COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Pedippi 2 mg/ml and 4 mg/ml, powder for oral suspension

(omeprazole)

NL/H/4504/001-002/DC

Date: 5 December 2019

This module reflects the scientific discussion for the approval of Pedippi 2 mg/ml and 4 mg/ml, powder for oral suspension. The procedure was finalised at 2 September 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
GERD	Gastro-Oesophageal Reflux Disease
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Pedippi 2 mg/ml and 4 mg/ml, powder for oral suspension, from Xeolas Pharmaceuticals Limited.

The product is indicated for:
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-oesophageal reflux disease (GERD)

Children over 1 months of age

- Treatment of reflux esophagitis
- Symptomatic treatment of heartburn and acid regurgitation in GERD

Children over 4 years of age and adolescents

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

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Losec 20 mg, gastro-resistant capsules which has been registered in the Netherlands by AstraZeneca B.V. since 9 November 1988.

The concerned member states (CMS) involved in this procedure were France, Ireland, Portugal and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application. The legal base is appropriate on basis of the change in indications, pharmaceutical form and strength.

II. QUALITY ASPECTS

II.1 Introduction

Pedippi is a white to off-white, slightly yellow powder. The powder in the bottle may contain dark specks due to sweetener. After constitution, each ml of the 2 mg/ml strength contains 2 mg of omeprazole and each bottle (90 ml) contains 180 mg of omeprazole. Each ml of the 4 mg/ml strength contains 4 mg of omeprazole and each bottle (90 ml) contains 360 mg of omeprazole.

The powder is packed in amber plastic (PET) bottles fitted with a red Polypropylene (PP) closure cap, enclosed in an aluminium foil pouch.

The excipients are: sodium hydrogen carbonate (E500), potassium hydrogen carbonate (E501), sodium alginate (E401), maltitol (E965), mannitol (E421), sucralose (E955), xanthan gum (E415), natural vanilla flavouring containing maltodextrin (maize), silicon dioxide (E551) and vegetable oil fats, natural mint flavouring containing gum Arabic/acacia gum (E414) and pulegone, titanium dioxide (E171), sodium benzoate (E211) and sodium methyl parahydroxybenzoate (E219)

II.2 Drug Substance

The active substance is omeprazole, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Omeprazole is a white powder which is very slightly soluble in water, soluble in methylene chloride, sparingly soluble in ethanol (96%) and in methanol. It dissolves in dilute solutions of alkali hydroxides. Omeprazole exhibits chirality and polymorphism. The active substance is a racemic mixture. Different polymorphic forms are possible. The two suppliers produce omeprazole form B.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with the addition of a test for particle size distribution and residual solvents. Additionally, the polymorphic form is controlled in the drug substance specification to guarantee compliance with form B, which was used in the biobatch. Batch analytical data demonstrating compliance with this specification have been provided for a sufficient amount of batches.

Stability of drug substance

Stability data on the active substance from one supplier have been provided for three full-scale batches stored at 2-8°C (60 months) and 25°/60% RH (6 months). No significant changes occurred and the proposed retest period of 60 months is justified.

The active substance from the other supplier is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained.

The development focused on obtaining a formulation that protects the active substance from degradation in the acidic environment of the stomach, while ensuring its availability for absorption in the more alkaline environment of the small intestine. In alternative to approved gastro-resistant capsules, the MAH proposed an immediate release dosage form, where a carbonate buffering system is used to protect the active substance from gastric acid degradation. A balanced sodium bicarbonate/potassium bicarbonate buffering system was developed taking into account the European Commission Directive 2006/141/EC and WHO recommendations with respect to limit of sodium intake and ratio of sodium to potassium in oral preparations for paediatric use.

The proposed preservative system is a mixture of sodium benzoate and sodium methyl parahydroxybenzoate, whose safety is sufficiently justified.

The proposed test conditions of the dissolution method and the acceptance criteria have been adequately described. Due to the rapid decomposition of omeprazole already at pH 1.2 and 4.5, the use of a medium with neutral to basic pH is sufficiently justified. The method is capable of discriminating between batches with different critical aspects i.e. particle size of the active substance.

