OMEPRAZOLE 10 MG, 20 MG AND 40 MG GASTRO-RESISTANT HARD CAPSULES

(omeprazole)

PL 36884/0001, PL 36884/0002, PL 36884/0003, PL 36884/0004, PL 36884/0005 AND PL 36884/0006

UKPAR

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LAY SUMMARY
Omeprazole 10 mg, 20 mg and 40 mg gastro-resistant hard capsules
(omeprazole)

This is a summary of the public assessment report (PAR) for Omeprazole 10 mg gastro-resistant hard capsules (PL 36884/0001 and PL 36884/0004), Omeprazole 20 mg gastro-resistant hard capsules (PL 36884/0002 and PL 36884/0005) and Omeprazole 40 mg gastro-resistant hard capsules (PL 36884/0003 and PL 36884/0006). It explains how Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules. For practical information about using Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules, patients should read the Patient Information Leaflet or contact their doctor or pharmacist.

What are Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules and what are they used for?

Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules contain the active substance omeprazole. Omeprazole works by reducing the amount of acid produced in the stomach. These medicines are prescribed to treat the following conditions in adults:

- Gastro-esophageal reflux disease (GERD). This is where acid from the stomach escapes into the gullet (the tube which connects the throat to the stomach) causing pain, inflammation and heartburn.
- Ulcers in the upper part of the intestine (duodenal ulcer) or stomach (gastric ulcer).
- Ulcers which are infected with bacteria called Helicobacter pylori. If this condition is present, the doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.
- Ulcers caused by medicines called NSAIDs (Non-Steroidal Anti-Inflammatory Drugs). Omeprazole can also be used to stop ulcers from forming if NSAIDs are being taken.
- Too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome)

These medicines are prescribed to treat the following conditions in children over 1 year of age weighing up to 10 kg:

- Gastro-esophageal reflux disease (GERD). In children, the symptoms of the condition can include the return of stomach contents into the mouth, being sick (vomiting) and poor weight gain.

These medicines are prescribed to treat the following conditions in children over 4 years of age:

- Ulcers which are infected with bacteria called Helicobacter pylori. If this condition is present, the doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.

Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules are generic medicines. This means that they are similar to reference medicines already authorised in the European Union (EU) called Losec 10 mg, 20 mg and 40 mg hard gastro-resistant capsules in the UK.
How do Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules work?

Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules belong to a group of medicines called proton pump inhibitors. They work by reducing the amount of acid produced by the stomach.

How are Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules used?

These particular medicines can only be obtained with a prescription from a pharmacy. The prescribed dose is dependent on the condition for which treatment is required. It is recommended that the capsules are taken in the morning. Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules should preferably be taken without food and swallowed whole with half a glass of water. The capsule contents must not be crushed or chewed as they contain coated pellets which stop the medicine from being broken down by the acid in the stomach. However, in the event of difficulty in swallowing, the capsule may be opened and the pellets swallowed whole with water.

Please read Section 3 of the Patient Information Leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

What benefits of Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules have been shown in studies?

Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules are generic medicines; therefore studies in patients have been limited to tests to determine that this medicine is bioequivalent to the UK medicine Losec 10 mg, 20 mg and 40 mg hard gastro-resistant capsules. Two medicines are bioequivalent when they produce the same levels of the active substance in the body for the same duration of action.

What are the possible side effects from Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules?

Because Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules are generic medicines and these medicines are considered to be bioequivalent to the UK reference medicine Losec 10 mg, 20 mg and 40 mg hard gastro-resistant capsules, the benefits and possible side effects are taken therefore as being the same as those of the reference medicine.

A full list of all the potential side effects for Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules can be found in Section 4 of the Patient Information Leaflet.
Why are Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules approved?

