Public Assessment Report

UK PAR

Esomeprazole 20 mg Gastro-Resistant Tablets
(Esomeprazole magnesium dihydrate)

UK Licence No: PL 40496/0007

Brillpharma Limited
LAY SUMMARY

Esomeprazole 20 mg Gastro-Resistant Tablets
(Esomeprazole magnesium dihydrate)

This is a summary of the Public Assessment Report (PAR) for Esomeprazole 20 mg Gastro-Resistant Tablets (PL 40496/0007). It explains how the application for Esomeprazole 20 mg Gastro-Resistant Tablets was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use for Esomeprazole 20 mg Gastro-Resistant Tablets.

For practical information about using Esomeprazole 20 mg Gastro-Resistant Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘for Esomeprazole Tablets’ in this Lay Summary.

What are Esomeprazole Tablets and what are they used for?
This medicine is the same as Esomeprazole 20 mg Gastro-Resistant Tablets (PL 17907/0384; Bristol Laboratories Limited), which are already authorised in the UK. The licence holder (Bristol Laboratories Limited) for Esomeprazole 20 mg Gastro-Resistant Tablets (PL 17907/0384) has agreed that its own scientific data can be used as a basis for the grant of an identical licence for Esomeprazole 20 mg Gastro-Resistant Tablets (PL 40496/0007) (informed consent).

Esomeprazole Tablets are used to treat the following conditions:

In adults and young people aged 12 years and above:
• 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 the patient has this condition, the doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.

In adults:
• Stomach ulcers caused by medicines called NSAIDs (Non-Steroidal Anti-Inflammatory Drugs). Esomeprazole can also be used to stop stomach ulcers from forming if the patient is taking NSAIDs.
• Too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome).

How do Esomeprazole Tablets work?
The active ingredient, esomeprazole (as esomeprazole magnesium dihydrate), belongs to a group of medicines called ‘proton pump inhibitors’, which work by reducing the amount of acid that the stomach produces.

How are Esomeprazole Tablets used?
Esomeprazole Tablets are available as gastro-resistant tablets and are taken by mouth (orally). Esomeprazole Tablets can only be obtained on prescription.

The patient should always take this medicine exactly as his/her doctor has advised. The patient should check with his/her doctor or pharmacist if unsure.

The tablets should be swallowed whole with a drink of water. Esomeprazole Tablets can be taken with food or on an empty stomach.

The tablets should not be chewed or crushed. This is because the tablets contain coated pellets which
stop the medicine from being broken down by the acid in the stomach. It is important that the pellets are not damaged.

The tablets can be taken at any time of day.

Esomeprazole Gastro-resistant tablets are not recommended for children less than 12 years old.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

**What benefits of Esomeprazole Tablets have been shown in studies?**
The application for Esomeprazole Tablets (PL 40496/0007) is considered to be identical to the previously authorised licence for Esomeprazole 20 mg Gastro-Resistant Tablets, (PL 17907/0384, Bristol Laboratories Limited), with the same benefits and risks. So, no new studies have been provided for Esomeprazole Tablets. However, reference is made to the studies for Esomeprazole 20 mg Gastro-Resistant tablets, PL 17907/0384, authorised to Bristol Laboratories Limited).

**What are the possible side effects of Esomeprazole Tablets?**
Like all medicines, Esomeprazole Tablets can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Esomeprazole Tablets, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

**Why are Esomeprazole Tablets approved?**
No new or unexpected safety concerns arose from this application. The MHRA, therefore, considered that the benefits of Esomeprazole Tablets outweigh their risks; and the grant of a Marketing Authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of Esomeprazole Tablets?**
A Risk Management Plan has been developed to ensure that Esomeprazole Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Esomeprazole Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Esomeprazole Tablets**
A Marketing Authorisation was granted in the UK to Brillpharma Limited on 13 April 2017.

The full PAR for Esomeprazole Tablets follows this summary.

For more information about treatment with Esomeprazole Tablets read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2017.
Esomeprazole 20 mg Gastro Resistant Tablets

(Esomeprazole magnesium dihydrate)

PL 40496/0007

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

I Introduction ........................................... Page 5
II Quality aspects ........................................ Page 5
III Non-clinical aspects ................................. Page 7
IV Clinical aspects ....................................... Page 7
V User consultation ....................................... Page 8
VI Overall conclusion, benefit/risk assessment and recommendation Page 8

Steps taken after authorisation - Summary Page 13
I. INTRODUCTION
The Medicines and Healthcare products Regulatory Agency (MHRA) granted Brillpharma Limited a Marketing Authorisation for the medicinal product Esomeprazole 20 mg Gastro-Resistant Tablets (PL 40496/0007) on 13 April 2017. The product is a Prescription Only Medicine (POM) indicated for the following:

In adults:
- **Gastro-oesophageal Reflux Disease (GORD)**
  - treatment of erosive reflux oesophagitis
  - long-term management of patients with healed oesophagitis to prevent relapse
  - symptomatic treatment of gastro-oesophageal reflux disease (GORD)

- **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**
  - 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**

In adolescents from the age of 12 years:
- **Gastro-esophageal Reflux Disease (GORD)**
  - treatment of erosive reflux esophagitis
  - long-term management of patients with healed oesophagitis to prevent relapse
  - symptomatic treatment of gastro-esophageal reflux disease (GORD)

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

The application was submitted as an informed consent application according to Article 10c of Directive 2001/83/EC, as amended, cross-referring to Esomeprazole 20 mg Gastro-Resistant Tablets (PL 17907/0384; Bristol Laboratories Limited), which was authorised on 02 December 2014 following an incoming Decentralised Procedure, with the Netherlands as Reference Member State and the UK as a Concerned Member State.

No new data were submitted nor were necessary to be submitted for this application, as the data are identical to those of the previously granted cross-reference product.

II. QUALITY ASPECTS
II.1 Introduction
This is an informed consent application for Esomeprazole 20 mg Gastro-Resistant Tablets (PL 40496/0007) submitted under Article 10c of Directive 2001/83/EC, as amended.

The application for Esomeprazole 20 mg Gastro-Resistant Tablets (PL 40496/0007) cross-refers to the reference product Esomeprazole 20 mg Gastro-Resistant Tablets (PL 17907/0384; Bristol Laboratories Limited), which was authorised in the UK on 02 December 2014. The application is considered valid.
II.2 Drug substance
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

II.3 Medicinal Product
Name
The proposed name of the product is Esomeprazole 20 mg Gastro-Resistant Tablets. The product has been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack sizes
Each Esomeprazole 20 mg Gastro-Resistant Tablet contains 20 mg of esomeprazole (as esomeprazole magnesium dihydrate), as the active substance. The tablets are administered orally (by mouth).

The product is packaged in aluminium blisters in pack sizes of 3, 7, 7x1, 14, 15, 25x1, 28, 30, 50, 50x1, 56, 60, 90, 98, 100x1, 100 and 140 gastro-resistant tablets.

Not all pack sizes may be marketed.

The proposed shelf life for the product is 2 years, with the special storage conditions. ‘Do not store above 25°C.’

The packaging, proposed shelf-life and storage conditions are consistent with the details registered for the cross-reference product.

Legal status
The product is available as a Prescription Only Medicine (POM).

Marketing Authorisation Holder/Contact Persons/Company
Brillpharma Limited, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG, UK.

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory CV has been provided.

Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

Finished product/shelf-life specification
The proposed finished product specification is consistent with the details registered for the cross-reference product.

TSE Compliance
With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for
human consumption. In addition, the supplier has confirmed that no ruminant material, other than calf rennet, is used during the production of lactose monohydrate. This is consistent with the cross-reference product.

**Bioequivalence**

No bioequivalence data are required to support this simple abridged application because the proposed product is manufactured to the same formula and utilises the same processes as the reference product Esomeprazole 20 mg Gastro-Resistant Tablets (PL 17907/0384; Bristol Laboratories Limited).

**Product Name and Appearance**

See Section II.3 ‘Medicinal Product, Name’ for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

**Summary of Product Characteristics (SmPC)**

The proposed SmPC is consistent with the details registered for the cross-reference product.

**Patient Information Leaflet (PIL) and Labelling**

PIL

The PIL has been prepared in line with the details registered for the cross-reference product.

**Carton and labelling**

The proposed artwork is consistent with the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation, the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The data submitted with the application are acceptable. The grant of a Marketing Authorisation is recommended.

III. NON-CLINICAL ASPECTS

**Introduction**

As this is an informed consent application submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

**Ecotoxicity/Environmental Risk Assessment (ERA)**

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is an identical version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

**Discussion on the non-clinical aspects**

The grant of a Marketing Authorisation is recommended.

IV. CLINICAL ASPECTS

**Introduction**

As this is an informed consent application submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.
Pharmacovigilance and Risk Management Plan (RMP)
The Marketing Authorisation Holder has provided details of a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that they have the services of a qualified person responsible for pharmacovigilance, and have the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

An acceptable Risk Management Plan (RMP) has been submitted. A summary of safety concerns is listed in the following table.

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Important potential risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Concomitant use with antiretroviral protease inhibitor drugs</td>
<td>• Delayed or incorrect diagnosis of malignancy due to masking of symptoms or effects on diagnostic tests</td>
</tr>
<tr>
<td>• Serious hepatic ADRs and use in patients with severe hepatic impairment</td>
<td>• Vitamin B12 deficiency</td>
</tr>
<tr>
<td>• Concomitant use with drugs metabolised by CYP2C19 and CYP3A4</td>
<td>• Increased risk of pneumonia</td>
</tr>
<tr>
<td>• Hypomagnesaemia</td>
<td></td>
</tr>
<tr>
<td>• Fractures</td>
<td></td>
</tr>
<tr>
<td>• Gastrointestinal infections</td>
<td></td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended.

V. USER CONSULTATION
User-testing of the PIL for Esomeprazole 20 mg Gastro-Resistant Tablets) has been accepted based on the successful user-testing of the PIL for the reference product Esomeprazole 20 mg Gastro-Resistant Tablets (PL 17907/0384; Bristol Laboratories Limited), as the ‘parent PIL’.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
QUALITY
The data for this application are consistent with those previously assessed for the cross-reference product and as such have been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for this type of application.
EFFICACY
This application is identical to the previously granted licence for Esomeprazole 20 mg Gastro-Resistant Tablets (PL 17907/0384; Bristol Laboratories Limited, UK).

SAFETY
No new safety data were supplied or required for this application. Esomeprazole has a well-established safety profile. No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE
The SmPC and PIL are satisfactory, and consistent with those for the cross-reference product. The labelling text complies with statutory requirements and is satisfactory.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. Extensive clinical experience with esomeprazole is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is, therefore, considered to be positive.
In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL is available on the MHRA website. The current labelling is presented below:

The labelling text below is that agreed at the end of the national procedure. The Marketing Authorisation Holder has committed to submit the labelling for review to the regulatory authorities before marketing any pack size.

| PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING |
| CARTON |

1. **NAME OF THE MEDICINAL PRODUCT**
   - Esomeprazole 20 mg Gastro-Resistant Tablets

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   - Each gastro-resistant tablet contains 20 mg of esomeprazole (as magnesium dihydrate).

3. **LIST OF EXCIPIENTS**
   - Also contains sucrose and lactose. See leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**
   - 3 Gastro-resistant Tablets
   - 7 Gastro-resistant Tablets
   - 14 Gastro-resistant Tablets
   - 15 Gastro-resistant Tablets
   - 25 Gastro-resistant Tablets
   - 28 Gastro-resistant Tablets
   - 30 Gastro-resistant Tablets
   - 50 Gastro-resistant Tablets
   - 56 Gastro-resistant Tablets
   - 60 Gastro-resistant Tablets
   - 90 Gastro-resistant Tablets
   - 98 Gastro-resistant Tablets
   - 100 Gastro-resistant Tablets
   - 140 Gastro-resistant Tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   - For oral use
   - Read the package leaflet before use.
   - Swallow the tablets whole with liquid. Do not chew or crush the tablets

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**
   - Keep out of the sight and reach of children.
<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.</td>
<td>OTHER SPECIAL WARNING(S), IF NECESSARY</td>
</tr>
<tr>
<td>8.</td>
<td>EXPIRY DATE</td>
</tr>
<tr>
<td></td>
<td>EXP: MM/YYYY</td>
</tr>
<tr>
<td>9.</td>
<td>SPECIAL STORAGE CONDITIONS</td>
</tr>
<tr>
<td></td>
<td>Do not store above 25°C</td>
</tr>
<tr>
<td>10.</td>
<td>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</td>
</tr>
<tr>
<td>11.</td>
<td>NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</td>
</tr>
<tr>
<td></td>
<td>Brillpharma Limited, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG, UK</td>
</tr>
<tr>
<td>12.</td>
<td>MARKETING AUTHORISATION NUMBER(S)</td>
</tr>
<tr>
<td></td>
<td>PL 40496/0007</td>
</tr>
<tr>
<td>13.</td>
<td>BATCH NUMBER</td>
</tr>
<tr>
<td></td>
<td>BN:</td>
</tr>
<tr>
<td>14.</td>
<td>GENERAL CLASSIFICATION FOR SUPPLY</td>
</tr>
<tr>
<td></td>
<td>Medicinal product subject to medical prescription</td>
</tr>
<tr>
<td>15.</td>
<td>INSTRUCTIONS ON USE</td>
</tr>
<tr>
<td>16.</td>
<td>INFORMATION IN BRAILLE</td>
</tr>
<tr>
<td></td>
<td>Esomeprazole 20 mg Gastro-Resistant Tablets</td>
</tr>
<tr>
<td>1. <strong>NAME OF THE MEDICINAL PRODUCT</strong></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Esomeprazole 20 mg Gastro-Resistant Tablets</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. <strong>NAME OF THE MARKETING AUTHORISATION HOLDER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Brillpharma Limited</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. <strong>EXPIRY DATE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP: {MM/YYYY}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. <strong>BATCH NUMBER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>BN:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. <strong>OTHER</strong></th>
</tr>
</thead>
</table>
Esomeprazole 20 mg Gastro-Resistant Tablets
(Esomeprazole magnesium dihydrate)

PL 40496/0007

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>