One pivotal bioequivalence study has been performed to demonstrate bioequivalence of the highest strength of omeprazole test product with the reference product Losec 20 mg capsules under fasting conditions. The objective was to determine comparative bioavailability of test product with European reference product. Also several supporting PK studies were performed. Batch analysis results of the reference product batches used in the bioequivalence studies were provided.

Comparative dissolution profiles of test and reference products are not considered of relevance in view of the differences in formulations (delayed release vs immediate release).
For the lower 2 mg/ml strength a biowaiver has been requested.
Since a 5 mL syringe is provided in the packaging, a test for uniformity of delivered doses was performed at 5 mL and 2.1 ml.

Manufacturing process

The product is a conventional dosage form, which consists of two solid phases: a granulate containing the drug substance (filled in the cap) and a diluent blend (filled in the bottle). The drug product is manufactured according to a standard process which involves the preparation of the two blends. The level of detail provided in the process description is sufficient. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

The excipients, except vanilla and mint flavours, comply with the Ph. Eur. requirements. No Ph. Eur. monograph exists for vanilla and mint flavours; thus, these are controlled according to in-house specification. These specifications are acceptable.

Microbiological attributes

The MAH has demonstrated that the presence of preservatives is necessary in order to prevent microbial proliferation. The safety of the preservatives is supported by bibliographic data.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage forms. The specification includes tests for: appearance, loss on drying, identification, assay, related substances, microbial quality, pH, dissolution and uniformity of dosage units. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three production scale batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production scale batches of each strength stored at 25°C/60% RH (23 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. Photostability studies, performed on both powder and constituted product showed that the product is stable when stored in the original packaging, but degradation was observed when directly exposed to light. On basis of the data submitted, a shelf life can be granted for the dry powder of 24 months with the storage condition: “Do not store above 25°C. Store in the original foil pouch in order to protect from light and moisture.” The constituted suspension was granted a shelf

life of 28 days. The labelled storage conditions after reconstitution are: “The constituted suspension should be stored in a refrigerator (2°C-8°C). Store in the original container in order to protect from light. Keep the bottle tightly closed. For up to 2 days it may be stored below 25°C.”

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Pedippi has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Pedippi is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Losec which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Esomeprazole is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this hybrid application, the MAH has submitted 5 clinical trials; four bioequivalence and one efficacy/pharmacodynamic study. In addition, the MAH submitted scientific evidence from medical literature to support its application.

Table 1. Conducted clinical trials

Study number	Description
376-15	Pivotal comparative bioavailability study comparing proposed omeprazole oral suspension 4 mg/ml with the reference product, Losec 20mg capsules
BA 04/07	Supportive efficacy/pharmacodynamic study of proposed omeprazole oral suspension (enabling formulation) in paediatric patients
454-14	Supportive comparative bioavailability study comparing proposed omeprazole oral suspension 2 mg/ml (intermediate formulation) with the reference product, Losec 10 mg capsules
375-15	Supportive comparative bioavailability study comparing proposed omeprazole oral suspension 4mg/ml (intermediate formulation) with the reference product, Losec 20 mg capsules
0104-16	Supportive comparative bioavailability study comparing proposed omeprazole oral suspension 4 mg/ml with the clinical formulation of Losec 20 mg capsules used in paediatric efficacy/PK studies and a fasted/fed arm with proposed omeprazole oral suspension 4 mg/ml relevant to the paediatric setting

Furthermore, literature data was submitted to support the use of the omeprazole oral suspension in children. The published studies, 251 (efficacy and safety) and 250 (PK/PD) and 292 (retrospective efficacy study), conducted in the paediatric setting (patients 0 to 2 years) are especially of importance, as in these studies the Losec capsule was used, of which the content of the capsule was suspended in sodium hydrogen carbonate solution before administration. To bridge the data from these studies to the oral suspension, the MAH evaluated the bioavailability of the 4 mg/ml oral suspension versus the Losec capsule, of which the content of the capsule was suspended in sodium hydrogen carbonate solution before administration (study 0104-16).

IV.2 Pharmacokinetics

Bioequivalence studies

Pivotal study 376-15: single-dose under fasting condition, Pedippi 4 mg/ml, powder for oral suspension vs. Losec 20 mg, gastro-resistant capsules

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 19-44 years. Each subject received a single dose (20 mg; 5 ml 4 mg/ml oral suspension or one 20 mg capsule) of one of the 2 esomeprazole formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

For the test arm and reference arm, blood samples were taken pre-dose and at 0.083, 0.167, 0.25, 0.333, 0.5, 0.667, 0.833, 1, 1.333, 1.667, 2, 2.333, 2.667, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 20 and 24 after administration. For the reference arm, blood samples were taken pre-dose and at 0.333, 0.667, 1, 1.333, 1.667, 2, 2.333, 2.667, 3, 3.333, 3.667, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 20 and 24 h after administration.

The design of the study is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Two subjects withdrew from the study for personal reasons and one subject was replaced. Therefore, a total of 27 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of esomeprazole under fasted conditions.

Treatment N=27	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	t_{lag} (h)	$t_{1/2}$ (h)
Test	1510 ± 1940	1533 ± 1940	696 ± 329	0.5 (0.25 – 1.67)	0.0 (0.0 – 0.083)	1.3 ± 1.1
Reference	1621 ± 2041	1648 ± 2094	558 ± 359	2.0 (1.0 – 4.5)	0.67 (0.0 – 3.33)	1.4 ± 1.4
***Ratio (90% CI)**	0.99 (0.94 – 1.05)	0.99 (0.94 – 1.05)	1.38 (1.23 – 1.55)	--	--	--
CV (%)	12.4	12.1	25.4	--	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
tlag lag time
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Supportive studies BA 04/07, 454-14, 375-15 and 0104-16
To bridge the data from the published literature efficacy/safety studies, in which the content of the 20 mg Losec delayed release capsule was suspended in sodium hydrogen carbonate solution before administration, the results of the bioavailability study 0104-16 showed that

the 4 mg/ml oral suspension administered under fasting conditions, is bioequivalent with Losec 20 mg capsule, administered as a suspension of its content in sodium hydrogen carbonate solution under fasting conditions. In principle, the results of the efficacy/safety studies can thus be extrapolated to the 4 mg/ml oral suspension.

The omeprazole 4 mg/ml oral suspension has been developed as a dosage form suitable for children. Milk provides essential nutrition for infants/toddlers and is consumed regularly. To improve compliance, it may be preferable to administer the dose with a small quantity of milk. If a dose is to be administered to infants with milk, healthcare professionals recommend that the dose be added to a small quantity (e.g. 20-30 ml milk) to ensure that administration of the full dose can be verified. The bioavailability study 0104-16 showed that administration of the 4 mg/ml oral suspension with a volume of 70 ml milk (infant formula milk) and 170 ml water the bioavailability of omeprazole decreased with 21%. However, the applicant indicated that taking into account the proposed patient population, a pragmatic recommendation informed by the bioavailability data is “once daily, on an empty stomach 30-60 minutes before meals”. Therefore the food/milk interaction, although limited, is not of concern, as the oral suspension should be taken without food.

IV.3 Pharmacodynamics and clinical efficacy

Omeprazole in proposed omeprazole oral suspensions is released immediately, whereas the omeprazole in the omeprazole reference product is characterised by modified-release characteristics. In line with this, C_{max} of proposed omeprazole oral suspensions is achieved earlier with a higher amplitude compared to the C_{max} after administration of the reference product. It is, however, known that the inhibition of acid secretion with omeprazole is related to the area under the plasma concentration-time curve (AUC) and not to the actual plasma concentration at a given time.

<u>Clinical studies in paediatric patients</u>
Supportive study BA 04/07 is the only clinical study conducted by the MAH in paediatric GERD patients under one year of age. Scientific evidence of supportive study BA 04/07 is however limited due to the limited number of included study patients (n= 12), potential selection bias due to open patient selection by the investigators, potential information bias due to the open-label study design and lack of comparative treatment, considerable dropout of included study patients (3/12= 25%), symptom control was not evaluated, and limited follow-up time.
After administration of test omeprazole oral suspension at a dose of 1.5 mg/kg/day during three consecutive days in study BA 04/07, gastric pH was above 4 during 99.7% of time. However, after oral administration of the reference omeprazole product, gastric pH is ≥ 3 during about 17 out of 24 hours. Hence, it appears that test omeprazole oral suspension at a dose of 1.5 mg/kg/day decreases gastric pH more compared to a 20 mg dose of the reference omeprazole product. Therefore, the test omeprazole oral suspension should be administered at a lower dose to induce similar pharmacodynamic effects as a 20 mg dose of the reference omeprazole product. A dose of 1.0 mg/kg once daily in paediatric patients

aged 1 month up to 1 year appears to be more appropriate than a dose of 1.5 mg/kg/day based on submitted data of study BA 04/07 and submitted pharmacokinetic data.

Data indicate that pharmacokinetics and pharmacodynamics (time that intragastric pH >4) of omeprazole in children <24 months are similar to older children and to adults. The pharmacokinetic and pharmacodynamic data are supportive for omeprazole dosing on a milligram-per-kilogram basis in these patients. As at a dose of 1 mg/kg AUC and the related pharmacodynamics response (time that intragastric pH >4) is comparable to those observed in children 1-16 years, the recommended dose for paediatrics aged 1 - 12 months is 1 mg/kg. A dose of 1.5 mg/kg would result in a higher exposure compared to those observed in in children 1-16 years and adults receiving the SmPC recommended dose.
Furthermore, as known for omeprazole, the use of AUC as the primary parameter for comparing omeprazole immediate-release and delayed-release formulations is acceptable based on pharmacokinetics and pharmacodynamics, mechanism of action and clinical grounds. The other dose recommendation for children >1 year of age in the SmPC are in line with those already approved for Losec delayed release capsules.

In conclusion, in line with the reference product the current GERD indication for paediatric patients aged one year and above may be extended to paediatric patients aged one month and above. This also applies to the reflux oesophagitis indication in respective age range, since pharmacological effects of omeprazole are the same.

Bridging with reference product
The MAH justified bridging between proposed omeprazole oral suspensions and the reference omeprazole product in paediatric patients. In the pivotal relative bioavailability study 376-15, proposed omeprazole oral suspension showed equivalent AUC to reference Losec omeprazole capsules with a ratio of 99.1% (90% confidence interval 93.6 – 104.9%). These results in adults are supported by three other relative bioavailability studies in adults, which also showed equivalent AUC to the reference product. Hence, bridging between proposed and reference omeprazole product is allowed in adult patients.

IV.1 Clinical safety

Frequently reported adverse drug reactions of omeprazole concern abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyp, and headache. AUC of proposed omeprazole oral suspensions and reference omeprazole product are similar in patients of different age, indicating a similar total systemic exposure. In line with this, the safety profile of these omeprazole formulations in paediatric subjects aged 0 up to 2 years was found to be similar in submitted documentation. Palatability of proposed omeprazole product was acceptable in paediatric study patients.

IV.2 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 Pedippi.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	- Hyperkalaemia - Risk of masking symptoms of more serious conditions - Gastrointestinal effects/infections related to acid inhibition - Severe cutaneous reactions
Missing information	- Long-term treatment with omeprazole in children (with GERD)

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Losec. The MAH demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic, pharmacodynamic, efficacy and safety profile of this reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Pedippi 2 mg/ml and 4 mg/ml, powder for oral suspension have a proven chemical-pharmaceutical quality and are hybrid forms of Losec 20 mg, gastro-resistant capsules. Losec is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Pedippi with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 September 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse