UKPAR IMODIUM LIQUICAPS 2MG SOFT CAPSULES
IMODIUM 2MG SOFT CAPSULES
PL 15513/0367
PL 15513/0369

UKPAR

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LAY SUMMARY

The MHRA granted McNeil Products Limited Marketing Authorisations (licences) for the medicinal products Imodium Liquicaps 2mg Soft Capsules and Imodium 2mg Soft Capsules on 4 September 2012. These products, to be available as general sales licence (PL 15513/0367) and pharmacy (PL 15513/0369) medicines, are to be used to treat short-term diarrhoea and diarrhoea associated with irritable bowel syndrome.

These products contain the active ingredient loperamide hydrochloride, a substance that helps reduce diarrhoea by slowing down an overactive bowel. This allows water and salts that are usually lost in diarrhoea to be absorbed by the body.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Imodium Liquicaps 2mg Soft Capsules and Imodium 2mg Soft Capsules outweigh the risks, hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA considered that the applications for Imodium Liquicaps 2mg Soft Capsules and Imodium 2mg Soft Capsules (PL 15513/0367 and 0369) could be approved. These are line-extensions to the existing UK product Imodium Capsules (PL 00242/0028).

The products are general sales licence (PL 15513/0367) and pharmacy (PL 15513/0369) medicines for the symptomatic treatment of:

- acute diarrhoea in adults and children aged 12 years and over.
- acute episodes of diarrhoea associated with Irritable Bowel Syndrome in adults aged 18 years and over following initial diagnosis by a doctor.

These applications were submitted according to Article 8.3 of 2001/83/EC, as amended, containing the known active substance loperamide hydrochloride. These products are line-extensions of Imodium 2mg Capsules (PL 00242/0028).

Loperamide is an anti-diarrhoeal agent that binds preferentially to the \( \mu \)-opiate receptor in the gut wall. It inhibits the release of acetylcholine and prostaglandins, thereby reducing propulsive peristalsis, and increasing intestinal transit time. In man, loperamide prolongs the transit time of intestinal contents, reduces the daily faecal volume, increases the viscosity and bulk density, and diminishes the loss of fluid and electrolytes. Loperamide increases the tone of the anal sphincter, thereby reducing incontinence and urgency.

No new preclinical data have been submitted with these applications, which is acceptable given that the applications use a known active substance that has been in clinical use for many years.

In support of these applications, the marketing authorisation holder has submitted a single bioequivalence study, comparing the proposed products with Imodium 2mg Quick Dissolve Tablets and Imodium 2mg Capsules (Janssen-Cilag).

With the exception of the bioequivalence study, no new clinical data have been submitted with these applications, which is acceptable considering that these are line-extensions to granted products that use a known active substance.

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.
PHARMACEUTICAL ASSESSMENT

S. Active substance
INN: Loperamide hydrochloride
Chemical name: 4-(4-chlorophenyl)-4-hydroxy-N,N-dimethyl-α,α-diphenyl-1-piperidinebutanamide monohydrochloride
Structure:

Molecular formula: C_{29}H_{33}ClN_{2}O_{2}.HCl
Molecular weight: 513.50
Appearance: White to almost white powder,
Properties: Slightly soluble in water, freely soluble in alcohol and in methanol. It shows polymorphism.

All aspects of the manufacture and control of the active substance loperamide hydrochloride have been covered by a European Pharmacopoeia Certificate of Suitability.

P. Medicinal Product
Other Ingredients
Other ingredients consist of the pharmaceutical excipients propylene glycol monocaprylate, propylene glycol, gelatin, glycerol 99%, brilliant blue (E133), soya lecithin, medium-chain triglycerides and purified water.

With the exception of propylene glycol monocaprylate, soya lecithin and brilliant blue (E133), all of the excipients comply with their respective European Pharmacopoeia monographs. Propylene glycol monocaprylate and soya lecithin comply with suitable US National Formulary specifications, and brilliant blue (E133) complies with EU Directive 95/45CE (concerning the use of colourants).

With the exception of gelatin, none of the excipients are sourced from animal or human origin. Suitable European Directorate for the Quality of Medicines Certificates of Suitability have been provided for all suppliers of gelatin, to show that the gelatin is sourced in compliance with current guidelines concerning the minimisation of risk of transmission of TSE/BSE. 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 a globally acceptable and stable additional pharmaceutical form of Imodium product, containing 2mg loperamide hydrochloride in a soft capsule.

A satisfactory account of the pharmaceutical development has been provided.

Comparative dissolution data have been provided for these products versus the originator product used in the bioequivalence study (Imodium 2mg Tablets).

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 and has shown satisfactory results.

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

Container-Closure System
The finished product is packaged in aluminium/polyvinylchloride/polyvinylidene chloride blisters in pack sizes of 6 soft capsules (PL 15513/0367) and 12 soft capsules (PL 15513/0369).

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 18 months, with the storage conditions “Do not store above 25°C” and “Store in the original package to protect from moisture. Keep blister in the outer carton to protect from light.”

Bioequivalence/bioavailability
The data from one bioequivalence study have been submitted with these applications.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPCs, PILs and labels are pharmaceutically 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 the package leaflet contains.
MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of marketing authorisations is recommended.
NON-CLINICAL ASSESSMENT

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

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

A suitable justification has been provided for non-submission of an environmental risk assessment. As these products contain active substance and excipients that have been used in the EU for many years, there is not considered to be a significant environmental risk. Further, as these products would compete with a view to being used in place of other loperamide hydrochloride products, 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 these products from a non-clinical viewpoint.
CLINICAL ASSESSMENT

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

A three-way crossover, blinded, single-dose, fasting, bioequivalence study of Loperamide HCl 2 mg Liquigel Capsules versus Imodium® 2 mg Quick Dissolve Tablets and Imodium™ 2 mg Capsules in normal, healthy, non-smoking male and female subjects

Volunteers underwent an overnight fast of at least 10 hours followed by a single dose of one of the following with 240ml water:

Product A – 4 x Loperamide Hydrochloride 2mg Liquigel Capsules
Product B – 4 x Imodium 2mg Quick Dissolve Tablets
Product C – 4 x Imodium 2mg Capsules

Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 72 hours post dose. The three treatment arms were separated by a minimum 7-day washout period.

The non-transformed and transformed pharmacokinetic results for amounts of loperamide hydrochloride are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Geometric Mean (%CV)</th>
<th>Arithmetic Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Loperamide HCl 2 mg Liquigel Capsules (A)</td>
<td>Imodium® 2 mg Quick Dissolve Tablets (B)</td>
</tr>
<tr>
<td>AUC₉₆₉₆ (ng hr/mL)</td>
<td>29.24 (60.56)</td>
<td>33.48 ± 19.33</td>
</tr>
<tr>
<td>AUC₉₉₉₉ (ng hr/mL)</td>
<td>31.61 (59.05)</td>
<td>36.10 ± 26.65</td>
</tr>
<tr>
<td>Cₘ₉₉₉₉ (µg/mL)</td>
<td>1.59 (61.41)</td>
<td>1.56 (59.93)</td>
</tr>
<tr>
<td>Tₘ₉₉₉₉ (hr)*</td>
<td>3.00 (1.00 - 8.00)</td>
<td>3.85 (0.30 - 12.00)</td>
</tr>
<tr>
<td>tₙ₉₉₉₉ (hr)</td>
<td>17.02 ± 2.80</td>
<td>17.80 ± 3.01</td>
</tr>
<tr>
<td>Kₙ₉₉₉₉ (hr⁻¹)</td>
<td>0.04 ± 0.01</td>
<td>0.04 ± 0.01</td>
</tr>
</tbody>
</table>

The relative bioavailability data, comparing Product A (Loperamide Hydrochloride 2mg Liquigel Capsules) versus Product C (Imodium 2mg Capsules) are presented below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Potency Uncorrected Data</th>
<th>Potency Corrected Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₉₆₉₆</td>
<td>97.82% - 114.03%</td>
<td>103.01%</td>
</tr>
<tr>
<td>AUC₉₉₉₉</td>
<td>97.32% - 112.83%</td>
<td>104.79%</td>
</tr>
<tr>
<td>Cₘ₉₉₉₉</td>
<td>97.40% - 111.30%</td>
<td>106.89%</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Parameter</th>
<th>90% C.I.</th>
<th>Ratio of Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₉₆₉₆</td>
<td>93.53% - 109.49%</td>
<td>101.41%</td>
</tr>
<tr>
<td>AUC₉₉₉₉</td>
<td>95.34% - 108.34%</td>
<td>100.63%</td>
</tr>
<tr>
<td>Cₘ₉₉₉₉</td>
<td>93.53% - 112.65%</td>
<td>107.64%</td>
</tr>
</tbody>
</table>
The 90% confidence intervals for $C_{\text{max}}$ and AUC for Loperamide Hydrochloride 2mg Liquigel Capsules versus Imodium 2mg Capsules are within predefined acceptance criteria. The data support the claim that the test product is bioequivalent to the reference product.

**Pharmacodynamics**
No new pharmacodynamic data have been submitted with these applications and none are required.

**Efficacy**
No new efficacy data have been submitted with these applications and none are required.

**Safety**
With the exception of the safety data generated during the bioequivalence study, no new safety data have been submitted with these applications and none are required. No new or unexpected safety concerns were raised from the safety data submitted.

**SmPC, PIL, Labels**
The SmPCs, PILs and labels are medically acceptable. The SmPCs are consistent with those for the originator product.

**Clinical Expert Report**
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Conclusion**
The grant of marketing authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Imodium Liquicaps 2mg Soft Capsules and Imodium 2mg Soft 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. A suitable justification has been provided for non-submission of an Environmental Risk Assessment.

EFFICACY
Bioequivalence has been demonstrated between these products and their respective reference product (Imodium 2mg Capsules).

SAFETY
No new or unexpected safety concerns arise from these applications.

The SmPCs, PILs and labelling are satisfactory and consistent with those for the originator product.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new preclinical 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 loperamide hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
### STEPS TAKEN FOR ASSESSMENT

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<thead>
<tr>
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<th>Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation applications on 2 December 2009</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 5 January 2010</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossier on 22 June 2011 and on the clinical dossier on 6 October 2010</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information relating to the quality dossier on 15 January 2011, 13 May 2011, 23 September 2011 and 19 January 2012, and relating to the clinical dossier on 25 October 2010</td>
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<tr>
<td>5</td>
<td>The applications were determined on 4 September 2012</td>
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IMODIUM 2MG SOFT CAPSULES
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STEPS TAKEN AFTER ASSESSMENT

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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SUMMARY OF PRODUCT CHARACTERISTICS
PATIENT INFORMATION LEAFLET

The current approved UK versions of the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for these products are available on the MHRA website.
LABELLING

Imodium LiquiCaps 2mg Soft Capsules can relieve diarrhoea quickly and effectively. Each soft capsule contains 2mg Loperamide hydrochloride. Also contains aspartame, saccharin, and ISO 3651/0367-9.