IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

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.

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I. INTRODUCTION

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Esomeprazole 20mg Gastro-resistant Tablets, from Brillpharma Limited on 29th March 2018.

Adults
- **Gastro-Oesophageal Reflux Disease (GERD)**
treatment of erosive reflux esophagitis
long-term management of patients with healed esophagitis to prevent relapse
symptomatic treatment of gastro-esophageal reflux disease (GERD)
- **In combination with an appropriate antibacterial therapeutic regimen for the eradication of *Helicobacter pylori* and** healing of *Helicobacter pylori* associated duodenal ulcer and prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.
-**Patients requiring continued NSAID therapy**
Healing of gastric ulcers associated with NSAID therapy. Prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.
- **Prolonged treatment after i.v. induced prevention of rebleeding of peptic ulcers**
- **Treatment of Zollinger Ellison Syndrome**
- **Adolescents (from age 12)**
- **Gastro-Oesophageal Reflux Disease (GERD)**
treatment of erosive reflux esophagitis
long-term management of patients with healed esophagitis to prevent relapse
symptomatic treatment of gastro-esophageal reflux disease (GERD)
- **In combination with antibiotics in treatment of duodenal ulcer caused by *Helicobacter pylori***

This application for a marketing authorisation was submitted in accordance with Article 10c of Directive 2001/83/EC and is referred to as an 'informed consent' application. This means that the Marketing Authorisation Holder for Esomeprazole 20mg Gastro Resistant Tablets , an authorised medicinal product in Europe, has permitted the applicant to refer to their dossier to obtain an authorisation for Esomeprazole 20mg Gastro Resistant Tablets. Esomeprazole 20mg Gastro Resistant Tablets has the same qualitative and quantitative composition in terms of actives substances and the same pharmaceutical form as Esomeprazole 20mg Gastro Resistant Tablets.

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	Esomeprazole 20mg Gastro Resistant Tablets
Name(s) of the active substance(s) (INN)	Esomeprazole Magnesium Dihydrate
Pharmacotherapeutic classification (ATC code)	A02BC05
Pharmaceutical form and strength(s)	20mg
Marketing Authorisation Number(s) in Ireland (PA)	PA22749/023/001
Marketing Authorisation Holder	Brillpharma (Ireland) Limited

II. QUALITY ASPECTS

II.1. Introduction

This application is for Esomeprazole 20mg Gastro Resistant Tablets

II.2 Drug substance

The active substance is Esomeprazole Magnesium Dihydrate,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

Esomeprazole 20mg Gastro Resistant Tablets contains 20 mg Esomeprazole (as Magnesium Dihydrate).

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/*Ancillary Substances*)

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 tablets, 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 Esomeprazole 20mg Gastro Resistant Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is the same as that present Nexium 20mg Gastro resistant Tablets on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

N/A

III.6 Discussion on the non-clinical aspects

This active substance is the same as that present Nexium 20mg Gastro resistant Tablets on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

IV. CLINICAL ASPECTS

IV.5 Clinical Safety

Pharmacovigilance System

The marketing authorisation holder (MAH) submitted a summary of the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

Risk Management Plan

The RMP version 1.1 (date of final sign off 7/3/2014) is considered acceptable.
Routine risk minimisation measures are considered sufficient.

Summary of safety concerns	
Important identified risks	Use in patients with severe hepatic impairment
	Microscopic colitis
	Malabsorption of Vitamin B12
	Visual disturbances
	Interference with chromogranin A blood test
Important potential risks	Delayed diagnosis of gastric cancer
	Hypomagnesaemia
	Fractures
	Chronic use of proton pump inhibitors and the risk of pneumonia
	Increased risk of *Clostridium difficile*-associated diarrhoea with proton pump inhibitors (specifically)
	Congenital cardiac malformation following in utero exposure
	Reduced effect of co-administered drugs that depend on gastric pH for absorption, especially atazanavir
	Decrease in absorption of iron
	Interactions with other medicinal products (especially warfarin or coumarin derivatives, phenytoin, atazanavir, nelfinavir, digoxin, methotrexate, tacrolimus, clopidogrel)
	Use in patients with glucose intolerance
Missing information	Use in pregnancy and lactation
	Use in patients with severe renal impairment

Summary table of risk minimisation measures
Summary of safety concerns and planned risk minimisation activities

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks		
Use in patients with severe hepatic impairment	The risks associated with the use of the drug product in patients with severe hepatic impairment are described in the SPC Sections 4.2, 4.8, 5.2 and the PIL Sections 2, 3, 4, and appropriate advice is provided to the prescriber to minimise these risks.	None
Microscopic colitis	The risk of microscopic colitis associated with the use of the drug product is described in the SPC Section 4.8 and the PIL Section 4, and appropriate advice is provided to the prescriber to minimise these risks.	None
Malabsorption of Vitamin B12	The risk of malabsorption of Vitamin B12 associated with the use of the drug product is described in the SPC Section 4.4 and the PIL Section 3, and appropriate advice is provided to the prescriber to minimise these risks.	None

