Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Esomeprazole 20 mg gastro-resistant tablets
Esomeprazole 40 mg gastro-resistant tablets

esomeprazole magnesium trihydrate

PL 53475/0012 - 0013

Biovantic Pharma Limited

LAY SUMMARY

Esomeprazole 20 mg & 40 mg gastro-resistant tablets
esomeprazole magnesium trihydrate

This is a summary of the Public Assessment Report (PAR) for Esomeprazole 20 mg & 40 mg gastro-resistant tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Esomeprazole 20 mg & 40 mg gastro-resistant tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Esomeprazole 20 mg & 40 mg gastro-resistant tablets and what are they used for?

These products are generic medicines. This means that these medicines are the same as, and considered interchangeable with reference medicines, already authorised, called Nexium 20mg gastro-resistant tablets (PL 17901/0068) and Nexium 40mg gastro-resistant tablets (PL 17901/0069).

Esomeprazole is used to treat the following conditions:
Adults:

- 'Gastroesophageal reflux disease' (GERD). This is where acid from the stomach escapes into the gullet (the tube which connects the throat to the stomach) causing pain, inflammation and heartburn.
- Ulcers in the stomach or upper part of the gut (intestine) that are infected with bacteria called 'Helicobacter pylori'. If patients have this condition, their doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.
- Stomach ulcers caused by medicines called NSAIDs (Non-Steroidal Anti-Inflammatory Drugs). Esomeprazole can also be used to stop stomach ulcers from forming if patients are taking NSAIDs.
- Too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome).
- Prolonged treatment after prevention of rebleeding of ulcers with intravenous Esomeprazole.

Adolescents aged 12 years and above:

- 'Gastroesophageal reflux disease' (GERD).
- Ulcers in the stomach or upper part of the gut (intestine) that are infected with bacteria called 'Helicobacter pylori'. If you have this condition, your doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.

How do Esomeprazole 20 mg & 40 mg gastro-resistant tablets work?

Esomeprazole belongs to a group of medicines called 'proton pump inhibitors'. They work by reducing the amount of acid that the stomach produces.

How are Esomeprazole 20 mg & 40 mg gastro-resistant tablets used?

The pharmaceutical form of these medicines is gastro-resistant tablets and the route of administration is oral (by mouth).

The tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed.

For patients who have difficulty in swallowing, the tablets can also be dispersed in a glass of non-carbonated water. Stiruntil the tablets break up and then drink the mixture straight away or within 30 minutes. The mixture should always be stirred just before drinking it. To make sure that the patient has taken all of the medicine, rinse the glass with half a glass of water and drink it. The solid pieces containing the medicine should not be chewed or crushed.

If the patient cannot swallow at all, the tablet can be mixed with some water and put into a syringe. It can then be given to patients through a tube directly into the stomach ('gastric tube'). More information is available in the Summary of Product Characteristics and Patient Information Leaflet available on the MHRA website.

The patient's doctor will tell them how many tablets to take and how long to take them for. This will depend on the patient's condition, how old they are and how well their liver works.

If the patient is taking this medicine for a long time, their doctor will want to monitor them (particularly if they are taking it for more than a year).

For further information on how Esomeprazole 20 mg & 40 mg gastro-resistant tablets are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Esomeprazole 20 mg & 40 mg gastro-resistant tablets have been shown in studies?

Because Esomeprazole 20 mg & 40 mg gastro-resistant tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Esomeprazole 20 mg & 40 mg gastro-resistant tablets?

For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Esomeprazole 20 mg & 40 mg gastro-resistant tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

Why were Esomeprazole 20 mg & 40 mg gastro-resistant tablets approved?
It was concluded that, Esomeprazole 20 mg & 40 mg gastro-resistant tablets have been shown to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Esomeprazole 20 mg & 40 mg gastro-resistant tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Esomeprazole 20 mg & 40 mg gastro-resistant tablets. The RMP details the important risks of Esomeprazole 20 mg & 40 mg gastro-resistant tablets, how these risks can be minimised, any uncertainties about Esomeprazole 20 mg & 40 mg gastro-resistant tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Esomeprazole 20 mg & 40 mg gastro-resistant tablets:

