IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Appizped 10mg/15ml oral solution
Omeprazole
PA22784/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This procedure is a repeat use MRP procedure with IE as the reference member state and Germany, Denmark, Austria, Norway, Poland, Czech Republic, Slovak Republic, Latvia, Lithuania, Estonia, Belgium as concerned member state (CMS).

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Appizped 10mg/15ml oral solution & Appizped 20mg/15ml oral solution, from Proveca Pharma Limited on <date of authorisation>.

This is a hybrid product and the legal basis for this application is article 10 (3) of Directive 2001/83/EC as amended.

HPRA was RMS in this decentralised procedure and Greece, Finland, Sweden and Italy were CMSs. The CMS's in the RUP are Germany, Denmark, Austria, Norway, Poland, Czech Republic, Slovak Republic, Latvia, Lithuania, Estonia, Belgium.

This medicinal product has been approved with the following indications:

Adults

- Treatment of duodenal ulcers
- Prevention of relapse of duodenal ulcers
- Treatment of gastric ulcers
- Prevention of relapse of gastric ulcers
- In combination with appropriate antibiotics, *Helicobacter pylori (H. pylori)* eradication in peptic ulcer disease
- Treatment of NSAID-associated gastric and duodenal ulcers
- Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk
- Treatment of reflux esophagitis
- Long-term management of patients with healed reflux esophagitis
- Treatment of symptomatic gastro-esophageal reflux disease

Paediatric use
Children over 1 month of age

- Treatment of reflux esophagitis
- Symptomatic treatment of heartburn and acid regurgitation in gastro-esophageal reflux disease

Children over 4 years of age and adolescents

- In combination with antibiotics in treatment of duodenal ulcer caused by *H. pylori*

This medicinal product is subject to prescription, which may be renewed.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Appizped 10mg/15ml oral solution
Name(s) of the active substance(s) (INN)	Omeprazole
Pharmacotherapeutic classification (ATC code)	A02BC01
Pharmaceutical form and strength(s)	Oral solution. 10mg/15ml
Marketing Authorisation Number(s) in Ireland (PA)	PA22784/001/001

Marketing Authorisation Holder	Proveca Pharma Limited
MRP/DCP No.	IE/H/1238/001/DC
Reference Member State	Ireland
Concerned Member State	EL – FI – SE – IT (Original DCP), Germany, Denmark, Austria, Norway, Poland, Czech Republic, Slovak Republic, Latvia, Lithuania, Estonia, Belgium (MR-RUP)

II. QUALITY ASPECTS

II.1. Introduction

This application is for Appizped 10mg/15ml & 20mg/15ml oral solution.

II.2 Drug substance

The active substance is omeprazole, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

For the 10 mg/15 ml strength: After mixing, each 15 ml of oral solution contains 10 mg of omeprazole.
For the 20 mg/15 ml strength: After mixing, each 15 ml of oral solution contains 20 mg of omeprazole.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for oral solutions and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Appizped 10mg/15ml & 20mg/15ml oral solution.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance has been available on the European/Irish market for more than 30 years. No new nonclinical data have been submitted.

III.2 Pharmacology

No new nonclinical pharmacology studies have been provided. Omeprazole is a well-known active substance and the safety and efficacy is well characterised clinically. Therefore, the absence of new pharmacology studies or the discussion of relevant safety pharmacology studies for this hybrid application is acceptable.

III.3 Pharmacokinetics

No new nonclinical pharmacokinetic studies have been provided. Omeprazole is a well-known active substance that has been administered clinically for over 20 years thus the pharmacokinetics are well-understood, and the summary of nonclinical pharmacokinetic studies is acceptable for this procedure. It is noted that the proposed liquid formulation of omeprazole differs from the gastro-resistant tablet of the reference product, however, the clinical pharmacokinetics are more relevant for discussion on this aspect.

III.4 Toxicology

Omeprazole is an active substance with a well-established clinical profile and thus additional toxicology studies were not performed for this application. The overview based on the literature, in addition to a supportive evaluation for the excipients used in this new formulation, is therefore acceptable.

