67 (3.50- 20.0)**
***Ratio (90% CI)**	**100.9 (96.41-105.60)**	**101.2 (96.84-105.72)**	**113.4 (105.12-122.40)**	**-**

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=118 observations, b) N=115 observations

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%.

Discussion and overall conclusion
The bioequivalence studies and the 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.

Studies 0102-17 and 0103-17:
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, since the confidence intervals for C_{max} and AUC_{0-t} both with and without correction of content in both fasted and fed studies fell within the acceptance limits of 80.00-125.00 the difference of 6.1% is considered acceptable.

The result of $AUC_{0-\infty}$ in the fed study 0102-17 was however non-bioequivalent. 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. One explanation for the non-bioequivalence in $AUC_{0-\infty}$ could be that bioequivalence for $AUC_{0-\infty}$ was evaluated including fewer observations compared to the AUC_{0-t} resulting in a reduced power. 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 0102-17 is hence considered acceptable in this case.

Study 0209-18:
The applicant performed an additional study in the fed state, study 0209-18, and bioequivalence was demonstrated for all parameters in this study.

Conclusion:
Based on the submitted bioequivalence studies, Omeprazole LF is considered bioequivalent with Losec.

Absence of studies with the additional strengths of 10 mg and 20 mg is acceptable, as all conditions for biowaiver for additional strengths, 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.

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 Omeprazole LF.

Safety specification

Summary of safety concerns	
Important identified risks	none
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 submitted Risk Management Plan, version 1.0 signed 2022-03-22 is considered 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

The package leaflet 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 study was performed by the company Pharmalex and is dated 01-10-2018. The language used for the purpose of user testing the PL was English.

The results show that the package leaflet 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

The quality of the generic product, Zemograc, is found adequate. There are no objections to approval of Zemograc, 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 benefit/risk is considered positive, and 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 Zemograc, 10 mg, 20 mg, 40 mg, Gastro-resistant capsule, hard was positively finalised on 2023-06-14.

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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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