Public Assessment Report

Decentralised Procedure

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

UK/H/5483/001/DC
UK/H/5483/002/DC
PL 36390/0159
PL 36390/0160

Cipla (EU) Limited
Lay Summary

This is a summary of the public assessment report (PAR) for Esomeprazole 20 mg and 40 mg gastro-resistant tablets (PL 36390/0159-0160). It explains how Esomeprazole 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 gastro-resistant tablets.

For practical information about using Esomeprazole gastro-resistant tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Esomeprazole gastro-resistant tablets and what are they used for?
Esomeprazole gastro-resistant tablets are ‘generic medicines’. This means that Esomeprazole gastro-resistant tablets are similar to ‘reference medicines’ already authorised in the European Union (EU) called Nexium 20 mg and 40 mg gastro-resistant tablets.

Esomeprazole gastro-resistant tablets are used in adults and young people aged 12 years and above to treat gastro-oesophageal reflux disease (GORD). 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. The tablets are also used to treat ulcers in the stomach or upper part of the gut (intestine) that are infected with bacteria called Helicobacter pylori.

Esomeprazole gastro-resistant tablets may also be used in adults only to treat or prevent stomach ulcers caused by medicines called NSAIDs (non-steroidal anti-inflammatory drugs); to treat an excess of acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome); and to prevent (through prolonged treatment) the rebleeding of ulcers following treatment with intravenous esomeprazole.

How do Esomeprazole gastro-resistant tablets work?
Esomeprazole belongs to a group of medicines called the ‘proton pump inhibitors’. Proton pumps are found on cells that line the stomach and are used by these cells to produce stomach acid. Esomeprazole works by inhibiting the action of the proton pumps, therefore reducing the amount of acid that the stomach produces.

How are Esomeprazole gastro-resistant tablets used?
A doctor should decide how many tablets their patient should take and for how long. This will depend on the patient’s condition, the age of the patient and how well their liver works.

To treat heartburn caused by GORD the usual dose is one 40 mg tablet once a day for 4 weeks if the patient’s food pipe (gullet) has been slightly damaged. Treatment may be continued for a further 4 weeks if the gullet has not healed by the end of the first 4 weeks treatment. The usual dose once the gullet has healed is one 20 mg tablet once a day. Patients with heartburn caused by GORD whose gullet has not been damaged will usually be given one 20 mg tablet once a day. When the condition has been
controlled, the doctor may advise their patient to take the medicine as and when they need it, up to a maximum of one 20 mg tablet once a day.

To treat ulcers caused by *Helicobacter pylori* infection and to stop them coming back the usual dose is one 20 mg tablet twice a day for one week. Antibiotics such as amoxicillin or clarithromycin will be taken at the same time to treat the infection.

To treat stomach ulcers caused by NSAIDs the usual dose is one 20 mg tablet once a day for 4 to 8 weeks. To prevent stomach ulcers in patients taking NSAIDs the usual dose is one 20 mg tablet once a day.

To treat Zollinger-Ellison syndrome the usual dose is one 40 mg tablet twice a day. The doctor will adjust the dose depending on the patient’s needs and will also decide how long the patient needs to take the medicine for. The maximum dose is 80 mg twice a day.

When the tablets are used for prolonged treatment after prevention of rebleeding of ulcers with intravenous esomeprazole the usual dose is one 40 mg tablet once a day for 4 weeks.

The medicines can only be obtained from a pharmacy with a prescription.

**What benefits of Esomeprazole gastro-resistant tablets have been shown in studies?**
Because Esomeprazole gastro-resistant tablets are generic medicines, studies in patients have been limited to tests to determine that Esomeprazole gastro-resistant tablets are bioequivalent to the reference medicines, Nexium 20 mg and 40 mg gastro-resistant tablets. Two medicines are bioequivalent when they produce the same levels of active substance in the body.

**What are the possible side effects of Esomeprazole gastro-resistant tablets?**
Because Esomeprazole gastro-resistant tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are taken as being the same as those of the reference medicines.

**Why are Esomeprazole gastro-resistant tablets approved?**
It was concluded that, in accordance with EU requirements, Esomeprazole gastro-resistant tablets have been shown to have comparable quality and to be bioequivalent to Nexium 20 mg and 40 mg gastro-resistant tablets. Therefore, the MHRA decided that, as for Nexium 20 mg and 40 mg gastro-resistant tablets, the benefits of Esomeprazole gastro-resistant tablets are greater than their risks and recommended that they can be approved for use.