It was concluded that, in accordance with EU requirements, Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules have been shown to have comparable quality and to be comparable to the UK reference medicines Losec 10 mg, 20 mg and 40 mg hard gastro-resistant capsules. Therefore it was decided that, that, as with the reference medicine, its benefits are greater than its risks and it was recommended that they can be approved to help reduce the amount of acid that the stomach produces.

What measures are being taken to ensure the safe and effective use of Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules?

Safety information has been included in the Summary of Product Characteristics and in the Patient Information Leaflet for Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules

Marketing Authorisations were granted in the UK on 06 August 2014. For more information about treatment with Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules, read the Patient Information Leaflet, or contact your doctor or pharmacist.

This summary was last updated in September 2014. The full PAR for Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules follows this summary.
OMEPRAZOLE 10 MG, 20 MG AND 40 MG GASTRO-RESISTANT HARD CAPSULES

PL 36884/0001, PL 36884/0002, PL 36884/0003, PL 36884/0004, PL 36884/0005 AND PL 36884/0006

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Marketing Authorisations to Morpharma Ltd for the medicinal products Omeprazole 10 mg gastro-resistant hard capsules (PL 36884/0001 and PL 36884/0004), Omeprazole 20 mg gastro-resistant hard capsules (PL 36884/0002 and PL 36884/0005) and Omeprazole 40 mg gastro-resistant hard capsules (PL 36884/0003 and PL 36884/0006) on 06 August 2014.

These applications for Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules were submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the EU reference product, Mopral 10 mg and 20 mg microgranules gastro-résistants en gélule (gastro-resistant capsules), authorised to AstraZeneca (France) on 13 March 1996 and 15 April 1987 respectively and Losec 40 maagsapresistente Capsules authorised to AstraZeneca B.V. Zoetermeer on 14 June 1991. The corresponding UK reference products are Losec 10 mg, 20 mg and 40 mg capsules. Losec 10 mg (PL 00017/0337), 20 mg (PL 00017/0238) and 40 capsules (PL 00017/0320) were granted Marketing Authorisations to Astra Pharmaceuticals Limited on 06 January 1994, 09 May 1989 and 10 September 1992, respectively. Following a change of ownership the Marketing Authorisations were transferred to the current Marketing Authorisation Holder, AstraZeneca UK Limited on 14 June 2002 (Losec 10 mg; PL 17901/0132, 20 mg; PL 17901/0133 and 40 mg; PL 17901/0134). The reference products have been authorised in the EEA for at least 10 years, therefore, the legal basis of these applications is acceptable.

Omeprazole 10, 20 and 40 mg gastro-resistant hard capsules are prescription only medicines (legal basis POM) and are indicated for the following conditions:

**Adults**
- Treatment of duodenal ulcers
- Prevention of relapse of duodenal ulcers
- Treatment of gastric ulcers
- Prevention of relapse of gastric ulcers
- In combination with appropriate antibiotics, *Helicobacter pylori* (*H. pylori*) eradication in peptic ulcer disease
- Treatment of NSAID-associated gastric and duodenal ulcers
- Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk
- Treatment of reflux esophagitis
- Long-term management of patients with healed reflux esophagitis
- Treatment of symptomatic gastro-esophageal reflux disease
- Treatment of Zollinger-Ellison syndrome

**Paediatric use**

*Children over 1 year of age and ≥ 10 kg*
- Treatment of reflux esophagitis
- Symptomatic treatment of heartburn and acid regurgitation in gastro-esophageal reflux disease

*Children and adolescents over 4 years of age*
• In combination with antibiotics in treatment of duodenal ulcer caused by *H. pylori*.

The active substance in Omeprazole 10 mg, 20 mg and 40 mg gastro-resistant hard capsules is omeprazole. Omeprazole, a racemic mixture of two enantiomers, reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.

Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H+ K+-ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.

