Public Assessment Report

UKPAR

Loperamide Hydrochloride and Simeticone 2 mg / 125 mg Tablets

(Loperamide hydrochloride and simeticone)

UK Licence No: PL 12063/0138-0139

Wrafton Laboratories Limited (trading as Perrigo).
LAY SUMMARY

Loperamide Hydrochloride and Simeticone 2 mg / 125 mg Tablets
(Loperamide hydrochloride 2 mg, simeticone equivalent to 125 mg dimeticone, tablet).

This is a summary of the Public Assessment Report (PAR) for Loperamide Hydrochloride and Simeticone 2 mg / 125 mg Tablets (PL 12063/0138-139). It explains how Loperamide Hydrochloride and Simeticone 2 mg / 125 mg 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 Loperamide Hydrochloride and Simeticone 2 mg / 125 mg Tablets.

The products will be collectively referred to as Loperamide Hydrochloride and Simeticone Tablets throughout the remainder of this public assessment report (PAR).

For practical information about using Loperamide Hydrochloride and Simeticone Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Loperamide Hydrochloride and Simeticone Tablets and what are they used for?
Loperamide Hydrochloride and Simeticone Tablets are a ‘hybrid generic medicine’. This means that they are similar to a ‘reference medicine’ containing the same active substances, already authorised in the European Union (EU), called Imodium Plus Caplet (McNeil Products Limited; a pharmacy (P) medicine available from pharmacies) and Imodium Plus Comfort Tablets (McNeil Products Limited; a general sales list (GSL) medicine).

Loperamide Hydrochloride and Simeticone Tablets are used to treat sudden short-lived (acute) attacks of diarrhoea and calm additional abdominal discomfort such as cramps, wind and bloating.

This medicine is for use in adults and children aged 12 years and over.

How do Loperamide Hydrochloride and Simeticone Tablets work?
This medicine contains the active ingredient loperamide hydrochloride, which helps reduce diarrhoea by slowing down an overactive bowel, which helps the body to absorb water and salts from the bowel. This medicine also contains simeticone, which is an anti-foaming agent that breaks up trapped wind in the bowel that causes cramps and bloating.

How are Loperamide Hydrochloride and Simeticone Tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth).

The patient must always use this medicine exactly as described in the patient information leaflet or as their doctor or pharmacist has told them. The patient must check with their doctor or pharmacist if they are not sure.

The patient should:
• swallow the correct number of tablets whole with a drink of water
• not use more than the stated dose shown in the table below
• only use the score line to help break the tablet if they have difficulty swallowing it whole.
Dosage for adults and children 12 years and over:

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults over 18 years old</td>
<td>Swallow two tablets initially, followed by one tablet after each loose bowel movement.</td>
</tr>
<tr>
<td>Children and young adults (12 to 18 years)</td>
<td>Swallow one tablet initially, followed by one tablet after each loose bowel movement.</td>
</tr>
</tbody>
</table>

- Do not take more than 4 tablets in any 24 hour period.
- Do not take for more than 48 hours. If symptoms persist for more than 48 hours talk to your doctor.

Children under 12 years old
This medicine is not recommended for children under 12 years old.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can be obtained without a prescription:
- PL 12063/0138 is on the general sales list (GSL).
- PL 12063/0139 is a pharmacy (P) medicine available from pharmacies.

What benefits of Loperamide Hydrochloride and Simeticone Tablets have been shown in studies?
For the active loperamide, studies in patients have been limited to tests to determine that the medicine is bioequivalent to the reference medicine, Imodium Plus Caplet (McNeil Products Limited). Two medicines are bioequivalent when they produce the same measure of therapeutic effect in the body.

For the active ingredient simeticone, no clinical studies are necessary as simeticone in not absorbed into the body.

What are the possible side effects of Loperamide Hydrochloride and Simeticone Tablets?
Like all medicines, Loperamide Hydrochloride and Simeticone Tablets can cause side effects, although not everybody gets them.

Common side effects (may affect less than 1 in 10 people but more than 1 in 100 people):
- Headache
- Feeling sick
- A change in the way some things taste

For the full list of all side effects reported with this medicine, see section 4 of the package leaflet available on the MHRA website.

For the full list of restrictions, see the package leaflet.

Why are Loperamide Hydrochloride and Simeticone Tablets approved?
The MHRA decided that the benefits of Loperamide Hydrochloride and Simeticone Tablets outweigh the identified risks and it was recommended that they be approved for use.
What measures are being taken to ensure the safe and effective use of Loperamide Hydrochloride and Simeticone Tablets?
A risk management plan (RMP) has been developed to ensure that Loperamide Hydrochloride and Simeticone Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPC) and the package leaflets for Loperamide Hydrochloride and Simeticone Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Loperamide Hydrochloride and Simeticone Tablets
Marketing Authorisations were granted in the UK on 30 September 2016.