**What measures are being taken to ensure the safe and effective use of Esomeprazole gastro-resistant tablets?**
Suitable safety information has been included in the Summaries of Product Characteristics and package leaflet for Esomeprazole gastro-resistant tablets, including the appropriate precautions to be followed by healthcare professionals and patients.
Other information about Esomeprazole gastro-resistant tablets
The Marketing Authorisations for Esomeprazole gastro-resistant tablets were granted in the UK on 27 October 2014.

This summary was last updated in December 2014.

The full PAR for Esomeprazole gastro-resistant tablets follows this summary.
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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 could be approved. These are prescription only medicines (POM).

Esomeprazole 20 mg gastro-resistant tablets are indicated in adults for:

**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**

Esomeprazole 20 mg gastro-resistant tablets are indicated in adolescents from the age of 12 years for:

**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 antibiotics in treatment of duodenal ulcer caused by *Helicobacter pylori*

**Esomeprazole 40 mg gastro-resistant tablets are indicated in adults for:**

**Gastro-oesophageal Reflux Disease (GORD)**
- treatment of erosive reflux oesophagitis

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

**Treatment of Zollinger Ellison syndrome**

Esomeprazole 40 mg gastro-resistant tablets are indicated in adolescents from the age of 12 years for:

**Gastro-oesophageal Reflux Disease (GORD)**
- treatment of erosive reflux oesophagitis
These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and BG, CY, DK, FI, IE, MT, NO, PL, RO, SE and SK as Concerned Member States (CMS). These applications were made under Article 10(1) of Directive 2001/83/EC, as amended, as so-called generic applications. The reference medicinal products for these applications are Nexium 20 mg and 40 mg gastro-resistant tablets, which were first authorised to AstraZeneca AB in Sweden on 10 March 2000 and then to AstraZeneca UK Limited in the UK on 27 July 2000 (PL 17901/0068-0069). The reference products have been authorised in the EEA for at least 10 years, therefore, the legal basis of these applications is acceptable.

Esomeprazole 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 pharmacodynamic activity.

No new non-clinical data were submitted, which is acceptable given that the applications are for generic medicinal products of originator products that have been in clinical use for over 10 years.

The applicant has submitted reports of four bioequivalence studies. Assurance has been provided that the studies have been conducted according to the principles of Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer 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 of 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 considers that the pharmacovigilance system, as described by the MA holder, fulfils the requirements and provides adequate evidence that the MA 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. The MA holder has provided a Risk Management Plan (RMP).

The lack of an Environmental Risk Assessment (ERA) with these applications for generic products is acceptable.

The RMS and CMS considered that the applications could be approved at Day 210 of the procedure on 18 September 2014. After a subsequent national phase, the Marketing Authorisations were granted in the UK on 27 October 2014.
II  Quality aspects

II.1 Introduction
The gastro-resistant tablets are pink coloured, capsule shaped, biconvex and film coated. The 20 mg tablets and 40 mg tablets are debossed with ‘20’ and ‘40’, respectively, on one side and both tablet strengths are plain on the other side.

The tablet excipients are hypromellose, sucrose, maize starch, liquid glucose, talc, methacrylic acid - ethylacrylate copolymer (1:1) dispersion 30 %, sodium laurilsulfate, polysorbate 80, triethyl citrate, macrogol, microcrystalline cellulose, crospovidone, hypromellose, stearyl alcohol, silica colloidal anhydrous (which make up the pellets), crospovidone, lactose monohydrate, cellulose microcrystalline, silica colloidal anhydrous and magnesium stearate (which make up the tablet core) and hypromellose, titanium dioxide (E171), and macrogol (which make up the tablet coating). The 20 mg tablets also contain iron oxide red (E172) in the tablet coating and the 40 mg tablets also contain erythrosine aluminium lake (E127) and iron oxide black (E172) in the tablet coating.

The tablets are stored in packs of plain aluminium blister foil along with 3 ply aluminium laminated film. Blister packs of 3, 7, 14, 15, 25, 28, 30, 50, 56, 60, 90, 98, 100 and 140 tablets have been authorised.

II.2 Drug Substance
INN:  Esomeprazole magnesium dihydrate
Chemical name: Di-[(S)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulphinyl] benzimidazole]magnesium dihydride

Structure:

\[
\begin{align*}
\text{Molecular formula:} & \quad C_{34}H_{36}N_6O_6S_2Mg_2H_2O \\
\text{Molecular weight:} & \quad 749.2
\end{align*}
\]

An Active Substance Master File (ASMF) has been provided by the manufacturer, covering the manufacture and control of the active substance.