With the exception of the two pharmacokinetic studies comparing the Marketing Authorisation Holder’s Omeprazole 20 mg gastro-resistant hard capsules versus the reference product Mopral 20 mg Capsules and Omeprazole 40 mg gastro-resistant hard capsules versus the reference product Losec 40 mg capsules, no new clinical studies were conducted. This is acceptable given that these applications were based on being generic medicinal products of reference products that have been licensed for over 10 years. The pharmacokinetic studies were carried out in accordance with Good Clinical Practice (GCP).

The MHRA 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.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Omeprazole

INN: Omeprazole
Chemical name: (RS)-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-
sulfinyl]-1H-benzimidazole

Structure:

```
\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}
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Molecular formula: C_{17}H_{19}N_{3}O_{3}S
Molecular weight: 345.42
Physical form: White or almost white powder
Solubility: Very slightly soluble in water, soluble in methylene chloride, sparingly
soluble in alcohol and methanol. It dissolves in dilute solutions of alkali
hydroxides.

Omeprazole is the subject of a European Pharmacopoeia monograph.

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

DRUG PRODUCT
Other ingredients

Other ingredients consist of the following pharmaceutical excipients: Hypromellose, talc, titanium
dioxide (E171), methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30% (also containing sodium
lauroylsulfate and polysorbate 80), triethylcitrate, ethylcellulose, oleic acid, colloidal anhydrous silica,
sugar spheres (sucrose and maize starch), gelatin, printing ink (shellac and black iron oxide (E172).

With the exception of the ethylcellulose aqueous dispersion and the printing ink (shellac and black iron
oxide E172), all excipients used comply with their respective European Pharmacopoeia monograph.
Ethylcellulose aqueous dispersion and the printing ink (shellac and black iron oxide E172) are tested
against the requirements of the USP/NF. The colouring agents used comply with EU Directive 95/45/EC
and ICH/283/95, concerning the use of colours in foodstuff.

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

With the exception of gelatine and oleic acid, none of the excipients contain materials of animal or
human origin. The suppliers of gelatin and oleic acid have provided Certificates of Suitability from the
European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that they are
manufactured in line with current European guideline concerning minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

**Pharmaceutical development**

The objective of the pharmaceutical development programme was to produce robust and safe products containing omeprazole that are similar in physico-chemical characteristics and bioequivalent to the reference products.

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the applicant’s products versus the reference products.

**Manufacture**

A satisfactory batch formula has been provided for the manufacture of omeprazole capsules, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product.

Process validation has been carried out on three production-scale batches of pellets and three batches of capsules. The results are satisfactory.

**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. Certificates of Analysis have been provided for all working standards used.

**Container Closure System**

The finished product is packaged in a high density polyethylene container with a screw-cap tamper–evident closure and containing a desiccant capsule.

Omeprazole 10 mg and 20 mg gastro-resistant hard capsules are available in pack sizes of 14 and 28 capsules. Omeprazole 40 mg gastro-resistant capsules are available in pack sizes of 7, 14 and 28 capsules.

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

**Stability**

Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 3 years for the unopened bottle (container) and 28 days once opened, with storage conditions of “Do not store above 30°C” and “Keep the bottle tightly closed in order to protect from moisture”.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPCs, PIL and labels are acceptable from a pharmaceutical perspective.

The results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC (as amended) for the package leaflet were provided. 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 it contains.

MAA form

The MAA forms are satisfactory from a pharmaceutical perspective.

Expert report (Quality Overall Summary)

The applicant’s quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

NON-CLINICAL ASSESSMENT

As the pharmacodynamic, pharmacokinetic and toxicological properties of omeprazole are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate literature review of the product’s pharmacology and toxicology.

A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this product is intended for generic substitution with products currently marketed, the environmental burden is not expected to increase. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

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

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

In support of these applications, the Marketing Authorisation Holder has submitted two bioequivalence studies, as presented below:

Study 1:
A single and multiple dose, open-label, randomised, 2-period, 2-sequence crossover study, comparing the pharmacokinetics of the test product Omeprazole 20 mg Capsules and the
reference product Mopral 20 mg Capsules in healthy volunteers under fasting conditions following a single and multiple oral dose administration and under fed conditions after a multiple oral dose administration.

The trial was conducted in two separate groups. In each study period the subject received a multiple 20 mg dose of either the test or reference drug formulation once daily on 7 consecutive days under fasting conditions with 240ml of water. An 8th dose was administered on the morning of the 8th day, thirty minutes after a high fat breakfast. For group 1 each study period was separated by a washout period of 17 days. For group 2 each study period was separated by a washout period of 15 days.

Samples were taken at pre-dose and up to 24 hours post dose.

A summary of the main pharmacokinetic results for this study is presented below:

**Single-dose Fast (Day 1):**

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GEOMETRIC LS MEANS</th>
<th>RATIO</th>
<th>90% CONFIDENCE LIMITS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TEST</td>
<td>REFERENCE</td>
<td>LOWER</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>246.59</td>
<td>247.07</td>
<td>100.61</td>
</tr>
<tr>
<td>A&lt;sub&gt;UC&lt;/sub&gt;</td>
<td>381.99</td>
<td>381.94</td>
<td>99.78</td>
</tr>
<tr>
<td>A&lt;sub&gt;UC&lt;/sub&gt;</td>
<td>396.81</td>
<td>400.55</td>
<td>99.02</td>
</tr>
</tbody>
</table>

**Multiple-dose Fast (Day 7)**

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GEOMETRIC LS MEANS</th>
<th>RATIO</th>
<th>90% CONFIDENCE LIMITS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TEST</td>
<td>REFERENCE</td>
<td>LOWER</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>399.38</td>
<td>416.94</td>
<td>95.79</td>
</tr>
<tr>
<td>A&lt;sub&gt;UC&lt;/sub&gt;</td>
<td>702.82</td>
<td>762.89</td>
<td>92.13</td>
</tr>
<tr>
<td>A&lt;sub&gt;UC&lt;/sub&gt;</td>
<td>725.85</td>
<td>806.41</td>
<td>90.01</td>
</tr>
</tbody>
</table>
Multiple-dose Fed (Day 8)

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GEOMETRIC LS MEANS</th>
<th>RATIO</th>
<th>90% CONFIDENCE LIMITS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TEST</td>
<td>REFERENCE</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>207.80</td>
<td>214.36</td>
<td>96.94</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$</td>
<td>511.06</td>
<td>564.95</td>
<td>90.46</td>
</tr>
<tr>
<td>$\text{AUC}_{\text{tot}}$</td>
<td>540.94</td>
<td>599.59</td>
<td>90.22</td>
</tr>
</tbody>
</table>

$\text{AUC}_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
$C_{\text{max}}$ maximum plasma concentration

The 90% confidence interval of the test/reference ratio for $\text{AUC}_{0-t}$, and $C_{\text{max}}$ was within the pre-defined limits of 80.00-125.00%, as specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). In conclusion, bioequivalence has been demonstrated between Omeprazole 20 mg Capsules and Mopral 20 mg Capsules.

Study 2:

