Public Assessment Report

Decentralised Procedure

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

(Omeprazole)

Procedure No: UK/H/4493/001-3/DC
UK/H/5025/001-3/DC
UK/H/5040/001-3/DC

UK Licence No: PL 00289/1469-71, 1654-6 & 1658-60

TEVA UK LIMITED.
LAY SUMMARY

On 01 August 2012, Austria, Belgium, Germany, Denmark, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Luxembourg, Netherlands, Norway, Sweden and the UK agreed to grant Marketing Authorisations to Teva UK Limited for the medicinal products Omeprazole 10 mg, 20 mg and 40 mg Gastro-resistant hard Capsules (PL 00289/1469-71, 1654-6 & 1658-60; UK/H/4493, 5025 & 5040/001-3/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 25 October 2012. These are Prescription-Only Medicines (POM).

Omeprazole 10 mg, 20 mg and 40 mg Gastro-resistant Capsules are used 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 your throat to your 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 you have this condition, your 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). This medicine can also be used to stop ulcers from forming if you are taking NSAIDs.
- Too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome).

In children:

Children over 1 year of age and who weigh more than or equal to (≥) 10 kg:
- Gastro-esophageal reflux disease (GERD). 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. In children, the symptoms of the condition can include the return of stomach contents into the mouth (regurgitation), being sick (vomiting) and poor weight gain.

Children and adolescents over 4 years of age:
- Ulcers which are infected with bacteria called ‘Helicobacter pylori’. If your child has this condition, your doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.

No new or unexpected safety concerns arose from these applications and it was judged that the benefits of taking Omeprazole 10 mg, 20 mg and 40 mg Gastro-resistant hard Capsules outweigh the risks and therefore Marketing Authorisations were granted.
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## Module 1

| **Product Name** | Omeprazole 10 mg Gastro-resistant hard Capsules  
Omeprazole 20 mg Gastro-resistant hard Capsules  
Omeprazole 40 mg Gastro-resistant hard Capsules |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1 and 10.3 (for Spain [10 mg &amp; 40 mg], Austria [10mg], Hungary [10 mg] and Belgium [10 mg] only).</td>
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<tr>
<td><strong>Active Substances</strong></td>
<td>Omeprazole</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Gastro-resistant hard capsules</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>10 mg, 20 mg and 40 mg.</td>
</tr>
</tbody>
</table>
| **MA Holder** | Teva UK Limited  
Brampton Road,  
Hampden Park,  
Eastbourne,  
East Sussex BN22 9AG  
UK |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | UK/H/4493/01-2/DC:Austria, Belgium, Germany, Denmark, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Luxembourg, Netherlands, Norway & Sweden |
| | UK/H/4493/03/DC:Austria, Belgium, Germany, Denmark, Greece, Spain, Finland, Hungary, Ireland, Italy, Luxembourg, Netherlands, Norway & Sweden |
| | UK/H/5025/01-2/DC: Germany, Spain, Finland, France, Netherlands and Sweden |
| | UK/H/5025/03/DC: Germany, Spain, Finland, Netherlands and Sweden |
| | UK/H/5040/01-3/DC: Germany and Spain |
| **Procedure Number** | UK/H/4493/001-3/DC  
UK/H/5025/001-3/DC  
UK/H/5040/001-3/DC |
| **Timetable** | Day 210– 01 August 2012. |
Module 2

Summary of Product Characteristics

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.
Module 3
Patient Information Leaflet

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.
Module 4
Labelling

The following labelling is the approved mock-up labelling for procedure numbers UK/H/4493/01-03/DC (PL 00289/1469-71) and is included as representative labelling. The mock-up labelling for procedures UK/H/5025 and 5040/01-3/DC (PL 00289/1654-6 and 1654-6) is consistent with this labelling:

Carton:
Blister:
Carton:

Blister:
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 Omeprazole 10 mg, 20 mg and 40 mg Gastro-resistant hard Capsules (PL 00289/1469-71, 1654-6 & 1658-60; UK/H/4493, 5025 & 5040/001-3/DC) could be approved. These applications were submitted via the decentralised procedure, with the UK as Reference Member State (RMS) and Austria, Belgium, Germany, Denmark, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Luxembourg, Netherlands, Norway and Sweden as Concerned Member States (CMS). These products are prescription-only medicines (POM).

Omeprazole 10 mg, 20 mg and 40 mg Gastro-resistant hard Capsules are indicated for:

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 oesophagitis
- Long-term management of patients with healed reflux oesophagitis
- Treatment of symptomatic gastro-oesophageal reflux disease
- Treatment of Zollinger-Ellison syndrome.

Paediatric use:
Children over 1 year of age and ≥10 kg:
- Treatment of reflux oesophagitis.
- Symptomatic treatment of heartburn and acid regurgitation in gastrooesophageal reflux disease.

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

These are abridged applications submitted under Article 10(1) and 10(3) [in Spain (10 mg and 40 mg strengths), Austria (10 mg strength only), Hungary (10 mg strength only) and Belgium (10 mg strength only)] of Directive 2001/83/EC as amended, cross-referring to Losec Capsules 10 mg, 20 mg and 40 mg (AstraZeneca UK Ltd), which were first authorised in the EEA on 01 May 1989 (20 mg), 06 January 1994 (10 mg) and 10 September 1992 (40 mg), respectively. The reference products have been registered in the EEA for more than 10 years, hence the period of data exclusivity has expired.

Omeprazole, a proton pump inhibitor and 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.

No new non-clinical studies were conducted, which is acceptable given that the products are intended to be generic and hybrid versions of the originator products that have been licensed for over 10 years.

One bioequivalence study (single dose) was submitted to support these applications, comparing the test product Omeprazole 40 mg Gastro-resistant hard Capsules (Teva UK Limited) with the reference product Losec 40 mg Capsules (AstraZeneca AB).

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were for products that are intended to be generic and hybrid versions of the originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with 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, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 01 August 2012. After the subsequent national phase, the licences were granted in the UK on 25 October 2012.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Omeprazole 10 mg Gastro-resistant hard Capsules  
| Name(s) of the active substance(s) (INN) | Omeprazole  
| Pharmacotherapeutic classification (ATC code) | Proton pump inhibitors (A02B C01).  
| Pharmaceutical form and strength(s) | 10 mg, 20 mg and 40 mg gastro-resistant capsule, hard.  
| Reference numbers for the Mutual Recognition Procedure | UK/H/4493/001-3/DC  
| | UK/H/5025/001-3/DC  
| | UK/H/5040/001-3/DC  
| Reference Member State | United Kingdom  
| Concerned Member State | UK/H/4493/01-2/DC:Austria, Belgium, Germany, Denmark, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Luxembourg, Netherlands, Norway & Sweden  
| | UK/H/4493/03/DC:Austria, Belgium, Germany, Denmark, Greece, Spain, Finland, Hungary, Ireland, Italy, Luxembourg, Netherlands, Norway & Sweden  
| | UK/H/5025/01-2/DC: Germany, Spain, Finland, France, Netherlands and Sweden  
| | UK/H/5025/03/DC: Germany, Spain, Finland, Netherlands and Sweden  
| | UK/H/5040/01-3/DC: Germany and Spain  
| Marketing Authorisation Number(s) | PL 00289/1469-71, 1654-6 & 1658-60  
| Name and address of the authorisation holder | Teva UK Limited  
| | Brampton Road,  
| | Hampden Park,  
| | Eastbourne,  
| | East Sussex BN22 9AG  
| | UK  

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Omeprazole
Chemical names: 5-Methoxy-2-[(RS)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]1Hbenzimidazole

Structure:

\[
\text{Molecular formula: } C_{17}H_{19}N_{3}O_{3}S \\
\text{Molecular mass: } 345.4 \\
\text{Appearance: } \text{Omeprazole is a white or almost white powder, sensitive to light.} \\
\text{Solubility: } \text{Omeprazole is very slightly soluble in water, soluble in methylene chloride, sparingly soluble in ethanol and methanol and dissolves in dilute solutions of alkaline hydroxides.}
\]

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 (EDQM) Certificate of Suitability.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients sugar spheres (sucrose and corn starch), sodium starch glycolate, sodium laurilsulfate, povidone, trisodium phosphate dodecahydrate, hypromellose, methacrylic acid - ethyl acrylate copolymer (1:1), triethyl citrate, sodium hydroxide, titanium dioxide, talc, erythrosine (E127), water, gelatin, quinoline yellow (E104), shellac, polyvinylpyrrolidone, propylene glycol and sodium hydroxide. In addition:

- the 10 mg strength also contains red oxide yellow (E172);
- the 20 and 40 mg strengths also contain indigo carmine (E132).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of trisodium phosphate which is controlled to National Formulary (NF) specifications. Satisfactory certificates of analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that it is manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).
No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**
The objective of the development programme was to formulate stable, robust, gastro-resistant hard capsules containing 10 mg, 20 mg or 40 mg omeprazole, which could be considered generic and hybrid medicinal products of Losec Capsules 10 mg, 20 mg and 40 mg (AstraZeneca UK Ltd).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale on all strengths and has shown satisfactory results. In addition the Marketing Authorisation Holder (MAH) has committed to performing process validation on future additional commercial scale batches.

**Finished Product Specification**
The proposed finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**
All strengths of the finished product are packaged in:
- high density polyethylene bottles with tamper-proof child-resistant lids containing integral desiccant and are available in pack sizes of 5, 7, 14, 15, 20, 21, 28, 30, 42, 50, 56 (2x28), 60 (2x30), 84 (2x42), 90 (3x30), 98 (7x14), 100 (2x50), 250 (5x50) or 500 (10x50) capsules.
- Aluminium/aluminium foil blisters in pack sizes of 5, 7, 14, 15, 20, 21, 25, 28, 30, 35, 42, 50, 50x1 hospital pack, 56, 60, 98, or 100 capsules.

It has been stated that not all pack sizes may be marketed. However, the Marketing Authorisation Holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

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 food.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for both presentations (bottles and blisters) which reduces to 50 days (10 mg and 40 mg strength) and 56 days (20 mg strength) after first opening for the blister pack presentations only with the storage conditions:
Blister packs:
- ‘Store below 30°C in the original package in order to protect from moisture.’
Bottles:
- For the bottles; Store below 30°C. Keep the bottle tightly closed in order to protect from moisture

**Bioequivalence/bioavailability**
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPCs, PIL and labels are acceptable.

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 it contains.

**Marketing Authorisation Application (MAA) form**
The MAA forms are satisfactory.

**Quality Overall Summary**
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
There are no objections to the approval of these products from a pharmaceutical view-point.

**III.2 NON-CLINICAL ASPECTS**
As the pharmacodynamic, pharmacokinetic and toxicological properties of omeprazole are well-known, no new 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 review of the relevant pharmacology and toxicology.

Since Omeprazole 10 mg, 20 mg and 40 mg Gastro-resistant hard Capsules are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment (ERA) is therefore not deemed necessary.

There are no objections to the approval of these products from a non-clinical view-point.

**III.3 CLINICAL ASPECTS**

**Pharmacokinetics**
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open label, single-dose, single-centre study with a clinical phase under fed conditions (crossover replicate design, four-period, four-sequence) and a second clinical phase under fasting conditions (crossover design, two-period, two-sequence) to compare the pharmacokinetics of the test product Omeprazole 40 mg Gastro-resistant
hard Capsules (Teva UK Limited) versus the reference product Losec 40 mg Capsules (AstraZeneca AB).

All volunteers received a single oral dose of either the test or reference product as a 1 x 40 mg capsule. During the first phase (fed conditions), volunteers were given a high fat breakfast and 240 ml of water approximately 20 minutes prior to dosing. During the second phase (fasting conditions) the drug was administered after an overnight fast. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 24 hours (phase 1-fed conditions) and 14 hours (phase 2-fed conditions) post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for omeprazole under fed conditions (phase 1) are presented below [mean value, ±Standard deviation (±SD) and 90% confidence intervals]:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀₋₄ ng/ml/h</th>
<th>AUC₀₋∞ ng/ml/h</th>
<th>C_max ng/ml</th>
<th>t_max h</th>
<th>T½ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1828.21</td>
<td>1883.27</td>
<td>662.67</td>
<td>5.16</td>
<td>1.26</td>
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<tr>
<td>Reference</td>
<td>1973.40</td>
<td>1996.49</td>
<td>702.52</td>
<td>4.70</td>
<td>1.26</td>
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</table>

*Ratio (90% CI) 93.91 (88.59 – 99.56) 94.34 (89.08 – 99.92) 93.62 (84.58 - 103.62)

AUC₀₋∞ area under the plasma concentration-time curve from time zero to infinity
AUC₀₋₄ area under the plasma concentration-time curve from time zero to t hours
C_max maximum plasma concentration
T_max time for maximum concentration
T½ half-life
* ln-transformed values

The pharmacokinetic results for omeprazole under fasting conditions (phase 2) are presented below [mean value, ±Standard deviation (±SD) and 90% confidence intervals]:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀₋₄ ng/ml/h</th>
<th>AUC₀₋∞ ng/ml/h</th>
<th>C_max ng/ml</th>
<th>t_max h</th>
<th>T½ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>2082.62</td>
<td>2125.93</td>
<td>877.60</td>
<td>2.15</td>
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<td>Reference</td>
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<td>2255.64</td>
<td>984.28</td>
<td>1.75</td>
<td>1.09</td>
</tr>
</tbody>
</table>

*Ratio (90% CI) 93.15 (88.33 – 98.24) 93.46 (88.60 – 98.57) 89.06 (80.07 – 99.07)

AUC₀₋∞ area under the plasma concentration-time curve from time zero to infinity
AUC₀₋₄ area under the plasma concentration-time curve from time zero to t hours
C_max maximum plasma concentration
T_max time for maximum concentration
T½ half-life
* ln-transformed values

The 90% confidence intervals for AUC and C_max for test versus reference product for omeprazole are within predefined acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/, Corr) in both the fed and fasting states. Thus, the data support the claim that the test product is bioequivalent to the reference product.
As the 10 mg, 20 mg and 40 mg strengths of the product meet the criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence study on the 40 mg strength can be extrapolated to the 10 mg and 20 mg strengths.

Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for these applications.

Efficacy
No new efficacy data were submitted and none were required for these applications.

Safety
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were highlighted by the bioequivalence data.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable. The SmPCs are consistent with that for the originator products. The PIL is consistent with the SmPCs and in line with current guidelines. The labelling is in-line with current guidelines.

MAA Forms
The MAA forms are satisfactory.

Clinical Overview
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and 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.

Conclusion
There are no objections to the approval of these products from a clinical view-point.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The 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. The pharmacodynamic, pharmacokinetic and toxicological properties of omeprazole are well-known.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type. Bioequivalence has been demonstrated between the applicant’s Omeprazole 40 mg Gastro-resistant hard Capsules ((Teva UK Limited) and its respective reference product Losec 40 mg Capsules (AstraZeneca AB). As the 10 mg, 20 mg, 40 mg strengths of the product meet the biowaiver criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence study on the 40 mg strength can be extrapolated to the 10 mg and 20 mg strengths.

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

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference products, and in line 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. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with omeprazole is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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