General toxicity studies identified the stomach, liver and kidney as primary organs for toxicity. An assessment of genotoxicity as part of the initial registration for omeprazole did not indicate any potential teratogenicity, and there is some clinical evidence to suggest an increased risk of DNA damage with long-term use, albeit not sufficiently substantiated to warrant additional warnings for this product. No relevant effects were noted in relation to reproductive and developmental toxicity. An evaluation of the excipients for this proposed formulation was performed. The proposed levels of sodium bicarbonate, N-acetyl Lcysteine, domiphen bromide, glycerol and propylene glycol are considered to be justified based on available toxicology data and relevant guidance. In conclusion, the Applicant's evaluation of the toxicology based on literature and supportive data is acceptable.

III.5 Ecotoxicity/environmental risk assessment

Since Appizped 10 mg/15 ml oral solution and 20 mg/15 ml oral solution 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.6 Discussion on the non-clinical aspects

No new nonclinical data have been submitted to support this MAA which is acceptable for this type of application and legal basis. Omeprazole is an active substance with a well-established clinical profile and thus additional nonclinical studies are not warranted. An appropriate toxicological evaluation for the excipients used in this new formulation has been provided.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is a hybrid product and the legal basis for this application is article 10 (3) of Directive 2001/83/EC as amended. The legal base 10.3 is chosen based on the changes in pharmaceutical form, strength and indication. This hybrid decentralized procedure particularly concerns the acceptability of:
a) similarity in bioavailability and clinical effects of immediate release omeprazole 10mg/15ml and 20mg/15ml solutions with those of reference product Losec® omeprazole 20 mg capsules with modified release characteristics
b) treatment of reflux oesophagitis and symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease in patients aged 1 month up to one year of age
c) proposed posology of 1mg omeprazole per kilogram body weight once daily for the indications under b)
d) palatability and other aspects of patient acceptability.

The applicant conducted bioavailability studies in adults and referred to publications in the literature in order to support the marketing authorization application.

For this hybrid application, the applicant has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Appizped 10 mg/15 ml and 20 mg/15 ml oral solution is compared with the pharmacokinetic profile of the reference product Losec® 20 mg hard gastro-resistant capsules.

Study b2-20-EMOs, was a single-dose, randomised, three-period, three-treatment, six-sequence, crossover bioequivalence study. Appizped 10 mg/15 ml oral solution and Appizped 20 mg/15 ml oral solution, were compared to the reference product Losec® 20 mg hard gastro-resistant capsules, Astra Zeneca (current MAH: Cheplafarm Arzneimittel GmbH). Based on the pharmacokinetic parameters of the active substance, the reference capsules and test oral solution are bioequivalent with regards to the extent of absorption (AUC0-t.). Due to the different pharmaceutical forms in this hybrid application, a higher Cmax was observed. A higher Cmax is however not of clinical relevance, since it is known that the inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time (SmPC reference product). Omeprazole showed comparable PK between the Omeprazole 10mg/15ml oral solution and Omeprazole 20mg/15ml oral solution oral solution formulations.

Study b4-22-EMOs, was a single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study. Appizped 20 mg/15 ml oral solution, was compared to the reference product Losec® 20 mg hard gastro-resistant capsules, suspended in 8.4% sodium bicarbonate solution. Efficacy and safety data for omeprazole in pediatric patients from 0 to 2 years was generated through publicly available clinical studies, with Losec® 20 mg gastro-resistant capsule suspended in 8.4% sodium bicarbonate solution. Based on the pharmacokinetic parameters of the active substance, the test oral solution and reference capsules suspended in 8.4% sodium bicarbonate solution are bioequivalent with regards to the rate and extent of absorption.

Omeprazole is a well-known active substance used for the treatment of acid-related disorders for several decades.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Losec® 20mg gastro-resistant capsules, hard, marketed by CHEPLAPHARM Arzneimittel GmbH.

IV.2 Pharmacokinetics

The pharmacokinetic profile of omeprazole is well characterised.

Absorption
Omeprazole is acid labile and is therefore administered orally as a buffered solution. The buffer protects omeprazole from acid degradation, facilitating absorption. Absorption of omeprazole from <Product name> is rapid, with peak plasma levels occurring approximately 0.33 (0.17-1.50)* hours after dose. Absorption of omeprazole takes place in the small intestine and is

usually completed within 3-6 hours. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 60%.
* median (min.-max.)

Distribution
The apparent volume of distribution in healthy subjects is approximately 0.3 l/kg body weight. Omeprazole is 97% plasma protein bound.

Biotransformation
Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulfone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP2C19. However, due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP3A4 substrates. In addition, omeprazole lacks an inhibitory effect on the main CYP enzymes.

Approximately 3% of the Caucasian population and 15-20% of Asian populations lack a functional CYP2C19 enzyme and are called poor metabolisers. In such individuals the metabolism of omeprazole is probably mainly catalysed by CYP3A4. After repeated once -daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also higher, by 3 to 5 times. These findings have no implications for the posology of omeprazole.

Elimination
The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once-daily dosing. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. Almost 80% of an oral dose of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.

Linearity/non-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).
No metabolite has been found to have any effect on gastric acid secretion.

IV.3 Pharmacodynamics

The pharmacodynamics of omeprazole are well-known. Omeprazole, a racemic mixture of two enantiomers reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.

Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H + K+-ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.

IV.4 Clinical Efficacy

Efficacy data for omeprazole in paediatric patients from 0 to 2 years was generated through publicly available clinical studies, with Losec/Prilosec delayed release capsule contents suspended in 8.4% sodium hydrogen carbonate solution.

The applicant also provided a summary of several publications of studies where omeprazole was used orally in children aged 1+ months along with clinical guidelines, which are supportive.

IV.5 Clinical Safety

Safety data for omeprazole in paediatric patients from 0 to 2 years was generated through the publicly available clinical studies, with Losec/Prilosec delayed release capsule contents suspended in 8.4% sodium hydrogen carbonate solution. . The applicant also provided a summary of several publications of studies where omeprazole was used orally in children aged 1+ months along with clinical guidelines, which are supportive.

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 Appizped 10 mg/15 ml and 20 mg/15 ml oral solution.

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.

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

As this approval concerns a generic hybrid application, the applicant refers to the data of the reference medical product supported by bioequivalence studies and published clinical studies.

The pharmacokinetic data show that the bioavailability (AUC) of the oral solution is comparable to that of Losec 20 mg delayed release capsules. A higher Cmax was observed. A higher Cmax is however not of clinical relevance, since it is known that the inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time (SmPC reference product).

The proposed product Appizped 20 mg/15 ml oral solution, demonstrated a comparable AUC0-t and C max to Losec 20 mg gastro-resistant capsules suspended in 8.4% sodium bicarbonate solution. This manner of administration corresponds to the clinical formulation used in pivotal paediatric efficacy studies for omeprazole in children aged 0-24 months (e.g. study 251, AstraZeneca). This is to support the widening of the indication to children over 1 month of age at a dose of 1mg/kg once daily.

Omeprazole has a well-established safety profile informed by extensive clinical and post-marketing experience acquired across a range of formulations.

V. OVERALL CONCLUSIONS

This decentralized procedure concerns a hybrid application (Art 10.3) with respect to Appizped 10 mg/15 ml oral solution and Appizped 20 mg/15 ml oral solution. As reference product, Losec® 20 mg omeprazole delayed release capsules is chosen. Besides the differences in strength and formulation (oral solution vs. capsules), the paediatric age range for treatment of reflux oesophagitis and symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease, is different. The age range is one month and above compared to the reference omeprazole capsules (one year and above). Therefore, a particular dosing regimen is proposed for paediatric patients aged one month up to one year (i.e. 1 mg/kg/day).

The pharmacokinetic data show that the bioavailability (AUC) of the oral solution is comparable to that of Losec® 20 mg delayed release capsules. A higher Cmax was observed. A higher Cmax is however not of clinical relevance, since it is known that the inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time (SmPC reference product).

The proposed product Appizped 20 mg/15 ml oral solution, demonstrated a comparable AUC_{0-t} & C_{max} to Losec® 20 mg gastro-resistant capsules suspended in 8.4% sodium bicarbonate solution. This manner of administration corresponds to the clinical formulation used in pivotal paediatric efficacy studies for omeprazole in children aged 0-24 months (e.g. study 251, AstraZeneca). This is to support the widening of the indication to children over 1 month of age at a dose of 1mg/kg once daily.

Omeprazole has a well-established safety profile informed by extensive clinical and post-marketing experience acquired across a range of formulations.

The HPRA, on the basis of the data submitted considered that Appizped 10 mg/15 ml oral solution & Appizped 20 mg/15 ml oral solution have a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

The Marketing Authorisation Holder has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

VI. REVISION DATE

18/07/2029