The full PAR for Loperamide Hydrochloride and Simeticone Tablets follows this summary.

For more information about treatment with Loperamide Hydrochloride and Simeticone Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2016.
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<td></td>
<td>Table of content of the PAR update</td>
<td>Page 19</td>
</tr>
</tbody>
</table>
I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Wrafton Laboratories Limited, marketing authorisations for the medicinal products Loperamide Hydrochloride and Simeticone Tablets (PL 12063/0138-139). The Product Licence number PL 12063/0138 is available on the general sales list (GSL) and PL 12063/0139 is a pharmacy (P) medicine indicated for the symptomatic treatment of acute diarrhoea in adults and adolescents over 12 years when acute diarrhoea is associated with gas-related abdominal discomfort including bloating, cramping or flatulence.

The products applied for do not fully meet the requirements to be considered as generic products as simeticone acts locally in the gastro-intestinal tract, and therefore equivalence cannot be demonstrated to a reference medicinal product through investigation of bioequivalence. These fixed-dose combination products are supported by results from a bioequivalence study on the loperamide hydrochloride component and a biowaiver of the need to demonstrate bioequivalence for the locally-acting simeticone. Taking this into account, the legal basis under Article 10(3) of Directive 2001/83/EC, as amended (hybrid application) was designated for these applications.

The reference medicinal product which has been authorised in the Community for at least 10 years for these applications is Imodium Plus Chewable tablets (PA 0823/060/001) which was first authorised in Ireland on 14 August 1998 to McNeil Healthcare (Ireland) Ltd. The equivalent reference products in the UK are Imodium Plus Caplet, a pharmacy (P) medicine (McNeil Products Limited); and Imodium Plus Comfort Tablets, a general sales list (GSL) medicine (McNeil Products Limited). The reference product used in the bioequivalence study was Imodium Plus Caplet (McNeil Products Limited). This is acceptable.

Loperamide binds to the opiate receptor in the gut wall, reducing propulsive peristalsis, increasing intestinal transit time and enhancing resorption of water and electrolytes. Loperamide does not change the physiological flora.

Loperamide increases the tone of the anal sphincter. Loperamide Hydrochloride and Simeticone Tablets do not act centrally.

Simeticone is an inert surface-active agent with anti-foaming properties thereby potentially relieving gas-related symptoms associated with diarrhoea.

One bioequivalence study (conducted under fasting conditions) was submitted to support these applications for the active loperamide. The applicant has stated that the bioequivalence study was conducted in accordance with the protocol and all the other pertinent requirements of the ICH- Good Clinical Practice (GCP), Schedule Y and the principles enunciated in the Declaration of Helsinki (The WMA General Assembly, Seoul, 2008).

For the active simeticone, no specific requirements are necessary regarding proof of bioavailability and bioequivalence as simeticone is a chemically inert compound which is not absorbed or broken down in the body.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the applications were hybrid applications for products similar to an originator product that has been in clinical use for over 10 years.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products.
No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Loperamide Hydrochloride and Simeticone Tablets outweigh the risks and Marketing Authorisations were granted.

II QUALITY ASPECTS

II.1 Introduction

Each tablet contains 2 mg loperamide hydrochloride, and simeticone equivalent to 125 mg dimeticone. Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose (E460), sodium starch glycolate, hypromellose (E464), povidone (E1201), calcium phosphate (E341), mannitol (E421) and magnesium stearate (E572).

PL 12063/0138 (GSL medicine) is available in pack sizes of 6 tablets.
PL 12063/0139 (P medicine) is available in pack sizes of 6, 8, 10, 12, 15, 16, 18 and 20 tablets.

Both Marketing Authorisations (PL 12063/0138 & 0139) are packed into the following presentations:
- Push through blisters comprising transparent polyvinyl chloride (PVC)/polychlorotrifluoroethylene film, heat seal coating and aluminium foil.
- Push through blisters comprising transparent PVC/polyvinylidene chloride (PVdC) film, heat seal coating and aluminium foil.

The blisters are packaged into a printed outer carton. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substances

1. Loperamide hydrochloride

INN: Loperamide hydrochloride
Chemical name: 4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-N,N-dimethyl-2,2-diphenylbutanamide hydrochloride.

Structure:

\[
egin{align*}
\text{Cl} & \quad \text{OH} \\
\text{N} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{N} \quad \text{CH}_3 \\
\end{align*}
\]

Molecular formula: \( C_{29}H_{33}ClN_2O_2 \cdot HCl \)
Molecular weight: 513.5 g/mol
Description: White or almost white powder.
Solubility: Slightly soluble in water. It is freely soluble in ethanol (96%), isopropyl alcohol and methanol.
Loperamide hydrochloride is the subject of a European Pharmacopoeia monograph.

