Public Assessment Report

Decentralised Procedure

ESOMEPRAZOLE 20 MG GASTRO-RESISTANT TABLETS
ESOMEPRAZOLE 40 MG GASTRO-RESISTANT TABLETS

Procedure No: UK/H/5028/001-2/DC

UK Licence No: PL 15773/0927-8

ratiopharm GmbH
Lay summary

On 12 September 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations to ratiopharm GmbH for the medicinal products Esomeprazole 20 mg and 40 mg gastro-resistant tablets (PL 15773/0927-8; UK/H/5028/001-2/DC). These medicines are only available on prescription from your doctor and are used to treat the following:

In adults and young people aged 12 years and above:

- ‘Gastro-Oesophageal Reflux Disease’ (GORD). This is where acid from the stomach escapes into the gullet (the tube which connects your throat to your 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 you have this condition, your 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 Tablets can also be used to stop stomach ulcers from forming if you 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 esomprazole.

The active ingredient, esomeprazole, belongs to a group of medicines called ‘proton pump inhibitors’, which work by reducing the amount of acid that the stomach produces.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Esomeprazole 20 mg and 40 mg gastro-resistant tablets outweigh the risks and Marketing Authorisations were granted.
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Module 1
Information about the initial procedure

| Product Names | UK/H/5028/001/DC:  
|               | Esomeprazole 20 mg gastro-resistant tablets  
|               | UK/H/5028/002/DC:  
|               | Esomeprazole 40 mg gastro-resistant tablets  
| Type of Applications | Generic, Article 10(1)  
| Active Substance | Esomeprazole magnesium  
| Form | Gastro-resistant tablets  
| Strengths | 20 mg and 40 mg  
| MA Holder | ratiopharm GmbH  
|           | Graf-Arco-Straße 3, 89079 Ulm, Germany  
| Reference Member State (RMS) | UK  
| Concerned Member States (CMS) | Greece and Slovenia  
| Procedure Numbers | UK/H/5028/001-2/DC  
| Timetable | Day 210 – 12 September 2012  

Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4

The labelling text below is that agreed at the end of the Decentralised Procedure. The Marketing Authorisation Holder has committed to submit the UK labelling for review to the competent authority before marketing any pack size.

| PARTICULARS TO APPEAR ON THE OUTER PACKAGING |
| BLISTER PACK 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 Esomeprazole (as esomeprazole magnesium).

3. LIST OF EXCIPIENTS

Contains lactose and sucrose. Please see the enclosed leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

gastro-resistant tablet

7 gastro-resistant tablets
14 gastro-resistant tablets
15 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
100x1 gastro-resistant tablets
150 gastro-resistant tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Please read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:
9. **SPECIAL STORAGE CONDITIONS**

Store in the original package in order to protect from light and moisture.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

ratiopharm GmbH
Graf-Arco-Straße 3, 89070 Ulm,
Germany

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 15773/0927

13. **BATCH NUMBER**

Batch:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

Use as directed by the doctor.

16. **INFORMATION IN BRAILLE**

Esomeprazole 20 mg gastro-resistant tablets
1. **NAME OF THE MEDICINAL PRODUCT**

Esomeprazole 20 mg gastro-resistant tablets

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

ratiopharm GmbH
Graf-Arco-Straße 3, 89079 Ulm,
Germany

3. **EXPIRY DATE**

EXP:

4. **BATCH NUMBER**

Batch:

5. **OTHER**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

{Carton Box/Bottle Label}

1. NAME OF THE MEDICINAL PRODUCT

Esomeprazole 40 mg gastro-resistant tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant tablet contains 40 mg Esomeprazole (as esomeprazole magnesium).

3. LIST OF EXCIPIENTS

Contains lactose and sucrose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Gastro-resistant tablet

- 7 gastro-resistant tablets
- 14 gastro-resistant tablets
- 15 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
- 100x1 gastro-resistant tablets
- 150 gastro-resistant tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3, 89079 Ulm,
Germany

12. MARKETING AUTHORISATION NUMBER(S)

PL 15773/0928

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor

16. INFORMATION IN BRAILLE

Esomeprazole 40 mg gastro-resistant tablets
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

{BLISTER}

1. NAME OF THE MEDICINAL PRODUCT

Esomeprazole 40 mg gastro-resistant tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3, 89079 Ulm,
Germany

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER
Module 5
Scientific discussion during initial procedure

I. INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Esomeprazole 20 mg and 40 mg gastro-resistant tablets (PL 15773/0927-8; UK/H/5028/001-2/DC) could be approved. The products are prescription-only medicines (POM) indicated for the following:

- 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
- Prolonged treatment after i.v. induced prevention of rebleeding of peptic ulcers.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Greece and Slovenia as Concerned Member States (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the originator medicinal products Nexium 20 mg, and 40 mg enterotabletter (AstraZeneca AB, Sweden), which were authorised on 10 March 2000. The corresponding reference products in the UK are Nexium 20 mg and 40 mg Tablets (AstraZeneca UK Limited; PL 17901/0068-9), which were authorised in the UK on 27 July 2000.

The active ingredient, esomeprazole (as esomeprazole magnesium), belongs to the pharmacotherapeutic group of ‘proton pump inhibitors’ (ATC Code: A02B C05). Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific target mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell.

Five bioequivalence studies were submitted to support these applications, comparing the applicant’s test products Esomeprazole magnesium 40 mg Gastro-resistant Tablets (ratiopharm GmbH, Germany) and Esomeprazole magnesium 40 mg Delayed Release Tablets (ratiopharm GmbH, Germany) with the reference product Nexium MUPS 40 mg gastro-resistant tablets (AstraZeneca GmbH, Germany). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.
The Reference Member State (RMS) has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 12 September 2012. After a subsequent national phase, licences were granted in the UK on 09 November 2012.

### II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | UK/H/5028/001/DC: Esomeprazole 20 mg gastro-resistant tablets |
| Name(s) of the active substance (INN) | Esomeprazole magnesium |
| Pharmacotherapeutic classification (ATC code) | Proton pump inhibitor (ATC code: A02B C05) |
| Pharmaceutical form and strength(s) | Gastro-resistant tablets; 20 mg and 40 mg |
| Reference numbers for the Decentralised Procedure | UK/H/5028/001-2/DC |
| Reference Member State (RMS) | United Kingdom |
| Concerned Member States (CMS) | Greece and Slovenia |
| Marketing Authorisation Number(s) | PL 15773/0927-8 |
| Name and address of the authorisation holder | ratiopharm GmbH, Graf-Arco-Straße 3, 89079 Ulm, Germany |

### III. SCIENTIFIC OVERVIEW AND DISCUSSION

#### III.1 QUALITY ASPECTS

**ACTIVE SUBSTANCE**

INN: Esomeprazole magnesium

Chemical Names: 5-methoxy-2-\{(S)-[(4-methoxy-3,5-dimethyl-2-pyridyl) methyl]sulfonyl]benzimidazole magnesium (2:1); Bis[5-methoxy-2-\{(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulphinyl]-1H-benzimidazolato]magnesium

Molecular formula: \(C_{34}H_{36}MgN_6O_6S_2\)

Molecular mass: 713.1

![Molecular Structure](image)

```plaintext
Mg²⁺

[\[
\text{H}_2\text{CO} \quad \text{N}^- \quad \text{S} \quad \text{CH}_3 \\
\text{N} \quad \text{O} \quad \text{OCH}_3 \\
\text{CH}_3 \quad \text{CH}_3
\]
]_2
```
Appearance: A white to pale-cream coloured powder.
Solubility: Soluble in N,N-Dimethyl formamide, slightly soluble in water and methanol, practically insoluble in heptane.

Esomeprazole magnesium is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. 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 specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

**DRUG PRODUCT**
**Other Ingredients**
Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, talc, lactose monohydrate, maize starch, macrogol 8000, methacrylic acid - ethyl acrylate copolymer (1:1), sodium laurilsulfate, polysorbate 80, crospovidone type A, sugar spheres (sucrose and maize starch), povidone; hypromellose; light magnesium oxide, magnesium stearate, diethyl phthalate, colloidal anhydrous silica, titanium dioxide (E171), ethylcellulose, iron oxide red (E172), Opacode S-1-17823 black ink containing iron oxide black (E 172), shellac, propylene glycol and ammonium hydroxide. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of Opacode S-1-17823 black ink and its constituents and iron oxide red (E172). Opacode S-1-17823 black ink and its constituents are controlled to satisfactory in-house specifications. Iron oxide red (E172) is compliant with its United States Pharmacopoeia-National Formulary specification and is in compliance with current EU Directives concerning the use of colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

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.
Sugar spheres made from non-genetically and genetically modified materials have been used. The MAH has provided satisfactory justification to support the claim that the sugar spheres can be considered safe for human consumption and to the environment.

**Pharmaceutical Development**

The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the reference products Nexium 20 mg and 40 mg Tablets (AstraZeneca, EU). Suitable pharmaceutical development data have been provided for these applications.

Comparative *in-vitro* dissolution and impurity profiles have been provided for batches of the test products and appropriate reference products. The dissolution and impurity profiles were satisfactory.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

**Control of Finished Product**

The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**

The gastro-resistant tablets are packaged in either:

1. aluminium/aluminium blisters packed with the Patient Information Leaflet into cardboard outer cartons in pack sizes of 7, 14, 15, 28, 30, 50, 56, 60, 90, 98, 100 and 100x1 gastro-resistant tablets or
2. high-density polyethylene (HDPE) bottles, with white polypropylene closures with induction sealing and dessicant (silica gel canister), in pack sizes of 100 and 150 gastro-resistant 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 current European regulations concerning materials in contact with foodstuff.
**Stability**
Finished product stability studies were performed in accordance with current guidelines on batches of the finished products packed in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years for the blister and unopened HDPE packs has been set. Once opened, the shelf-life for the product in the HDPE bottles is 100 days. The storage conditions for the product are ‘Store in the original package in order to protect from light and moisture.’

**Bioequivalence**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies. The bioequivalence studies are discussed in Section III.3, Clinical Aspects.

**Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling**
The SmPCs, PIL and labelling text are satisfactory from a pharmaceutical perspective. The Marketing Authorisation Holder has committed to submitting mock-up livery for the PIL and labelling to the relevant competent authorities for approval before marketing any pack size.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the leaflet contains.

**Marketing Authorisation Application (MAA) Forms**
All aspects of the MAA forms are satisfactory from a pharmaceutical perspective.

**Expert Report (Quality Overall Summary)**
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
The grant of Marketing Authorisations is recommended.

### III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of esomeprazole magnesium are well-known, no further non-clinical studies are required and none have been provided.

**NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)**
The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

**ENVIRONMENTAL RISK ASSESSMENT**
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.
CONCLUSION
The grant of Marketing Authorisations is recommended.

III.3 CLINICAL ASPECTS
The clinical pharmacology of esomeprazole magnesium is well-known. With the exception of
data from the bioequivalence studies detailed below, no new pharmacodynamic or
pharmacokinetic data are provided or required for these applications.

Study 1
An open label randomised, two-treatment, two-sequence, two-period, single-dose
crossover study comparing the pharmacokinetics of the test product Esomeprazole
magnesium 40 mg Gastro-resistant Tablets (ratiopharm GmbH, Germany) and the
reference product Nexium MUPS tablets 40 mg (AstraZeneca, Germany) in healthy,
adult human subjects under fasting conditions.
The subjects were administered one tablet of either the test or the reference product with
200 ml of water, after at least a 10-hour overnight fast. Subjects fasted for 4 hours post-dose.
Lunch, snacks and dinner were provided at 4, 9 and 13 hrs post dose respectively. Water was
restricted 1 hr before and 2 hrs after dosing except for dosing; at the rest of the time water was
allowed ad libitum. Blood samples were collected before and up to and including 16 hours
after each administration. The washout period between the treatment phases was 13 days.
The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Esomeprazole Mg 40 mg (Test)</th>
<th>Nexium MUPS 40 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>1546.86</td>
<td>1648.42</td>
<td>93.84</td>
<td>85.59-102.88</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng/ml/h)</td>
<td>4710.84</td>
<td>4429.09</td>
<td>106.36</td>
<td>98.93-114.58</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng/ml/h)</td>
<td>4752.24</td>
<td>4463.59</td>
<td>106.46</td>
<td>98.93-114.58</td>
</tr>
</tbody>
</table>

C<sub>max</sub> maximum plasma concentration
AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours
AUC<sub>0-inf</sub> area under the plasma concentration-time curve from time zero to infinity
Ratios and 90% CI calculated from log-transformed data

The Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98
Rev 1/Corr**) defines the confidence limits as 80.00 to 125.00 % for AUC and C<sub>max</sub> values.
Thus, the data support the claim that the applicant’s test product Esomeprazole magnesium
40 mg Gastro-resistant Tablets is bioequivalent to the reference product Nexium MUPS
tablets 40 mg (Astra Zeneca, Germany) under fasting conditions.

Study 2 (Pilot study)
An open label, randomised, two-treatment, two-sequence, two-period, single-dose,
crossover, study comparing the pharmacokinetics of the test product Esomeprazole
magnesium 40 mg Delayed Release Tablets (ratiopharm GmbH, Germany) and the
reference product Nexium MUPS 40 mg Tablets (Astra Zeneca, Germany) in healthy,
human subjects under fed conditions.
The subjects were fasted for at least 10 hours prior to a standard high fat high calorie
breakfast. The subjects were administered one tablet of either the test or the reference product
with 200 ml of water, 30 minutes after the start of breakfast. Water was restricted 1 hr before
and 2 hrs after dosing except for dosing; at the rest of the time water was allowed ad libitum.
Subjects received lunch at 5.0 hours post dose, snacks at 9.0 hours post dose, dinner at 13.0
hours post dose and breakfast (Day 2) at 24.0 hours post dose in both the periods. Blood samples were collected before and up to and including 24 hours after each administration. The washout period between the treatment phases was 11 days. The pharmacokinetic results are presented below:

**Pharmacokinetic parameters (means, least square means ratios and confidence intervals [CI]) of esomeprazole**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Esomeprazole Mg 40 mg (Test)</th>
<th>Nexium® MUPS 40 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
<td>909.52</td>
<td>882.77</td>
<td>99.52</td>
<td>85.88-115.32</td>
</tr>
<tr>
<td>AUC(_{0-t}) (ng/ml/h)</td>
<td>2678.83</td>
<td>2635.12</td>
<td>98.66</td>
<td>88.99-109.38</td>
</tr>
<tr>
<td>AUC(_{0-\infty}) (ng/ml/h)</td>
<td>2708.58</td>
<td>2665.66</td>
<td>99.10</td>
<td>89.76-109.42</td>
</tr>
</tbody>
</table>

C\(_{\text{max}}\) maximum plasma concentration
AUC\(_{0-t}\) area under the plasma concentration-time curve from time zero to t hours
AUC\(_{0-\infty}\) area under the plasma concentration-time curve from time zero to infinity
Ratios and 90% CI calculated from log-transformed data

The *Note for Guidance on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1/Corr**) defines the confidence limits as 80.00 to 125.00 % for AUC and C\(_{\text{max}}\) values. Thus, the data support the claim that the applicant’s test product Esomeprazole magnesium 40 mg Delayed Release Tablets (Torrent Pharmaceuticals Limited, India) is bioequivalent to the reference product Nexium® MUPS 40 mg tablets (Astra Zeneca, Germany) under fed conditions.

**Study 3**

*An open label, randomised, two-treatment, two-sequence, two-period, single-dose, crossover, study comparing the pharmacokinetics of the test product Esomeprazole magnesium 40 mg Gastro-resistant Tablets (ratiopharm GmbH, Germany) and the reference product Nexium MUPS tablets 40 mg (Astra Zeneca, Germany) in healthy, human subjects under fed conditions.*

The subjects were fasted for at least 10 hours prior to a standard high fat high calorie breakfast. The subjects were administered one tablet of either the test or the reference product with 200 ml of water, 30 minutes after the start of breakfast. Water was restricted 1 hr before and 2 hrs after dosing, except for dosing; at the rest of the time water was allowed *ad libitum*. Subjects received lunch at 5.0 hours post dose, snacks at 9.0 hours post dose, dinner at 13.0 hours post dose and breakfast (Day 2) at 24.0 hours post dose in both the periods. Blood samples were collected before and up to and including 24 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:
Pharmacokinetic parameters (means, least square mean ratios and confidence intervals [CI]) of esomeprazole

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Esomeprazole Mg 40 mg (Test)</th>
<th>Nexium MUPS 40 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
<td>834.76</td>
<td>1006.07</td>
<td>82.97</td>
<td>74.57-92.33</td>
</tr>
<tr>
<td>AUC(_{0-t}) (ng/ml/h)</td>
<td>3369.21</td>
<td>3635.75</td>
<td>92.67</td>
<td>84.06-102.16</td>
</tr>
<tr>
<td>AUC(_{0-\infty}) (ng/ml/h)</td>
<td>3852.67</td>
<td>3659.71</td>
<td>93.93</td>
<td>84.95-103.85</td>
</tr>
</tbody>
</table>

C\(_{\text{max}}\) maximum plasma concentration
AUC\(_{0-t}\) area under the plasma concentration-time curve from time zero to t hours
AUC\(_{0-\infty}\) area under the plasma concentration-time curve from time zero to infinity
Ratios and 90% CI calculated from log-transformed data

The Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**) defines the confidence limits as 80.00 to 125.00 % for AUC and C\(_{\text{max}}\) values. As C\(_{\text{max}}\) does not lie within the acceptable limits of 80.00% to 125.00%, the data does not support the claim that the applicant’s test product Esomeprazole magnesium 40 mg Gastro-resistant Tablets (ratiopharm GmbH, ratiopharm GmbH) is bioequivalent to the reference product Nexium MUPS tablets 40 mg (AstraZeneca, Germany) under fed conditions.

Study 4
An open label, randomised, two-treatment, two-sequence, two-period, single-dose, crossover, study comparing the pharmacokinetics of the test product Esomeprazole magnesium 40 mg Gastro-resistant Tablets (ratiopharm GmbH, Germany) and the reference product Nexium® MUPS tablets 40 mg (AstraZeneca, Germany) in healthy, human subjects under fed conditions.

The subjects were fasted for at least 10 hours prior to a standard high fat high calorie breakfast. The subjects were administered one tablet of either the test or the reference product with 200 ml of water, 30 minutes after the start of breakfast. Water was restricted 1 hr before and 2 hrs after dosing, except for dosing; at the rest of the time water was allowed ad libitum. Volunteers received lunch at 5.0 hours post dose, snacks at 9.0 hours post dose, dinner at 13.0 hours post dose and breakfast (Day 2) at 24.0 hours post dose in both the periods. Blood samples were collected before and up to and including 24 hours after each administration. The washout period between the treatment phases was 4 days. The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Esomeprazole Mg 40 mg (Test)</th>
<th>Nexium® MUPS 40 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
<td>1195.05</td>
<td>1107.31</td>
<td>107.79</td>
<td>100.02-116.16</td>
</tr>
<tr>
<td>AUC(_{0-t}) (ng/ml/h)</td>
<td>3299.14</td>
<td>3064.86</td>
<td>112.16</td>
<td>105.45-119.29</td>
</tr>
<tr>
<td>AUC(_{0-\infty}) (ng/ml/h)</td>
<td>3330.32</td>
<td>3094.50</td>
<td>112.24</td>
<td>105.57-119.32</td>
</tr>
</tbody>
</table>

C\(_{\text{max}}\) maximum plasma concentration
AUC\(_{0-t}\) area under the plasma concentration-time curve from time zero to t hours
AUC\(_{0-\infty}\) area under the plasma concentration-time curve from time zero to infinity
Ratios and 90% CI calculated from log-transformed data
The Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**) defines the confidence limits as 80.00 to 125.00 % for AUC and $C_{\text{max}}$ values. Thus, the data support the claim that the applicant’s test product Esomeprazole magnesium 40 mg Gastro-resistant Tablets (Torrent Pharmaceuticals Limited, India) is bioequivalent to the reference product Nexium® MUPS tablets 40 mg (AstraZeneca, Germany) under fed conditions.

Study 5
An open label randomised, two-treatment, two-sequence, two-period, multi-dose crossover study comparing the pharmacokinetics of the test product Esomeprazole magnesium 40 mg Gastro-resistant Tablets (ratiopharm GmbH, Germany) and the reference product Nexium MUPS tablets 40 mg (AstraZeneca, Germany) in healthy, adult human subjects under fasting conditions. The subjects were administered one tablet of either the test or the reference product, with 200 ml of water after an overnight fast, for seven consecutive days (Days 1 to 7). The subjects were also fasted for 4 hours post dosing. Standard meals were provided in the form of lunch, snacks and dinner at 4, 9 and 13 hrs post-dose, respectively from Day 1 to Day 7 in each period. Water was restricted one hour before and two hours after dosing except for dosing; at rest of the time water was allowed ad libitum. Blood samples were collected before each administration on days 1 (duplicate) to 7 and up to 24 hours after administration on Day 7. The washout period between the treatment phases was 8 days. The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Esomeprazole Mg 40 mg (Test)</th>
<th>Nexium MUPS 40 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>2396.26</td>
<td>2556.18</td>
<td>93.67</td>
<td>89.70-97.82</td>
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<tr>
<td>AUC_{0-t} (ng/mL/h)</td>
<td>7755.16</td>
<td>7815.63</td>
<td>99.17</td>
<td>94.81-103.73</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$: maximum plasma concentration
AUC_{0-t}: area under the plasma concentration-time curve from time zero to t hours
Ratios and 90% CI calculated from log-transformed data

The Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**) defines the confidence limits as 80.00 to 125.00 % for AUC and $C_{\text{max}}$ values. Thus, the data support the claim that the applicant’s test product Esomeprazole magnesium 40 mg Gastro-resistant Tablets (ratiopharm GmbH, Germany) is bioequivalent to the reference product Nexium MUPS tablets 40 mg Tabletten (AstraZeneca, Germany) under steady-state conditions.

Overall pharmacokinetic conclusion
With the exception of one of the fed studies in which the lower confidence interval for $C_{\text{max}}$ fell outside of the acceptance range (Study 3, 90% CI = 74.57-92.33), the 90% confidence intervals for AUC and $C_{\text{max}}$ were within the acceptance range for all studies. Since the data generated during the fasted studies demonstrate bioequivalence, and a second, larger, fed study also demonstrated bioequivalence, the overall conclusion is that bioequivalence between the test product and reference product under fasted, fed and steady-state conditions has been adequately demonstrated.

A biowaiver has been granted to the 20 mg strength gastro-resistant tablets based on the studies conducted, in line with the current bioequivalence guideline.
Efficacy
The efficacy of esomeprazole magnesium is well-known. No new efficacy data have been submitted and none are required for applications of this type.

Safety
With the exception of the safety data generated during the bioequivalence studies, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues arose during the bioequivalence studies.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the Marketing Authorisation Holder, fulfils the requirements and provides adequate evidence that the Marketing Authorisation Holder has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are acceptable from a clinical perspective. The SmPCs are consistent with those for the reference products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

Clinical Expert Report (Clinical Overview)
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The quality characteristics of Esomeprazole 20 mg and 40 mg gastro-resistant tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of esomeprazole magnesium are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s 40 mg strength tablets (gastro-resistant and delayed release) and and the reference product Nexium MUPS tablets 40 mg (AstraZeneca, Germany); the results can be extrapolated to the 20 mg strength gastro-resistant tablets.

SAFETY
With the exception of the safety data from the bioequivalence studies, no new data were submitted and none are required for applications of this type. As the safety profile of esomeprazole magnesium is well known, no additional data were required. No new or unexpected safety concerns arose from the bioequivalence studies.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory, and consistent with those for the reference products, where appropriate, and consistent with current guidelines.

BENEFIT/RISK ASSESSMENT
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 is considered to have demonstrated the therapeutic value of the products. The benefit/risk balance is, therefore, considered to be positive.
# Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

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