Visual disturbances	The risks of visual disturbances associated with the use of the drug product is described in the SPC Section 4.8 and the PIL Section 4, and appropriate advice is provided to the prescriber to minimise these risks.	None
Interference with chromogranin A blood test	The risk of interference with chromogranin A blood test associated with the use of the drug product is described in the SPC Sections 4.4, 5.1 and the PIL Section 4, and appropriate advice is provided to the prescriber to minimise this risk.	None

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important potential risks		
Delayed diagnosis of gastric cancer	The risk of delayed diagnosis of gastric cancer associated with the use of the drug product is described in the SPC Sections 4.4, 4.8 and the PIL Sections 2, 4, and appropriate advice is provided to the prescriber to minimise this risk.	None
Hypomagnesaemia	The risk of hypomagnesaemia associated with the use of the drug product is described in the SPC Sections 4.4, 4.8 and the PIL Section 4, and appropriate advice is provided to the prescriber to minimise this risk.	None
Fractures	The risk of fractures associated with the use of the drug product is described in the SPC Sections 4.4, 4.8 and the PIL Sections 2, 4, and appropriate advice is provided to the prescriber to minimise this risk.	None
Chronic use of proton pump inhibitors and the risk of pneumonia	Evidences from the literature have reported the risks associated with the chronic use of PPIs and risk of pneumonia. Appropriate advice is provided to the prescriber to minimise this risk.	None
Increased risk of *Clostridium difficile*-associated diarrhoea with proton pump inhibitors (specifically)	The risk of *C. difficile*-associated diarrhoea with the use of the drug product is described in the SPC Sections 4.4, 4.8, 5.1, and the PIL Section 4 and appropriate advice is provided to the prescriber to minimise this risk.	None
Congenital cardiac malformation following in utero exposure	Evidences from the literature report the risk of congenital cardiac malformation following in utero exposure to the drug product. Appropriate advice is provided to the prescriber to minimise this risk.	None
Reduced effect of co-administered drugs that depend on gastric pH for absorption, especially atazanavir	The risk of reduced effect of co-administered drugs that depend on gastric pH for absorption, especially atazanavir, associated with the use of the drug product is described in the SPC	None

	Sections 4.3, 4.4, 4.5, and the PIL Section 2 and appropriate advice is provided to the prescriber to minimise this risk.	
Decrease in absorption of iron	Evidence from the literature has reported the risk of decrease in absorption of iron associated with the use of the drug product. Appropriate advice is provided to the prescriber to minimise this risk.	None
Interactions with other medicinal products (especially warfarin or coumarin derivatives, phenytoin, atazanavir, nelfinavir, digoxin, methotrexate, tacrolimus, clopidogrel)	The risk of interactions of other medicines (especially warfarin or coumarin derivatives, phenytoin, atazanavir, nelfinavir, digoxin, methotrexate, tacrolimus, clopidogrel) co-administered with the drug produc is described in the SPC Section 4.3, 4.4, 4.5 and the PIL Section 2, and appropriate advice is provided to the prescriber to minimise this risk.	None
Use in patients with glucose intolerance	The risks associated with the use of the drug product in patients with glucose intolerance are described in the SPC Sections 4.4 and the PIL Section 2, and appropriate advice is provided to the prescriber to minimise these risks.	None

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Missing information		
Use in pregnancy and lactation	The SPC Section 4.6 and the PIL Section 2 states that limited information is available regarding the use of the drug product in pregnant women, and no studies have been performed in lactating women. Therefore, the drug product should be used with caution during pregnancy and should not be used during breastfeeding.	Not applicable
Use in patients with severe renal impairment	The SPC Sections 4.2, 5.2 and the PIL Sections 2, 4 states that no clinical studies have been performed in patients with decreased kidney function, and there is limited clinical information in patients with severe kidney impairment. Therefore, the drug product should be used with caution in such patients.	Not applicable

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.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

V. OVERALL CONCLUSIONS

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

This application has been made under Article 10c of Directive 2001/83/EC referred to as 'informed consent' application. Esomeprazole 20mg Gastro Resistant Tabletsis the same as Esomeprazole 20mg Gastro Resistant Tablets. Esomeprazole 20mg Gastro Resistant Tablets is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The HPRA, on the basis of the data submitted considered that Esomeprazole 20mg Gastro Resistant Tablets was the same as the reference product and therefore granted a marketing authorisation.

VI. REVISION DATE

November 2019

VII. UPDATES

UPDATE

This section reflects the significant changes following finalisation of the initial procedure.

PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE