IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Esomeprazole 20 mg hard gastro-resistant capsules
Esomeprazole
PA1186/027/001

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 product was initially authorised under procedure numberNL/H/5306/01 with the Netherlands as RMS. The responsibility of RMS was transferred to Ireland on 30 November 2022 under procedure number IE/H/1272/001
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1186/027/001
Marketing Authorisation Holder: Chefaro Ireland DAC

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

The NL public assessment report published at the time of the initial marketing authorisation is provided herein

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Zantac esomeprazol 20 mg, hard gastro-resistant capsules, from Omega Pharma Nederland B.V.

The product is indicated for the short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults.

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 Nexium 20 mg, gastro-resistant tablets which has been registered in The Netherlands by AstraZeneca B.V. since 15 August 2000 by the mutual recognition procedure SE/H/0211/001/MR.

The concerned member states (CMS) involved in this procedure was Ireland.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as the pharmaceutical form is not the same (gastro-resistant capsules compared to tablets). In addition, the reference product is approved as a prescription drug in adults for the treatment of Gastroesophageal Reflux Disease (GERD), in combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori, in patients requiring continued NSAID therapy, for prolonged treatment after i.v. induced prevention of re-bleeding of peptic ulcers, and for the treatment of Zollinger Ellison Syndrome. The purpose of the current application is to seek approval for the short-term use of esomeprazole to treat reflux symptoms as a non-prescription medicine.

II. QUALITY ASPECTS

I.1 Introduction

Zantac esomeprazol is a capsule with an opaque yellow cap and an opaque white body imprinted in black with "20 mg" both on the cap and on the body. The capsule contains off-white to greyish spherical microgranules. Each capsule contains 20 mg esomeprazole (as magnesium dihydrate).

The capsules are packed in PA-Aluminium-PVC/Aluminium foil blisters.

The excipients are:
Capsule contents - sugar spheres (containing sucrose and maize starch), hypromellose, dimethicone emulsion 35% (containing dimethicone, propyl parahydroxybenzoate (E216), methyl parahydroxybenzoate (E218), sorbic acid, sodium benzoate, polyethylene glycol sorbitan monolaureate, octylphenoxy polyethoxy ethanol and propylene glycol), polysorbate 80, mannitol, diacetylated monoglycerides, talc, methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30 % containing copolymer of methacrylic acid and ethyl acrylate, sodium lauryl sulphate and polysorbate 80, triethyl citrate and stearoyl macrogolglycerides
Capsule shell - yellow iron oxide (E 172), titanium dioxide (E 171) and gelatin

Printing Ink - black iron oxide (E 172), shellac, ammonia, potassium hydroxide and propylene Glycol

I.2 DrugSubstance

The active substance is esomeprazole magnesium dihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Esomeprazole magnesium dihydrate is a white or slightly coloured powder. The polymorphic form A is consistently produced.

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. and CEPs. Batch analytical data demonstrating compliance with this specification have been provided for three production and six industrial scaled batches.

Stability of drug substance
The active substance is stable for 18-24 months (depending on CEP) when stored under the stated conditions. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

I.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 main development studies performed were regarding the characterisation of the innovator product, optimisation of the formulation to obtain a dissolution comparable to the innovator product and the performance of comparable dissolution studies. The excipients used in the products are well known. The choices of the packaging and manufacturing process are justified.
A total of seven bioequivalence studies have been submitted. One multiple dose study under fasting conditions and one single dose study under fed conditions, both with the 20 mg strength, were considered pivotal to assess bioequivalence for this product. Overall, the pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process consists of first making the enteric coated pellets. Sugar spheres are coated with a seal coating suspension, a suspension containing the active ingredient, a subcoating, an enteric coating and finally with a polishing suspension. The final blend is then lubricated and filled into capsules. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph. Eur. or USP-NF (diacetylated monoglycerides) except for dimethicone emulsion. The in-house specification for the dimethicone emulsion is acceptable. Functionality related characteristics of the excipients as mentioned in the Ph. Eur. monographs are controlled in the specifications.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, average weight, water content, uniformity of dosage units, assay, dissolution (acid

and buffer stage), related substances, assay and microbial quality. 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 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 six production scaled batches stored at 25°C/60% RH (24 months), 30°C/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 PVC-Al-PA/Al-blisters. The results of the stability studies showed out of specification results for appearance and some of the specified impurities at accelerated conditions. At intermediate condition out of specification results were observed for one specified impurity in three batches. At long term conditions no trends or out of specification results are observed. The proposed shelf-life of 24 months and storage condition 'Do not store above 25°C; Store in the original package in order to protect from moisture' are justified. The stability of esomeprazol microgranules and bulk capsules has been investigated for 12 months under normal conditions (25°C/60%RH). The results of all the tests are within the specifications. No trends are observed. Hence the proposed holding time of 9 months for the microgranules and the capsules is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The excipient gelatin is of animal origin. Appropriate certificates of suitability of the Ph.Eur. are provided.