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 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 specifications. Certificates of analysis have been provided for all working
standards. Batch analysis data are provided that comply with the proposed specification.

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

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

II.3 Medicinal Product

Pharmaceutical development
The aim of the pharmaceutical development of Esomeprazole 20 mg and 40 mg gastro-resistant tablets was to develop generic versions of the innovator product, Nexium 20 mg and 40 mg gastro-resistant tablets.

Comparable dissolution and impurity profiles were provided for the proposed and the reference products.

All excipients comply with their European Pharmacopoeia monographs with the exception of iron oxide red (E172), erythrosine aluminium lake (E127) and iron oxide black (E172), which are controlled in line with suitable specifications. Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients contain materials of animal or human origin, with the exception of lactose monohydrate. A satisfactory declaration of compliance with current TSE/BSE regulations has been provided by the supplier of lactose monohydrate.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the finished products, together with an appropriate account of the manufacturing process. The manufacturing process has been validated with commercial scale batches and is satisfactory.

Finished Product Specification
The finished product specifications are satisfactory. Test methods have been described that have been adequately validated, as appropriate. Batch data have been provided from commercial scale batches that comply with the release specification. Certificates of analysis have been provided for any working standards used.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years.
II.4 **Discussion on chemical, pharmaceutical and biological aspects**
The grant of marketing authorisations is recommended.

II.5 **SmPC, PIL and labelling**
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 following product labelling was approved for use in the UK:

**Esomeprazole 20 mg gastro-resistant tablets**

**Blister:**

![Esomeprazole 20 mg gastro-resistant tablets Blister Image]
Esomeprazole 20 mg and 40 mg gastro-resistant tablets

Carton:

Esomeprazole 20 mg gastro-resistant tablets

Esomeprazole 40 mg gastro-resistant tablets

Blister:
III Non-clinical aspects

III.1 Introduction
No new non-clinical data have been submitted and none are required for applications of this type. The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory.

III.2 Pharmacology
No new pharmacology data are required for these applications and none have been submitted.

III.3 Pharmacokinetics
No new pharmacokinetic data are required for these applications and none have been submitted.

III.4 Toxicology
No new toxicology data are required for these applications and none have been submitted.
III.5 Ecotoxicity/environmental risk assessment (ERA)
Since the formulations of Esomeprazole 20 mg and 40 mg gastro-resistant tablets are intended for generic substitution, they 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
The grant of marketing authorisations is recommended.

IV Clinical aspects

IV.1 Introduction
The applicant has submitted reports of four bioequivalence studies in support of these applications. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

STUDY 1 (20 mg, fasted)

Methods
A randomised, balanced, open label, two-sequence, two-treatment, two-period, crossover, single dose, bioequivalence study of Esomeprazole 20 mg gastro-resistant tablets, from Cipla Ltd, India with Nexium® 20 mg Tablets from AstraZeneca Ltd, UK, in normal, healthy, adult, male and female subjects under fasting conditions was conducted.

A total of 30 subjects (25 males and 5 females) were enrolled in the study. After an overnight fast of at least 10 hours, subjects were administered a single oral dose of the test or the reference product as per the randomisation schedule with 240 mL of water. The washout period was 7 days.

Blood samples were collected pre-dose and at intervals up to 16 hours post-dose.

30 subjects were enrolled and randomised; 29 completed both periods and were included in the pharmacokinetic and statistical analyses. One subject was withdrawn from the study due to an adverse event.

Bioequivalence was to be concluded if the confidence intervals fell within the range of 80.00-125.00% for Cmax and AUC0-t of esomeprazole.
Results

Pharmacokinetic parameters (n=29)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$ ng/ml/h</th>
<th>AUC$_{0-\infty}$ 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>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$_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC$_{0-t}$ 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

Adverse events
A total of three adverse events were reported, ranging from mild to moderate in intensity. The events included headache and fever and were all reported with the test product.

Conclusion
AUC$_{0-t}$ covered at least 80% of AUC$_{0-\infty}$ in all subjects. Bioequivalence has been demonstrated in the fasted state between the test and reference products after single doses of 20 mg.

STUDY 2 (20 mg, fed)

Methods
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 from Cipla Ltd, India with Nexium® 20mg tablet from AstraZeneca Ltd, UK in healthy adult male human subjects under fed conditions.

After an overnight fasting period of at least 10 hours, 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. The washout period was 7 days.

Blood samples were collected pre-dose and at intervals up to 24 hours post-dose.

40 subjects were enrolled and randomised; 35 completed both periods and were included in the pharmacokinetic and statistical analyses. One subject did not arrive in Period 3 due to a personal reason. In Period 1, one subject was discontinued from the
study before dosing due to a medical event and one subject was discontinued from the study due to an adverse event after dosing. In Period 3, one subject discontinued from the study before dosing due to an adverse event and one subject discontinued from the study due to an adverse event after dosing.

Bioequivalence was to be concluded if the confidence intervals so constructed fall within the range of 80.00-125.00% for $C_{\text{max}}$ and $AUC_{0-\infty}$ of esomeprazole.

Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$AUC_{0-t}$ ng/ml/h</th>
<th>$AUC_{0-\infty}$ 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>4.12</td>
<td>1.49</td>
</tr>
<tr>
<td>Reference</td>
<td>2052.16</td>
<td>2091.62</td>
<td>577.27</td>
<td>3.84</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>

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

$AUC_{0-t}$ 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

Adverse events
A total of seven adverse events were reported, ranging from mild to moderate in intensity. Five occurred with the reference product and two with the test product.

Conclusion
$AUC_{0-t}$ covered at least 80% of $AUC_{0-\infty}$ in all subjects. Bioequivalence has been demonstrated in the fed state between the test and reference products after single doses of 20 mg.

STUDY 3 (40 mg, fasted)

Methods
A randomised, balanced, open label, two-sequence, two-treatment, two-period, crossover, single dose, bioequivalence study of Esomeprazole 40 mg gastro-resistant tablets, from Cipla Ltd, India with Nexium® 40 mg Tablets from AstraZeneca Ltd, UK, in normal, healthy, adult, male and female human subjects under fasting conditions.

A total of 30 subjects (27 males and 3 females) were enrolled in the study. After an overnight fast of at least 10 hours, subjects were administered a single oral dose of the
Blood samples were collected pre-dose and at intervals up to 16 hours post-dose.

30 subjects were enrolled and randomised; all completed both periods and were included in the pharmacokinetic and statistical analyses.

Bioequivalence was to be concluded if the confidence intervals so constructed fall within the range of 80.00-125.00% for $C_{\text{max}}$ and AUC$_{0-t}$ of esomeprazole.

**Results**

### Pharmacokinetic parameters (n = 30)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$ ng/ml/h</th>
<th>AUC$_{0-\infty}$ 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>5401.51</td>
<td>5478.90</td>
<td>1682.74</td>
<td>2.50</td>
<td>1.55</td>
</tr>
<tr>
<td>Reference</td>
<td>5649.34</td>
<td>5717.94</td>
<td>1767.83</td>
<td>2.28</td>
<td>1.53</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>97.71 (92.45-103.28)</td>
<td>95.09 (88.57-102.10)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AUC$_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

AUC$_{0-t}$ 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

### Adverse events

A total of four adverse events were reported, all mild in intensity. Three occurred with the reference product, one with the test product.

### Conclusion

AUC$_{0-t}$ covered at least 80% of AUC$_{0-\infty}$ in all subjects. Bioequivalence has been demonstrated in the fasted state between the test and reference products after single doses of 40 mg.

### STUDY 4 (40 mg, fed)

**Methods**

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 40 mg gastro-resistant tablets from Cipla Ltd, India with Nexium® 40mg tablet from AstraZeneca Ltd, UK in healthy adult male human subjects under fed conditions.

After an overnight fasting period of at least 10 hours, 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. The washout period was 7 days.

Blood samples were collected pre-dose and at intervals up to 24 hours post-dose.

80 subjects were enrolled and randomised; 75 completed both periods and were included in the pharmacokinetic and statistical analyses. Two subjects were discontinued due to adverse events in Period 3. Two subjects did not arrive for Periods 2, 3 and 4 due to personal reasons and one subject withdrew his participation from study after dosing in Period 4 due to a personal reason.

Bioequivalence was to be concluded if the confidence intervals so constructed fell within the range of 80.00-125.00% for $C_{max}$ and AUC$_{0-t}$ of esomeprazole.

**Results**

**Pharmacokinetic parameters (N = 148, excluding one subject)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$ ng/ml/h</th>
<th>AUC$_{0-\infty}$ ng/ml/h</th>
<th>$C_{max}$ ng/ml</th>
<th>t$_{max}$ h</th>
<th>$T_{1/2}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>6123.15</td>
<td>6215.25</td>
<td>1416.63</td>
<td>4.76</td>
<td>1.98</td>
</tr>
<tr>
<td>Reference</td>
<td>6110.85</td>
<td>6204.91</td>
<td>1416.15</td>
<td>4.54</td>
<td>1.98</td>
</tr>
</tbody>
</table>

*Ratio (90% CI) 103.35 (97.23-109.86) 103.70 (96.38-111.58)

AUC$_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC$_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
$C_{max}$ maximum plasma concentration
T$_{max}$ time for maximum concentration (median)
$T_{1/2}$ half-life

*ln-transformed values

**Adverse events**

A total of eight adverse events were reported, ranging from mild to moderate in intensity. Three occurred with the reference product and five with the test product.

**Conclusion**

AUC$_{0-t}$ covered at least 80% of AUC$_{0-\infty}$ in all subjects. Bioequivalence has been demonstrated in the fed state between the test and reference products after single doses of 40 mg.

**Pharmacokinetic conclusion**

The 90% confidence intervals for AUC 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 are required for these applications and none have been submitted.

IV.4  Clinical efficacy
No new clinical efficacy data are required for these applications and none have been submitted.

IV.5  Clinical safety
No new clinical safety data are required for these applications and none have been submitted.

IV.6  Risk Management Plan
The applicant 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 20 mg and 40 mg gastro-resistant tablets. Routine pharmacovigilance activities and risk minimisation measures should be adequate for these products, which contains a widely used active substance with a well-established safety profile.

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

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypomagnesaemia, severe hypomagnesaemia can correlate with hypocalcaemia</td>
<td>Clinical manifestations of hypomagnesaemia, need for cautious use in patients receiving esomeprazole for prolonged duration, esomeprazole for with digoxin, regular monitoring of magnesium levels have been described in section 4.4 Special warnings and</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------</td>
</tr>
</tbody>
</table>
| Esomeprazole 20 mg and 40 mg gastro-resistant tablets                         | precautions for use  
Hypomagnesaemia has been added as undesirable effect in section 4.8 Undesirable effects                                                                                                                                                                                                                                                                          |                                        |
| Bronchospasm                                                                  | Bronchospasm has been added as undesirable effect in section 4.8 Undesirable effects                                                                                                                                                                                                                                                                                | None                                  |
| Hepatic failure and Hepatic encephalopathy in patients with pre-existing liver disease | Recommendation of prescribing esomeprazole at maximum dose of 20 mg has been specified in section 4.2 Posology and method of administration  
Hepatic failure and Hepatic encephalopathy has been added as undesirable effect in section 4.8 Undesirable effects                                                                                                                                                                      | None                                  |
| Erythema multiforme, Stevens-Johnson syndrome and Toxic epidermal necrolysis | Erythema multiforme, Stevens-Johnson syndrome and Toxic epidermal necrolysis has been added as undesirable effect in section 4.8 Undesirable effects                                                                                                                                                                                                 | None                                  |
| Fracture of the hip, wrist or spine                                           | Information regarding occurrence of fracture and cautious use has been specified in section 4.4 Special warnings and precautions for use  
Fracture of the hip, wrist or spine has been added as undesirable effect in section 4.8 Undesirable effects                                                                                                                                                                                                | None                                  |
| Interstitial nephritis                                                        | Recommendation of cautious use in patients with severe renal impairment has been specified in section 4.2 Posology and method of administration  
Interstitial nephritis has been added as undesirable effect in section 4.8 Undesirable effects                                                                                                                                                                                                                           | None                                  |
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of esomeprazole with neflunavir or atazanavir</td>
<td>As per Section 4.3 (Contraindications) and section 4.5 (Interaction with other medicinal products and other forms of interaction) of SPC as well as Section 2 (What you need to know before you take this medicine) of PIL, Concomitant use of esomeprazole with neflunavir or atazanavir is contraindicated.</td>
<td>None</td>
</tr>
<tr>
<td>Gastrointestinal infection</td>
<td>As per Section 4.4 (Special warnings and precautions for use), treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter. Gastrointestinal candidiasis has been added as rare adverse effect in section 4.8 (Undesirable effects) of SPC.</td>
<td>None</td>
</tr>
</tbody>
</table>

### IV.7 Discussion on the clinical aspects

The grant of Marketing Authorisations is recommended for these applications.

### V User consultation

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results show that the package leaflet 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 is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
Annex 1  Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y/N (version)</td>
</tr>
</tbody>
</table>