An open-label, single centre, single-dose, randomised, laboratory-blinded, crossover study comparing the pharmacokinetics of the test product Omeprazole 40 mg Capsules versus the reference product Losec 40 mg Capsules in healthy volunteers under fasting conditions.

Following an overnight fast, a single oral dose of the assigned formulation was administered with 240ml of water at ambient temperature. Samples were taken at pre-dose and up to 12 hours post dose. There was a washout period of 7 days between treatment periods.

A summary of the main pharmacokinetic results for this study is presented below:
Comparison of Results with Standards for Bioequivalence

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>TEST</th>
<th>REFERENCE</th>
<th>F (treatment)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN</td>
<td>C.V.</td>
<td>MEAN</td>
<td>C.V.</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>838.16</td>
<td>59.0</td>
<td>810.38</td>
<td>63.1</td>
</tr>
<tr>
<td>ln (C&lt;sub&gt;max&lt;/sub&gt;) (ng/mL)</td>
<td>6.5332</td>
<td>10.5</td>
<td>6.4975</td>
<td>10.4</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (hours)</td>
<td>2.00</td>
<td>43.4</td>
<td>1.75</td>
<td>47.8</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;T&lt;/sub&gt; (ng·h/mL)</td>
<td>1482.46</td>
<td>91.4</td>
<td>1554.44</td>
<td>96.6</td>
</tr>
<tr>
<td>ln (AUC&lt;sub&gt;T&lt;/sub&gt;) (ng·h/mL)</td>
<td>7.0000</td>
<td>11.1</td>
<td>7.0361</td>
<td>11.2</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;∞&lt;/sub&gt; (ng·h/mL)*</td>
<td>1572.10</td>
<td>93.0</td>
<td>1648.48</td>
<td>98.2</td>
</tr>
<tr>
<td>ln (AUC&lt;sub&gt;∞&lt;/sub&gt;) (ng·h/mL)*</td>
<td>7.0670</td>
<td>10.8</td>
<td>7.1122</td>
<td>10.6</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;T&lt;/sub&gt;/&lt;sub&gt;∞&lt;/sub&gt; (%)*</td>
<td>99.22</td>
<td>1.3</td>
<td>99.32</td>
<td>1.2</td>
</tr>
<tr>
<td>K&lt;sub&gt;e&lt;/sub&gt; (hour&lt;sup&gt;-1&lt;/sup&gt;)*</td>
<td>0.9014</td>
<td>31.4</td>
<td>0.8745</td>
<td>33.7</td>
</tr>
<tr>
<td>T&lt;sub&gt;½&lt;/sub&gt; (hours)*</td>
<td>0.89</td>
<td>50.9</td>
<td>0.91</td>
<td>47.4</td>
</tr>
</tbody>
</table>

For T<sub>max</sub>, the median is presented and the statistical analysis is based on ranks.
N.S. = Not Significant (p> 0.05)

* n=49

The 90% confidence interval of the test/reference ratio for AUC<sub>T</sub>/<sub>∞</sub>, and C<sub>max</sub> was within the pre-defined limits of 80.00-125.00%, as specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). In conclusion, bioequivalence has been demonstrated between Omeprazole 40 mg Capsules and Losec® 40 mg Capsules.

As the 10 mg, 20 mg and 40mg strengths of product meet all the criteria as specified in the Guideline on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results from the 20 mg strength and 40 mg strength can be extrapolated to the 10 mg strength.

**Efficacy**

No new data on efficacy have been submitted and none are required for these types of applications.
SAFETY
With the exception of the data submitted during the bioequivalence studies, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.

PHARMACOVIGILANCE SYSTEM/RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant 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.

EXPERT REPORT
The applicant’s clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
These are consistent with the SmPCs for the reference products and are satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORM (MAA)
These are satisfactory.

CONCLUSION
The grant of Marketing Authorisations is recommended for these applications.

OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Omeprazole 10 mg, 20 mg and 40 mg gastro-resistant hard capsules 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 and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s products and its respective reference products. As the 20 mg and 40 mg products meet all the criteria as specified in the Guideline on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results of the 20 mg and 40 mg strength can be extrapolated to the 10 mg strength capsules.
No new or unexpected safety concerns arose from these applications.

The SmPC, PIL and labelling are satisfactory, and consistent with those for the reference products.

**BENEFIT/RISK ASSESSMENT**
The quality of the products is acceptable, and no new non-clinical or new clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant’s products and the reference products. Extensive clinical experience with omeprazole is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is, therefore, considered to be positive.
**OMEPRAZOLE 10 MG, 20 MG AND 40 MG GASTRO-RESISTANT HARD CAPSULES**

PL 36884/0001, PL 36884/0002, PL 36884/0003, PL 36884/0004, PL 36884/0005 AND PL 36884/0006

**STEPS TAKEN FOR ASSESSMENT**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 02 December 2010</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant, the MHRA considered the applications valid 14 January 2011</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications, the MHRA requested further information relating to the dossiers 20 April 2011, 03 October 2011, 19 January 2012, 06 July 2012 and 22 November 2013</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 16 September 2011, 04 January 2012, 14 June 2012, 06 January 2013 and 03 June 2014</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 06 August 2014</td>
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</tbody>
</table>
OMEPAZOLE 10 MG, 20 MG AND 40 MG GASTRO-RESISTANT HARD CAPSULES

PL 36884/0001, PL 36884/0002, PL 36884/0003, PL 36884/0004, PL 36884/0005 AND PL 36884/0006

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
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Outcome
Summary of Product Characteristics and Patient Information Leaflet
The current approved UK versions of the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PIL) for these products are available on the MHRA website.
Labelling

PL 36884/0001
UKPAR Omeprazole 10 mg, 20 mg and 40 mg gastro-resistant hard Capsules

Each capsule contains 10 mg omeprazole. See also: Do not store above 30°C. Keep the container tightly closed in order to protect from moisture. Do not use after 28 days after first opening. Use as directed by the physician. Read the package leaflet before use. Metropharma GmbH, Tems Lane, Welwyn Garden City, Herts, AL7 1NJ, UK.

PL 36884/0001

Batch No.:
Dataline: 14446212581979

Product licence number: PL 36884/0001

Plastic Residue Testing

Omeprazole 10mg gastro-resistant capsules
28 Capsules

10 mg

Omeprazole 10mg gastro-resistant capsules
28 Capsules

10 mg

Omeprazole 10mg gastro-resistant capsules
28 Capsules

10 mg

READ DIRECTION

Omeprazole 10mg gastro-resistant capsules
28 Capsules

10 mg

Omeprazole 10mg gastro-resistant capsules
28 Capsules

10 mg

Plastic Residue Testing
UKPAR Omeprazole 10 mg, 20 mg and 40 mg gastro-resistant hard Capsules

PL 36884/0002
UKPAR Omeprazole 10 mg, 20 mg and 40 mg gastro-resistant hard Capsules

PL 36884/0003

Each capsule contains 40 mg omeprazole.
Contains sucrose. See leaflet for further information.
Keep out of the reach and sight of children.
Do not use above 30°C.
Keep the container tightly closed in order to protect from moisture.
Use as directed by the physician.
Read the package leaflet before use.

Omeprazole 40mg Gastro-resistant Capsules
7 Capsules
UKPAR Omeprazole 10 mg, 20 mg and 40 mg gastro-resistant hard Capsules

Omeprazole 10 mg
Gastro-resistant Capsules

Each capsule contains 10 mg omeprazole.

Contra-indications, Warnings, Precautions. See leaflet for full information.

Do not store above 30°C.

Keep out of the reach and sight of children.

Do not store above 30°C.

Keep the container tightly closed in order to protect from moisture. Do not use after the expiry date.

See leaflet for further information.

PL 36884/0001

Pack of 28 capsules

Mophar Ltd, Binlon, Wembley, Middlesex HA9 1NN, UK

Date of printing: 01/05/2005

Date of last revision: 01/05/2005
UKPAR Omeprazole 10 mg, 20 mg and 40 mg gastro-resistant hard Capsules

Each capsule contains 40mg omeprazole. Contains sucrose. See leaflet for further information.

Uses:
- Do not open above 30°C.
- Keep the container tightly closed in order to protect from humidity. Do not store after 28 days after first opening.

Use as directed by the physician. Read the package leaflet before use.

Plasmapharma Ltd, Ens Lane, Wethersley, Middlesex HA9 3HN, UK

PL 36844/0001

Batch No:

Expiry Date:

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