LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Omeprazol Medical Valley
(omeprazole)

SE/H/2391/01-03/MR

This module reflects the scientific discussion for the approval of Omeprazol Medical Valley. The procedure was finalised on 2021-07-06. 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 Omeprazol Medical Valley, 10 mg, 20 mg and 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 Omeprazol Medical Valley, 10 mg, 20 mg and 40 mg, gastro-resistant capsule, hard, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Medical Valley Invest AB, applies for a marketing authorisation in Sweden through a Swedish National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Losec, 10 mg, 20 mg and 40 mg, gastro-resistant capsules, hard, authorised in UK since 1994, 1989 and 1992 respectively, with AstraZeneca UK Limited as marketing authorisation holder.

The reference product used in the bioequivalence studies is Losec, 40 mg, gastro-resistant capsule, hard, from UK with AstraZeneca UK Limited 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 omeprazole are well known. As omeprazole is a widely used, well-known active substance, no studies are required and the applicant provides none.

A toxicity report of the impurity Omeprazol Carboxylate has been submitted. Applicant states that Omeprazol carboxylate is a degradation impurity that appears during the shelf life of the product. At the end of the shelf life, the content of omeprazol carboxylate may be above the qualification threshold established in the specific guidance ICH Q3B(R2) for impurities in drug products. Considering the maximum recommended omeprazol dose of 20 mg/daily, and 20-120 mg for patients with Zollinger-Ellison syndrome, the qualification threshold is 0.2 % or 3 mg TDI whichever is lower. Chemo intends to qualify the content of omeprazol carboxylate proposed in the specifications (1%).

According to the guideline ICH Q3B(R2) in case of missing safety information on the impurity, additional studies to obtain such data may be appropriate. Based on the regulatory framework applicable, the genotoxicity of omeprazol carboxylate can be correctly evaluated by two in vitro genotoxicity test, Bacterial mutation assay (Ames test), In vitro mamalian micronucleus assay in Human lymphocytes and one in vivo repeated dose toxicity study up to 3 months.

Applicant has performed following GLP studies to qualify the degradation product Omeprazol Carboxylate and is briefly presented below:

- Bacterial mutation assay (Ames test)
- *In vitro* mamalian micronucleus assay in Human lymphocytes
- 13-week repeated dose toxicity study in rat (preceded by a 21-day dose range finding study in rat, non-GLP).

Bacterial mutation assay (Ame's test, Study No B-02586, Vivotecnia; 2018)

Omeprazole carboxylate was tested for its mutagenic potential using Salmonella typhimurium and Escherichia coli strains: TA1535, TA1537, TA98, TA100 and pKM 101. The assay was performed with and without liver microsomal activation.

Results: no relevant increase in the number of revertant colonies was observed, at any dose level (range, 0.66-5.375 mg/plate), with any tester strain in the absence or presence of S9 metabolism.

In vitro Mammalian Micronucleus Assay in Human Lymphocytes with Omeprazole Carboxylate (*Study No: 182666; Eurofins Munich*)

The selection of the concentrations was based on data from a pre-experiment. In the main experiment without and with metabolic activation 1 mM test item was selected as the highest concentration. The other concentration used are indicated in the table below:

	Without S9		With S9
	*Exp. I, (*0.50, 0.75 and 1 mM)	*Exp. II , (*0.50, 0.75 and 1 mM)	*Exp. I , (*0.50, 0.75 and 1 mM)

Exposure period	4 h	44 h	4 h
Cytochalasin B exposure	40 h	43 h	40 h
Preparation interval	44 h	44 h	44 h
*Total culture period**	92 h	92 h	92 h

*Exposure started 48 h after culture initiation

The only finding observed, was in *experiment I* with metabolic activation, where a statistically significant enhancement ($p = 0.0126$) of cells with micronuclei was noted at a concentration of 0.75 mM. Since the corresponding frequency of micronucleated cells was within the historical control limits of the negative control and no dose-response relationship was observed, this increase was regarded as not biologically relevant.

It was concluded that during the study described and under the experimental conditions reported, the test item Omeprazole Carboxylate did not induce structural and/or numerical chromosomal damage in human lymphocytes and is considered to be non-mutagenic with respect to clastogenicity and/or aneugenicity in the in vitro Mammalian Cell Micronucleus Test.

13-week repeated-dose toxicity study of Omeprazole and its related impurity Omeprazole Carboxylate after oral administration to Sprague Dawley rats (*Study Number N-; Vivotecnia 2018)*

Groups of 10 male + 10 female rats given omeprazole at 130 and 400 mg/kg/day were compared to equal groups given omeprazole at the same dose levels added with 1% omeprazole carboxylate (130/1.3 and 400/4 mg/kg/day), respectively. One control group was included. Animals were dosed orally (by gavage) once daily for 13 consecutive weeks.

Overall, histopathological results confirmed that there was no meaningful difference in the occurrence of these findings between the groups treated with Omeprazole alone or Omeprazole + 1% impurity. Based on these results, it may be concluded that the repeated oral administration of Omeprazole at a dose level of 130 mg/kg/day and 400 mg/kg/day and omeprazole with 1% impurity (130/1.3 and 400/4 mg/kg/day) for 13 weeks to Sprague Dawley rats was in general terms well tolerated. Slight effects on cholesterol and triglycerides levels, increased kidneys and liver weight and microscopic changes in stomach, liver, kidney, thymus and lachrymal gland were observed at comparable incidence and severity in either groups receiving omeprazole and omeprazole with 1% impurity. For this reason, all the effects reported may be attributed to omeprazole itself and no effects are assigned to doses of omeprazole carboxylate impurity up to 4 mg/kg/day.

The toxicology report has been written by Laura Lopez Fuertes, DVM, PhD, registered toxicologist at Eurotox, Barcelona, Spain. The report is dated 21st December 2018. The report is based on three pivotal toxicity studies and one dose range finding study in rat.

Environmental Risk Assessment (ERA)

Since Omeprazol Medical Valley 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 Omeprazol Medical Valley from a non-clinical point of view

IV. CLINICAL ASPECTS

Pharmacokinetics

Three 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). Omeprazol Medical Valley 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 their 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, Omeprazol Medical Valley 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. An overview of literature data has been provided and is considered adequate to support the efficacy and safety of the product.

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 Medical Valley.

Safety specification

Sumary of safety concerns

Omeprazole	**RMP V 1.0**
	Safety concerns
Important Identified Risk	Severe hypomagnesaemia
	Risk of hypersensitivity reaction
	Risk of interaction with nelfinavir and atazanavir
	Risk of the fractures of the hip, wrist, or spine
Important Potential Risk	Risk of decreased absorption of vitamin B12
	Risk of inhibition of CYP2C19 and potential interaction with remedies metabolised this way
	Increased risk of gastrointestinal infections
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. The safety information in the proposed product information is aligned to the reference medicinal product.

Summary of the RMP
According to the applicant the submitted Risk Management Plan, version 1.0, signed June 23, 2020 is in line with the RMP for the reference product which 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 MPA;
- 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

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Omeprazol Orion, SE/H/1681/01-03/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Omeprazol Medical Valley, is found adequate. There are no objections to approval of Omeprazol Medical Valley, 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 ratio 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

Omeprazol Medical Valley, 10 mg, 20 mg and 40 mg, gastro-resistant capsule, hard was approved in the national procedure on 2021-07-06.

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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
SE/H/2391/01-03/MR	Initial Mutual Recognition Procedure	No	2023-05-30	Approval	N/A

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

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