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

2. **Simeticone**

INN: Simeticone

Chemical name: Mixture of $\alpha$-trimethylsilyl-$\omega$-methylpoly[oxy(dimethylsilanediyl)] and silicon dioxide

Structural formula:

\[
\text{H}_3\text{C} \begin{array}{c} \text{Si} \\ \text{O} \end{array} \text{CH}_3 + x\text{SiO}_2
\]

\[20 < n < 400\]

Appearance: Greyish-white, opalescent liquid.

Solubility: Practically insoluble in water

Simeticone is the subject of a European Pharmacopoeia monograph.

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

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 supporting a suitable retest period when stored in the proposed packaging.

**II.3. Medicinal Product**

**Pharmaceutical Development**

The objective of the development programme was to formulate a safe, efficacious, stable, tablet containing loperamide hydrochloride 2 mg and simeticone equivalent to 125 mg dimeticone that was comparable in performance to the reference medicinal product Imodium Plus Caplet (McNeil Products Limited). Suitable pharmaceutical development data have been provided for these applications.

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

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.
None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

**Manufacture of the product**
A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results.

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

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 3 years with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

**III NON-CLINICAL ASPECTS**

**III.1 Introduction**
As the pharmacodynamic, pharmacokinetic and toxicological properties of loperamide hydrochloride and simeticone are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

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

**III.2 Pharmacology**
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

**III.3 Pharmacokinetics**
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

**III.4 Toxicology**
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

**III.5 Ecotoxicity/environmental risk assessment (ERA)**
Since Loperamide Hydrochloride and Simeticone Tablets are intended for generic substitution, this 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**
No new non-clinical studies were conducted or necessary for this type of application.
There are no objections to the approval of these applications from a non-clinical viewpoint.

**IV CLINICAL ASPECTS**

**IV.1 Introduction**

Loperamide hydrochloride and simeticone are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data.

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of loperamide hydrochloride and simeticone.

Based on the data provided, Loperamide Hydrochloride and Simeticone 2 mg / 125 mg Tablets (Wrafton Laboratories Limited) can be considered bioequivalent to Imodium Plus Caplet (McNeil Products Limited) with respect to the active substance loperamide.

**IV.2 Pharmacokinetics**

In support of these applications, the applicant submitted results from the following bioequivalence study:

**STUDY**

A two stage, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study of the applicant’s test product Loperamide Hydrochloride and Simeticone 2 mg / 125 mg Tablets (Wrafton Laboratories Limited) versus the reference product Imodium Plus Caplets (McNeil Products Limited) in healthy, adult, subjects under fasting conditions.

After an overnight fast, subjects were administered a single oral dose (2 x 2 mg/125 mg) of either the test or reference product with 240 mL of water. Fasting was continued for 4 hours after dosing. Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. For each subject there were 2 dosing periods separated by a washout period of 7 days.

In the two-stage approach, an initial group of subjects were planned to be treated and their data was analysed. An additional group would be recruited in the second stage of the study (unless bioequivalence is demonstrated in the first stage) and the results from both groups would be combined in a final analysis. The design of the study is acceptable.

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

The applied dose for loperamide is 2 x 2 mg, to obtain sufficient measurable loperamide plasma concentrations with regard to the sensitivity of the analytical method.

**Results**

All subjects completed stage I of the study and were included in the analysis. Bioequivalence was established after stage I, the study was considered to have passed and concluded, and therefore conducting stage II of the study was not required.
Table: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\textsubscript{max} (median, range)) of loperamide under fasting conditions:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC\textsubscript{0-\infty} (pg.h/ml)</th>
<th>AUC\textsubscript{0-t} (pg.h/ml)</th>
<th>C\textsubscript{max} (pg/ml)</th>
<th>t\textsubscript{max} (h)</th>
<th>t\textsubscript{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>28338 ± 8972</td>
<td>31551 ± 10284</td>
<td>1462 ± 457</td>
<td>5.2 ± 1.5</td>
<td>22.9 ± 3.8</td>
</tr>
<tr>
<td>Reference</td>
<td>30564 ± 9058</td>
<td>33701 ± 10088</td>
<td>1623 ± 482</td>
<td>5.6 ± 1.3</td>
<td>21.3 ± 4.0</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>0.92 (0.85 – 1.01)</td>
<td>--</td>
<td>0.90 (0.83 – 0.96)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV (%)</td>
<td>14</td>
<td>--</td>
<td>11.5</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*In-transformed values

**Conclusion**

The 90% confidence intervals of the ln-transformed test/reference ratio for AUC and C\textsubscript{max} values for loperamide administered under fasting conditions lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product Loperamide Hydrochloride and Simeticone 2 mg / 125 mg Tablets (Wrafton Laboratories Limited) is bioequivalent to the reference product Imodium Plus Caplets (McNeil Products Limited).