Summary of safety concerns	
Important identified risks	• Risk of reduced plasma levels of clopidogrel and some of the Protease inhibitors (atazanavir and nelfinavir) due to interaction • Risk of hypomagnesaemia with long-term use. • Risk of bone fracture (particularly of hip, wrist, and spine) • Risk of decrease absorption of cyanocobalamine (vitamin B12) with long-term use • Risk of increase of plasma concentration of the drugs metabolised by CYP2C19 (diazepam, phenytoin etc.), upon concomitant use • Gastrointestinal infections
Important potential risks	• Risk of pneumonia with long-term use • Visual disturbances
Missing information	• Use in pregnant and lactating women • Use in patients with renal impairment

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Esomeprazole 20 mg & 40 mg gastro-resistant tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Esomeprazole 20 mg & 40 mg gastro-resistant tablets
Marketing Authorisations for Esomeprazole 20 mg & 40 mg gastro-resistant tablets were granted in the United Kingdom (UK) on 16 December 2022.

The full PAR for Esomeprazole 20 mg & 40 mg gastro-resistant tablets follows this summary.

This summary was last updated in June 2023.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Esomeprazole 20 mg & 40 mg gastro-resistant tablets (PL 53475/0012 - 0013) could be approved.

The products are approved for the following indications:
Adults:

- Gastroesophageal Reflux Disease (GERD)
- treatment of erosive reflux esophagitis
- long-term management of patients with healed esophagitis to prevent relapse
- symptomatic treatment of gastroesophageal reflux disease (GERD)
- In combination with appropriate antibacterial therapeutic regimens 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, for the healing of gastric ulcers associated with NSAID therapy, prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.
- Treatment of Zollinger Ellison Syndrome

Adolescents from the age of 12 years

- Gastroesophageal Reflux Disease (GERD)
- treatment of erosive reflux esophagitis
- long-term management of patients with healed esophagitis to prevent relapse
- symptomatic treatment of gastroesophageal reflux disease (GERD)
- In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori

The active substance in Esomeprazole 20 mg & 40 mg gastro-resistant tablets is esomeprazole magnesium trihydrate.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H+K+-ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Nexium 20mg gastro-resistant tablets (PL 17901/0068) and Nexium 40mg gastro-resistant tablets (PL 17901/0069) that have been licensed for suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for generic medicinal product of suitable reference product. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing Authorisations for Esomeprazole 20 mg & 40 mg gastro-resistant tablets were granted in the United Kingdom (UK) on 16 December 2022.

II QUALITY ASPECTS

II.1 Introduction

These products consist of gastro-resistant tablet containing either 22.21 mg esomeprazole magnesium trihydrate equivalent to 20 mg esomeprazole, or 44.42 mg esomeprazole magnesium trihydrate equivalent to 40 mg esomeprazole.

In addition to esomeprazole magnesium trihydrate, these products also contain the excipients sugar spheres (sucrose and starch); hypromellose; polysorbate 80; sodium hydroxide pellets, hydroxypropyl cellulose; talc; magnesium stearate; methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30%; triethyl citrate; glyceryl monostearate; silica colloidal anhydrous; cellulose microcrystalline; lactose monohydrate; crospovidone; povidone k-30; croscarmellose sodium; sodium stearyl fumarate; titanium dioxide; macrogol; iron oxide (red and yellow)

The finished products are packaged in OPA/Aluminium/PVC-Aluminium foil blisters in cartons of 7, 14, or 28 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

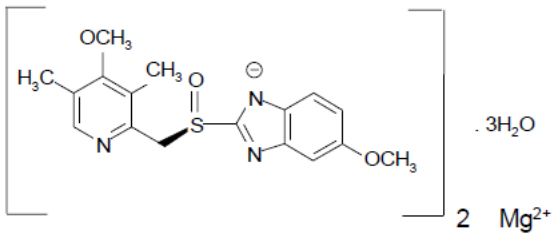
II.2 ACTIVE SUBSTANCE(S)

rINN: esomeprazole magnesium trihydrate

Chemical Name: Magnesium bis[5-methoxy-2-[-(S)-[(4-methoxy-3,5-dimethylpyridi-2-yl)methyl]sulfinyl]-1H-benzimidazole-1-ide] trihydrate

Molecular Formula: $C_{34}H_{36}MgN_6O_6S_2$, $3H_20$

Chemical Structure:



Molecular Weight: 767.2

Appearance: White or slightly coloured powder

Solubility: Slightly hygroscopic, slightly soluble in water, soluble in methanol, practically insoluble in heptane.

Esomeprazole magnesium trihydrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national pharmacopoeia monographs, or suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

With the exception of lactose, no excipients of animal or human origin are used in the final products. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.
These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years with the storage conditions ‘store in the original package (blister) in order to protect from moisture’, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of esomeprazole magnesium trihydrate are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology

No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification was provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the marketing authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects

The grant of marketing authorisations was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of esomeprazole magnesium trihydrate are well-known. With the exception of data from 2 bioequivalence studies, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of these studies) is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence studies:

Bioequivalence study 300-20; single dose, fasting.

This study was an open label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose, oral bioequivalence study comparing the test product Esomeprazole 40 mg gastro resistant tablets versus the reference products Nexium 40 mg, gastro-resistant tablets in healthy adult subjects under fasting conditions.

After fasting for 10 hours, subjects were administered a single dose of either the test or reference product. Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of 2 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Treatment	**AUC_{0-t}** **ng/ml/hr**	**$AUC_{0-\infty}$** **ng/ml/h**	**C_{max}** **ng/ml**	**t_{max}** **h**
Test	8146.766 ± 3759.3519	8299.218 ± 3739.8358	2145.633 ± 635.0277	2.50(1.25-4.50)
Reference	8243.759 ± 3009.9090	8311.270 ± 3060.2045	2333.930 ± 534.0223	2.25(1.00-4.00)
***Ratio Test (90% CI)**	94.61 (88.69-100.92)		90.42 (86.05-95.02)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

Bioequivalence study 481-16; single dose, fed.
This study was an open label, balanced, randomized, two-treatment, two-sequence, four-period, full replicate, crossover, single-dose, oral bioequivalence study comparing the test product Esomeprazole 40 mg Gastro Resistant Tablets versus the reference products Nexium 40 mg, Gastro-Resistant Tablets in healthy adult subjects under fed conditions.

The subjects were fed a high fat calorie breakfast thirty minutes before dosing. Subjects were then administered a single dose of either the test or reference product. Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of 2 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Treatment	**AUC_{0-t}** **ng/ml/hr**	**$AUC_{0-\infty}$** **ng/ml/h**	**C_{max}** **ng/ml**	**t_{max}** **h**
Test	7375.226±3378.0682	7417.922±3418.9725	1537.847±597.0275	4.50 (2.00-10.00)
Reference	7282.346±3443.5132	7322.012±3478.9938	1590.430±640.7806	4.00 (1.50-7.00)
***Ratio Test (90% CI)**	102.19 96.81-107.87		97.69 91.54-104.26	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional strength (Esomeprazole 20 mg) of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence studies on the 40 mg product strength can be extrapolated to the 20 mg product.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted for these applications and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence studies, no new safety data were submitted with these applications.

The safety data from the bioequivalence studies showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence studies.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations was recommended for these medicinal products.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the applications in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL 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.

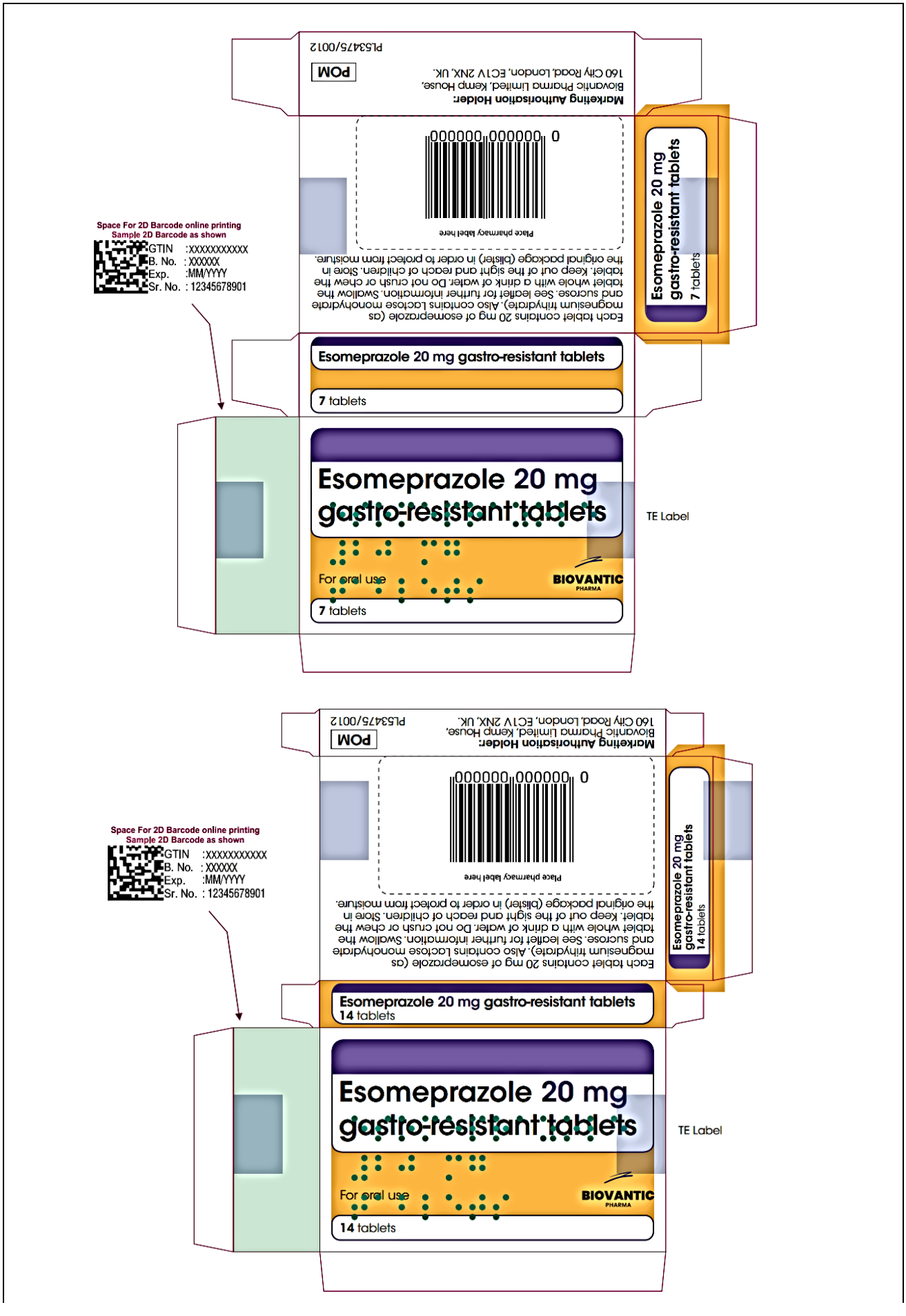
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with esomeprazole magnesium trihydrate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided on the following pages.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Sample 2D Barcode as shown
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B. No. : XXXXXX
Exp. :MM/YYYY
Sr. No. : 12345678901
Esomeprazole 20 mg gastro-resistant tablets
7 tablets
Esomeprazole 20 mg gastro-resistant tablets
For oral use
BIOVANTIC
PHARMA
7 tablets
TE Label
Marketing Authorisation Holder:
Biovantic Pharma Limited, Kemp House,
160 City Road, London, EC1V 2NX, UK.
POM
PL 53475/0012
Place pharmacy label here
Each tablet contains 20 mg of esomeprazole (as magnesium trihydrate). Also contains Lactose monohydrate and sucrose. See leaflet for further information. Swallow the tablet whole with a drink of water. Do not crush or chew the tablet. Keep out of the sight and reach of children. Store in the original package (blister) in order to protect from moisture.
Space For 2D Barcode online printing
Sample 2D Barcode as shown
GTIN :XXXXXXXXXXX
B. No. : XXXXXX
Exp. :MM/YYYY
Sr. No. : 12345678901
Esomeprazole 20 mg gastro-resistant tablets
14 tablets
Esomeprazole 20 mg gastro-resistant tablets
For oral use
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PHARMA
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TE Label
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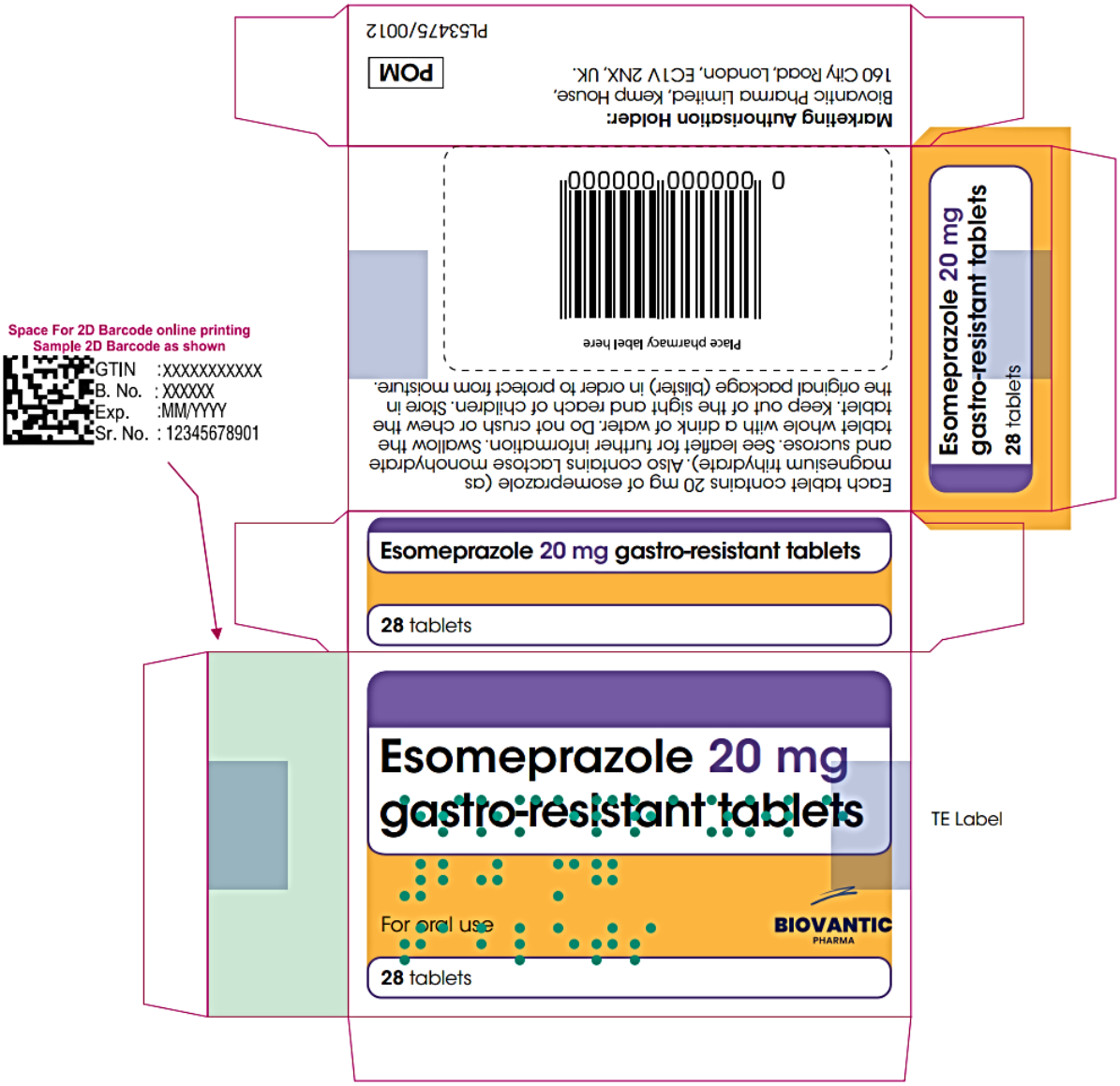
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Esomeprazole 20 mg gastro-resistant tablets
28 tablets
Space For 2D Barcode online printing
Sample 2D Barcode as shown
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B. No. : XXXXXX
Exp. :MM/YYYY
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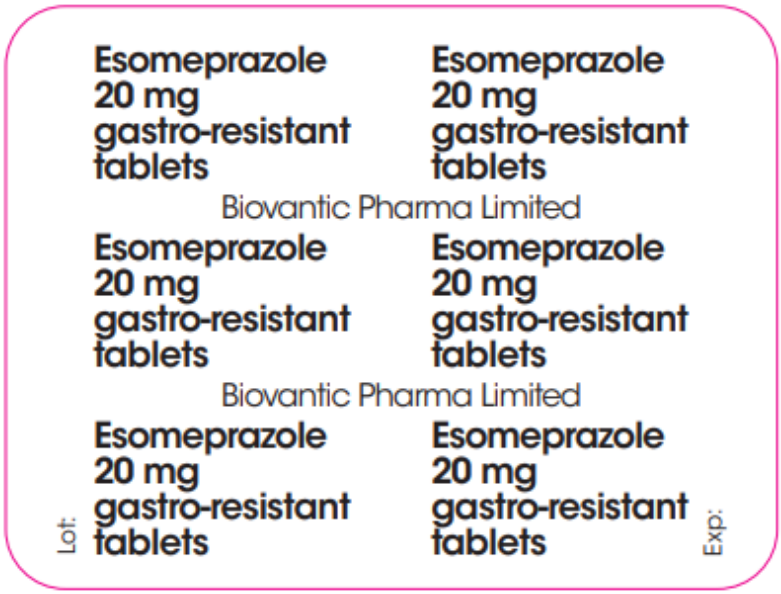
28 tablets
Esomeprazole 20 mg gastro-resistant tablets
For oral use
BIOVANTIC PHARMA
28 tablets
TE Label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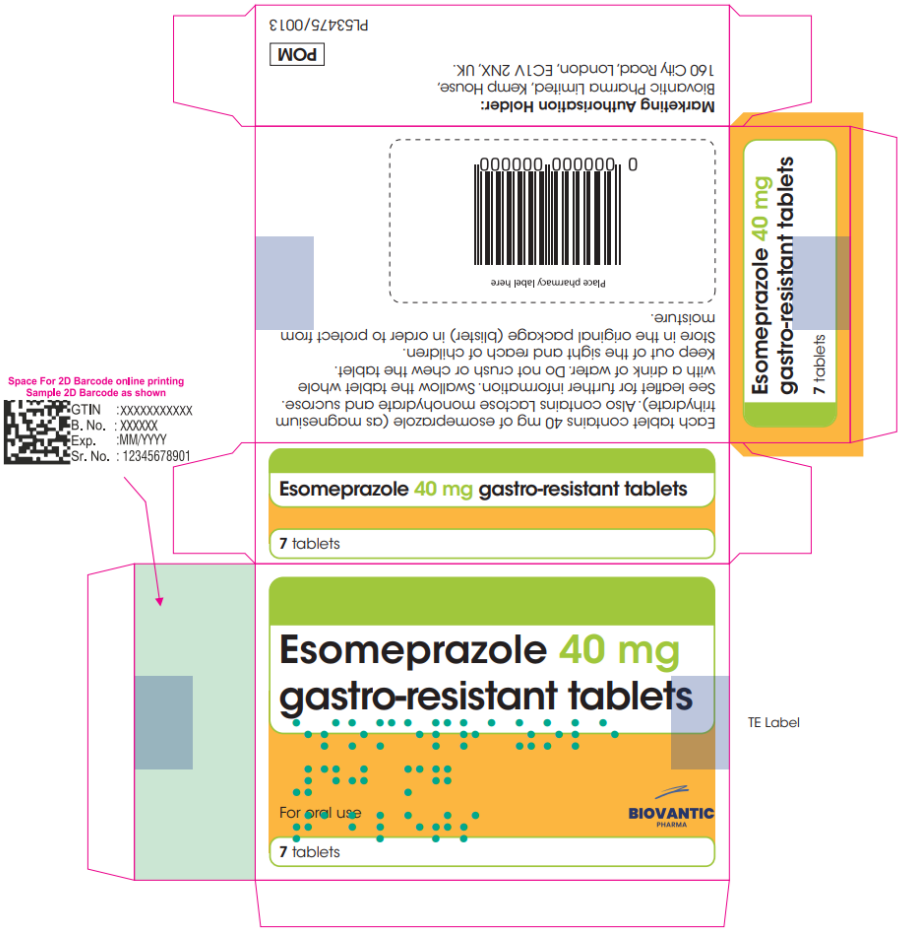
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Exp. :MM/YYYY
Sr. No. : 12345678901
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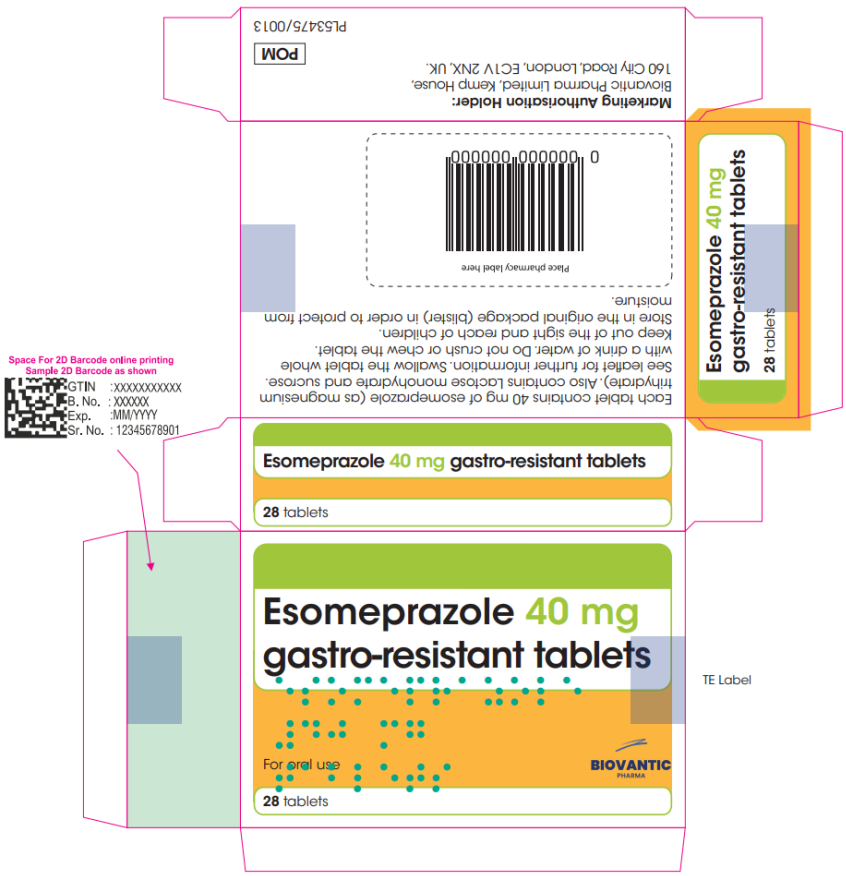
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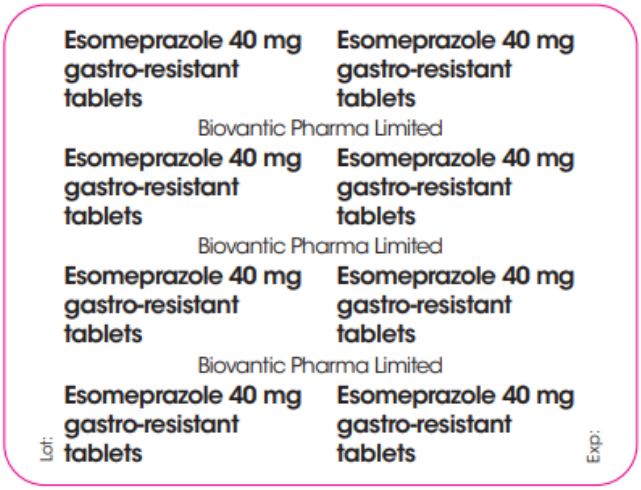
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Exp:

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**