I.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Zantac esomeprazol 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

I.1 Ecotoxicity/environmental risk assessment (ERA)
Since Zantac esomeprazol 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.

I.2 Discussion on the non-clinical aspects
This product is a hybrid formulation of Nexium 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

I.1 Introduction

Esomeprazole magnesium dihydrate 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.

This application is based on a dossier for a combined application concerning both 20 mg and 40 mg capsules. Therefore, also studies with a 40 mg strength have been submitted to support bioequivalence with the reference product for the 20 mg strength. The MAH has submitted two pivotal bioequivalence studies, which are discussed below.

I.2 Pharmacokinetics
The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Zantac esomeprazol (Omega Pharma Nederland B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Nexium (Astrazeneca, France).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Bioequivalence Study I – 20 mg under fasting conditions

Design

A multiple-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 80 healthy male and female subjects. Each subject received multiple doses (20 mg) of one of the two esomeprazole formulations. The tablets were orally administered with 240 ml water after an overnight fast of at least 10 hours every 24 hours for 7 days. There were 2 dosing periods, separated by a washout period of 15 days.

Blood samples were collected at on days 1, 5, 6, 7 and at the following times after the 7th dose on day 7: 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16 and 24 hours after administration of the products.

The design of the study is acceptable. Although this was a multiple dose study, considering that after dosing once daily no accumulation is observed, the results can be interpreted as a single dose.

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 did not return for check-in for the second period, two subjects withdrew from the study for personal reasons and one subject due to a positive pregnancy test. Therefore, 75 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean (CV%), t_{max} (median, range)) of esomeprazole magnesium dihydrate under fasted conditions.

Treatment N=75	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	1875 (49)	1884 (49)	830 (34)	1.50 (0.75 – 3.00)	1.26 (30)
Reference	1787 (49)	1796 (49)	783 (36)	1.25 (0.75 – 5.00)	1.23 (35)
***Ratio (90% CI)**	1.05 (1.02 – 1.09)	1.05 (1.02 – 1.09)	1.07 (1.02 – 1.13)	--	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life

**ln-transformed values*

Bioequivalence study II – 20 mg under fed conditions

Design

A single-dose, replicate, randomised, four-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 56 healthy male and female subjects. Each subject received a single dose (20 mg) of one of the 2 esomeprazole formulations. The tablet was orally administered with 240 ml water after a high fat, high caloric breakfast (consisting of eggs, butter, slice of toast, hash brown potatoes, whole milk and bacon). There were 4 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 14 and 16 hours after administration of the products.

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

Three subjects withdrew due to adverse events (vomiting and loose stool, and fever and sore throat), one subject was dismissed due to a non-compliance (positive urine hCG test), one subject withdrew for personal reasons and one subject was dismissed due to out-of-range mid-study lab results. Therefore, 50 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean (CV%), f esomeprazole magnesium dihydrate under fasted conditions.

Treatment **N=50**	**AUC_{0-t}** **(ng.h/ml)**	**$AUC_{0-\infty}$** **(ng.h/ml)**	**C_{max}** **(ng/ml)**
Test	671.7 (106)	729.5 (103)	262.3 (83)
Reference	657.8 (97)	696.6 (93)	253.1 (78)
***Ratio** **(90% CI)**	1.07 (0.96 – 1.20)	1.07 (0.97 – 1.18)	1.10 (0.94 – 1.29)
$AUC_{0-\infty}$ 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			

**ln-transformed values*

Bioequivalence has been shown for AUC_{0-t} and AUC_{0-inf}. For C_{max}, the 90% CI was 0.94 – 1.29, thus outside the normal acceptance criteria of 0.80 – 1.25. However, considering the intra-subject variability of >50%, the 90% can be widened to 0.70 – 1.43 for C_{max}

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and $C_{max}$are within the bioequivalence acceptance range of 0.80 – 1.25 (or the widened range). Based on the submitted bioequivalence studies Zantac esomeprazol is considered bioequivalent with Nexium.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

I.3 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 Zantac esomeprazol.

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

Important identified risks	None
Important potential risks	None
Missing information	None

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

I.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Nexium. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. OVERALL CONCLUSIONS

Zantac esomeprazol 20 mg, hard gastro-resistant capsules has a proven chemical-pharmaceutical quality and is a hybrid form of Nexium 20 mg gastro-resistant tablets. Nexium 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 Zantac esomeprazol with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 March 2022.

VI. REVISION DATE

25 April 2024

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From NL/H/5306/001 to IE/H/1272/001	N/A	30 November 2022	N/A