Public Assessment Report

UKPAR

Esomeprazole 20 mg gastro-resistant tablets
&
Guardium acid reflux control 20 mg gastro-resistant tablets

(esomeprazole magnesium dihydrate)

UK Licence Number: PL 36390/0189

CIPLA (EU) LIMITED
LAY SUMMARY

Esomeprazole 20 mg gastro-resistant tablets
&
Guardium acid reflux control 20 mg gastro-resistant tablets

(Esomeprazole, gastro-resistant tablets, 20 mg)

This is a summary of the Public Assessment Report (PAR) for Esomeprazole 20 mg gastro-resistant tablets, also named Guardium acid reflux control 20 mg gastro-resistant tablets (PL 36390/0189). It explains how Esomeprazole 20 mg gastro-resistant tablets / Guardium acid reflux control 20 mg gastro-resistant tablets 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 Esomeprazole 20 mg gastro-resistant tablets / Guardium acid reflux control 20 mg gastro-resistant tablets.

The product will be referred to as Esomeprazole Tablets throughout the remainder of this public assessment report (PAR).

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

What are Esomeprazole Tablets and what are they used for?
Esomeprazole Tablets are a ‘hybrid generic medicine’. This means that they are similar to a reference medicine containing the same active substance but is available for treatment of a different condition. The reference medicine for this product is Nexium 20mg Tablets, PL 17901/0068 (AstraZeneca).

Esomeprazole Tablets are used in the short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults.

How do Esomeprazole Tablets work?
The active ingredient in this medicine is called esomeprazole magnesium dihydrate and is one of a group of medicines called ‘proton pump inhibitors’. They work by reducing the amount of acid that your stomach produces.

How are Esomeprazole Tablets used?
The pharmaceutical form of this medicine is a gastro-resistant tablet. The route of administration of this medicine is oral (by mouth).

Dose
The recommended dose of one tablet (20 mg) should not be exceeded, even if the patient does not feel an improvement immediately. Tablets may need to be taken for 2 or 3 days in a row before reflux symptoms (for example, heartburn and acid regurgitation) get better. The treatment length is up to 14 days.

When reflux symptoms have completely gone the patient should stop taking this medicine. If reflux symptoms get worse or do not improve after taking this medicine for 14 days in a row, the patient should consult a doctor. If the patient has persistent or longstanding, frequently recurring symptoms even after treatment with this medicine, he/she should contact his/her doctor.
Taking this medicine
The tablet can be taken at any time of the day either with food or on an empty stomach. The tablet should be swallowed whole with a glass of water, without chewing or crushing the tablet. This is because the tablet contains coated pellets, which stop the medicine from being broken down by the acid in your stomach. It is important not to damage the pellets.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration (including an alternative method of taking this medicine), and the duration of treatment.

This medicine can be obtained without a prescription.

What benefits of Esomeprazole Tablets have been shown in studies?
Studies in patients have been limited to tests to determine that the medicine is bioequivalent to the reference medicine, Nexium 20 mg Tablets (AstraZeneca Limited). Two medicines are bioequivalent when they produce the same measure of therapeutic effect in the body.

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

For the full list of all side effects reported with this medicine, see section 4 of the package leaflet available on the MHRA website.

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

Why was this medicine approved?
The MHRA decided that this medicine’s benefits are greater than its risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Esomeprazole Tablets?
A risk management plan (RMP) 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 this medicine
The MHRA agreed to grant a marketing Authorisation for Esomeprazole Tablets on 28 November 2016.

The full PAR for this medicine follows this summary.

This summary was last updated in June 2018.
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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Cipla EU Limited, a Marketing Authorisation for the medicinal product Esomeprazole 20 mg gastro-resistant tablets (PL 36390/0189). The product is a general sales list (GSL) medicine indicated for the short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults.

This application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application, cross-referring to Nexium 20 mg Tablets which were originally licenced on 27 July 2000 to AstraZeneca UK Limited (PL 17901/0068).

Esomeprazole magnesium dihydrate is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamics activity.

Two bioequivalence studies were submitted to support this application:

1. A study under fed conditions comparing the applicant’s test product Esomeprazole 20 mg gastro-resistant tablets (each tablet containing esomeprazole magnesium dihydrate equivalent to 20 mg esomeprazole) with the reference product Nexium 20 mg tablets (each gastro-resistant tablet contains esomeprazole magnesium trihydrate equivalent to 20 mg esomeprazole) authorised to AstraZeneca Ltd, UK.

2. A study under fasting conditions comparing the applicant’s test product Esomeprazole 20 mg gastro-resistant tablets (each tablet containing esomeprazole magnesium dihydrate equivalent to 20 mg esomeprazole), with the reference product Nexium® 20 mg Tablets (each gastro-resistant tablet contains esomeprazole magnesium trihydrate equivalent to 20 mg esomeprazole) authorised to AstraZeneca Ltd, UK.

With the exception of the results of the bioequivalence studies detailed above, no new clinical data were submitted, which is acceptable given that this application was based on the product being shown to be bioequivalent to an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Esomeprazole Tablets outweigh the risks and a Marketing Authorisation was granted.
II QUALITY ASPECTS

II.1 Introduction
Each tablet contains 21.75 mg esomeprazole magnesium dihydrate (equivalent to 20 mg esomeprazole).

Other ingredients consist of the pharmaceutical excipients: hypromellose, sucrose, maize starch, liquid glucose, talc, methacrylic acid – ethylacrylate copolymer (1:1) dispersion 30 %, sodium lauryl sulfate, polysorbate 80, triethyl citrate, macrogol, microcrystalline cellulose, crospovidone, stearyl alcohol, silica colloidal anhydrous, lactose monohydrate and cellulose microcrystalline, magnesium stearate, titanium dioxide (E171), iron oxide red (E172).

The product is packed into oriented polyamide (OPA), aluminium, polyvinyl chloride (PVC)/aluminium blisters and is available in pack sizes of 7 and 14 tablets. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
INN: Esomeprazole magnesium dihydrate
Chemical name: Esomeprazole magnesium dihydrate is magnesium bis[5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-1H-benzimidazol-1-ide] dihydrate.

Structural formula:

![Structural formula](image)

Molecular formula: \( \text{C}_{34}\text{H}_{36}\text{MgN}_{6}\text{O}_{6}\text{S}_{2}\cdot 2\text{H}_{2}\text{O} \)
Molecular weight: 749.2
Appearance: White or slightly coloured powder, slightly hygroscopic.
Solubility: It is slightly soluble in water, soluble in methanol, practically insoluble in heptane.

Esomeprazole magnesium dihydrate is the subject of a European Pharmacopoeia monograph and the active supplier manufacturer applies requirements of the Ph.Eur. monograph.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.
II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable tablets containing 21.75 mg esomeprazole magnesium dihydrate per tablet that were comparable in performance to the reference product Nexium® 20 mg Tablets (AstraZeneca Limited). A satisfactory account of the pharmaceutical development has been provided.

Comparable in vitro dissolution profiles have been provided for this product and the reference product Nexium® 20 mg Tablets (AstraZeneca Limited).

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

It has been stated that the excipients are not of human or animal origin, except for the lactose. A signed TSE / BSE risk free declaration has been provided by the manufacturer of lactose monohydrate and is acceptable.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. In-house working standards are used which are compared to PhEur reference materials where available. Representative certificates have been provided.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with no special storage conditions.

Suitable post approval stability commitments have been provided to place a batch of the finished product under stability testing conditions each year.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of esomeprazole magnesium dihydrate are well-known, no new non-clinical studies are required and none have been provided.
The Non-clinical Overview is acceptable in terms of the literature review, given the extensive clinical experience with esomeprazole. There were no new findings identified that would change the risk: benefit balance for esomeprazole.

The grant of a Marketing Authorisation is recommended.

**III.2 Pharmacology**
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

**III.3 Pharmacokinetics**
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

**III.4 Toxicology**
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

**III.5 Ecotoxicity/environmental risk assessment (ERA)**
Since Esomeprazole Tablets are intended for generic substitution, this medicinal product will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

**III.6 Discussion on the non-clinical aspects**
No new non-clinical studies were conducted or necessary for this type of application.

There are no objections to the approval of this application from a non-clinical viewpoint.

**IV CLINICAL ASPECTS**

**IV.1 Introduction**
The clinical pharmacology of esomeprazole magnesium dihydrate is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of esomeprazole magnesium dihydrate.

Based on the data provided, Esomeprazole Tablets can be considered bioequivalent to Nexium 20 mg Tablets (AstraZeneca Limited).

**IV.2 Pharmacokinetics**
In support of this application, the applicant submitted the following reports of 2 single dose bioequivalence studies, one conducted under fasting conditions and one conducted under fed conditions.

**FASTING STUDY**
A randomised, balanced, open label, two-sequence, two-treatment, two-period, crossover, single dose, bioequivalence study of Esomeprazole 20 mg gastro-resistant tablets (each tablet containing esomeprazole magnesium dihydrate equivalent to 20 mg esomeprazole) with Nexium® 20 mg Tablets
(each gastro-resistant tablet contains esomeprazole magnesium trihydrate equivalent to 20 mg esomeprazole) authorised to AstraZeneca Ltd, UK, in 30 normal, healthy, adult, male and female human subjects (25 males and 5 females) under fasting conditions.

After an overnight fast subjects were administered a single oral dose of the test or the reference product with 240 mL of water. The duration of study was 9 days including the washout period of 7 days.

A total of 21 blood samples (5 mL each) were collected from the subjects in each period of the study from pre dose to 16.00 hours post-dose. Analysis of plasma concentrations of esomeprazole was performed by a validated LC-MS/MS analytical method. A non-compartmental method was used to calculate the pharmacokinetic parameters using drug concentration time profile. Statistical comparison of the pharmacokinetic parameters of both the formulations was performed to assess the bioequivalence of esomeprazole. Bioequivalence was to be concluded if the 90% confidence intervals of the mean ratios (based on log-transformed data) were within the range 80.00-125.00% for C<sub>max</sub> and AUC<sub>0-t</sub> with respect to esomeprazole.

Summary statistics for pharmacokinetic parameters for esomeprazole magnesium dihydrate are shown below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC&lt;sub&gt;τ&lt;/sub&gt; ng/ml/h</th>
<th>AUC&lt;sub&gt;∞&lt;/sub&gt; ng/ml/h</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; ng/ml</th>
<th>t&lt;sub&gt;max&lt;/sub&gt; h</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>2533.05</td>
<td>2572.52</td>
<td>944.75</td>
<td>2.26</td>
<td>1.37</td>
</tr>
<tr>
<td>Reference</td>
<td>2599.77</td>
<td>2642.85</td>
<td>984.13</td>
<td>2.24</td>
<td>1.41</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>94.85 (88.52-101.64)</td>
<td>95.43 (87.65-103.90)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AUC<sub>∞</sub> area under the plasma concentration-time curve from time zero to infinity
AUC<sub>τ</sub> area under the plasma concentration-time curve from time zero to t hours
C<sub>max</sub> maximum plasma concentration
T<sub>max</sub> time for maximum concentration (median)
T<sub>1/2</sub> half-life

*ln-transformed values
FED STUDY

A randomised, balanced, open label, two-treatment, four-period, two-sequence, single dose, replicate crossover bioequivalence study was performed to demonstrate the bioequivalence of Esomeprazole 20 mg gastro-resistant tablets (each tablet containing esomeprazole magnesium dihydrate equivalent to 20 mg esomeprazole) with Nexium® 20mg tablets (each gastro-resistant tablet contains esomeprazole magnesium trihydrate equivalent to 20 mg esomeprazole) authorised to AstraZeneca Ltd, UK in a total of 40 healthy adult male human subjects under fed conditions.

After an overnight fasting period subjects were given a high fat high calorie breakfast prior to dosing. A single dose of one tablet of either the test or reference product was administered orally with 240 ml of drinking water at the time of dosing. A washout period of 7 days was given between the doses.

A total of 20 blood samples of 5 ml each were collected during each study period from pre-dose (collected within 90 minutes prior to dosing) to 24.00 hours (post-dose) in the labelled vacuum blood collection tube containing K$_2$EDTA as an anticolagulant.

Analysis of plasma samples for concentrations of esomeprazole was completed using a validated LC-MS/MS method. A non-compartmental method was used to calculate pharmacokinetic parameters using drug concentrations versus time profile. Statistical comparison of the pharmacokinetic parameters of both the test and reference products were performed and assessed for bioequivalence. Bioequivalence was to be concluded if the 90% confidence intervals of the mean ratios (based on log-transformed data) were within the range 80.00-125.00% for C$_{\text{max}}$ and AUC$_{0-t}$ with respect to esomeprazole.

Summary statistics for pharmacokinetic parameters for esomeprazole magnesium dihydrate are shown below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{t}$ ng/ml/h</th>
<th>AUC$_{\infty}$ ng/ml/h</th>
<th>C$_{\text{max}}$ ng/ml</th>
<th>t$_{\text{max}}$ h</th>
<th>T$_{1/2}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>2086.80</td>
<td>2135.74</td>
<td>533.55</td>
<td>3.67</td>
<td>1.49</td>
</tr>
<tr>
<td>Reference</td>
<td>2052.16</td>
<td>2091.62</td>
<td>577.27</td>
<td>3.67</td>
<td>1.45</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>100.14 (92.50-108.40)</td>
<td>94.93 (86.36-104.36)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AUC$_{\infty}$: area under the plasma concentration-time curve from time zero to infinity
AUC$_{t}$: area under the plasma concentration-time curve from time zero to t hours
C$_{\text{max}}$: maximum plasma concentration
T$_{\text{max}}$: time for maximum concentration (median)
T$_{1/2}$: half-life

*ln-transformed values

Conclusion
The 90% confidence intervals for AUC$_{0-t}$ and C$_{\text{max}}$ were within the acceptance range for all studies. Bioequivalence has been demonstrated between the test and reference products.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.
IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP)
The Marketing Authorisation Holder (MAH) has submitted a risk management plan (RMP), 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 esomeprazole magnesium dihydrate.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is provided below:

**Table: Summary of safety concerns**

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
<th>Important identified risks</th>
<th>Important potential risks</th>
<th>Important missing information</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Hypomagnesaemia, severe hypomagnesaemia can correlate with hypocalcaemia</td>
<td>• Concomitant administration of esomeprazole to warfarin-treated patients</td>
<td>• Effects of use during breast feeding</td>
</tr>
<tr>
<td></td>
<td>• Bronchospasm</td>
<td>• Effects of use during pregnancy</td>
<td>• Effects in patients with decreased renal function</td>
</tr>
<tr>
<td></td>
<td>• Hepatic failure, encephalopathy in patients with pre-existing liver disease</td>
<td>• Use outside the authorised dose and duration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Interstitial nephritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Concomitant use of esomeprazole with nelfinavir or atazanavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Gastrointestinal infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Subacute cutaneous lupus erythematosus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.
IV.7 Discussion on the clinical aspects
There are no objections to the approval of this application from a clinical viewpoint.

The grant of a Marketing Authorisation is recommended for this application.

V User consultation
User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant making reference to Esomeprazole 20 & 40 mg Gastro-Resistant Tablets (PL 36390/0159-0160). The bridging report has successfully demonstrated how the key messages in the daughter PIL are covered within the parent PIL and has justified any differences. The design and layout are sufficiently identical to permit a comparison.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with esomeprazole magnesium dihydrate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Esomeprazole Tablets is presented below:
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Manufacturer</th>
<th>Code No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole 20 mg gastro-resistant tablets</td>
<td>CIPLA (EU) LIMITED</td>
<td></td>
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<tr>
<td>Esomeprazole 20 mg gastro-resistant tablets</td>
<td>CIPLA (EU) LIMITED</td>
<td></td>
</tr>
<tr>
<td>Esomeprazole 20 mg gastro-resistant tablets</td>
<td>CIPLA (EU) LIMITED</td>
<td></td>
</tr>
<tr>
<td>Esomeprazole 20 mg gastro-resistant tablets</td>
<td>CIPLA (EU) LIMITED</td>
<td></td>
</tr>
</tbody>
</table>

Code No.: XX/DRUGS/XXXX
<table>
<thead>
<tr>
<th>PAR Esomeprazole 20 mg gastro-resistant tablets</th>
<th>Guardium acid reflux control 20 mg gastro-resistant tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guardium Acid Reflux Control</strong></td>
<td><strong>Guardium Acid Reflux Control</strong></td>
</tr>
<tr>
<td>20mg Gastro Resistant Tablets</td>
<td>20mg Gastro Resistant Tablets</td>
</tr>
<tr>
<td>(Esomeprazole MA held by Cipla (EU) Limited)</td>
<td>(Esomeprazole MA held by Cipla (EU) Limited)</td>
</tr>
</tbody>
</table>

**PL 36390/0189**
Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of procedure</th>
<th>Date of end of procedure</th>
<th>Approval/Non-approval</th>
<th>Assessment report attached Y/N (version)</th>
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<tbody>
<tr>
<td>To update SmPC sections 4.2, 4.3, 4.5, 4.7, 4.8, 5.1, 5.2 and the PIL in line with the QRD template, plus minor editorial changes.</td>
<td>PL 36390/0189</td>
<td>SmPC and PIL</td>
<td>16/04/2018</td>
<td>16/05/2018</td>
<td>Approval</td>
<td>Y (Annex 1)</td>
</tr>
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</table>
Annex 1

Reference: PL 36390/0189 - 0011
Product: Esomeprazole 20 mg gastro-resistant tablets & Guardium acid reflux control 20 mg gastro-resistant tablets
Marketing Authorisation Holder: Cipla (EU) Limited
Active Ingredient(s): Esomeprazole magnesium dihydrate

Reason:
To update sections 4.2, 4.3, 4.5, 4.7, 4.8, 5.1 and 5.2 of the SmPC and the PIL in line with the QRD template, plus minor editorial changes.

Supporting Evidence
Updated sections of the SmPC and an updated PIL have been provided.

Evaluation
The updated SmPC sections and PIL are satisfactory.
The current SmPC and PIL are available on the MHRA website.

Decision – Granted 16/05/2018