Loperamide may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of loperamide. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**).

No bioequivalence data have been submitted for simeticone. Simeticone is a silicone polymer - polydimethylsiloxane - with 5% silicon dioxide (silica), also known as activated dimethicone. Simeticone has a very low surface tension and therefore forms a thin film that prevents materials adhering together. This 'surfactant' property gives it a defoaming activity, demonstrated in vitro and in vivo. It is a chemically inert compound, which is not absorbed or broken down in the body. Clinically the antifoaming action of simeticone has been considered the main mechanism of action of this compound. As a direct consequence of this action, pre-treatment of patients with simeticone improves the quality of visualization by reduction of bubbles and foam in digestive ultrasonography.

As simeticone is a chemically inert compound which is not absorbed, the lack of bioequivalence data is acceptable. In addition, as for loperamide, bioequivalence has been proven, showing thereby that the caplet dissolves and released its active substances similar to that of the reference product; it can also be assumed that this applies to simeticone.

**IV.3 Pharmacodynamics**

No new pharmacodynamic data were submitted and none were required for an application of this type.

**IV.4 Clinical efficacy**

No new efficacy data were submitted and none were required for an application of this type.
IV.5  Clinical safety
No new safety data were submitted and none were required for these applications.

IV.6  Risk Management Plan (RMP)
The marketing authorisation holder (MAH) 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 Loperamide Hydrochloride and Simeticone Tablets.

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

Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Severe skin reactions, including Stevens Johnson syndrome, Toxic Epidermal necrolysis and Erythema multiforme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileus (including paralytic ileus)</td>
<td></td>
</tr>
<tr>
<td>Megacolon (including toxic megacolon)</td>
<td></td>
</tr>
<tr>
<td>Risk of obstipation and toxic megacolon in patients with AIDS</td>
<td></td>
</tr>
<tr>
<td>Important potential risks</td>
<td>CNS toxicity due to relative overdose in patients with hepatic impairment.</td>
</tr>
<tr>
<td></td>
<td>Prolonged use masking an underlying condition requiring medical attention</td>
</tr>
<tr>
<td>Important missing information</td>
<td>Use during pregnancy and lactation</td>
</tr>
<tr>
<td></td>
<td>Effect on fertility</td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns. This is satisfactory.

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. The language used for the purpose of user testing the PIL was English.

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 loperamide hydrochloride and simeticone is considered to
have demonstrated the therapeutic value of the compounds. The benefit-risk is, therefore, considered to be positive.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

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 text is the approved label text for this medicine. No label mock-ups have been provided for these products. In accordance with medicines legislation, the products shall not be marketed in the UK until approval of the label mock-ups has been obtained:

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td>Loperamide Hydrochloride and Simeticone 2 mg / 125 mg Tablets</td>
</tr>
<tr>
<td>Loperamide Hydrochloride / Simeticone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>2. STATEMENT OF ACTIVE SUBSTANCES</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Each tablet contains 2 mg loperamide hydrochloride and simeticone equivalent to 125 mg dimeticone.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>3. LIST OF EXCIPIENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>4. PHARMACEUTICAL FORM AND CONTENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet</td>
</tr>
<tr>
<td>6 Tablets</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>5. METHOD AND ROUTES OF ADMINISTRATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>For oral use.</td>
</tr>
<tr>
<td>Swallow the tablets with water.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>7. OTHER SPECIAL WARNING(S), IF NECESSARY</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Talk to a doctor at once if you take too much of this medicine, even if you feel well.</td>
</tr>
<tr>
<td>Immediate medical advice should be sought in the event of an overdose, even if you feel well.</td>
</tr>
<tr>
<td>Do not exceed 4 tablets in 24 hours.</td>
</tr>
<tr>
<td>Do not take for more than 2 days unless instructed by your doctor.</td>
</tr>
<tr>
<td>Not recommended for children under 12 years.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>8. EXPIRY DATE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>
<To be overprinted in the format MM/YYYY>

9. SPECIAL STORAGE CONDITIONS

Not applicable

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

Not applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Wafion Laboratories Limited, Wafion, Braunton, Devon, EX33 2DL, UK.

12. MARKETING AUTHORISATION NUMBER(S)

PL 12063/0138

13. BATCH NUMBER

<To be overprinted>

14. GENERAL CLASSIFICATION FOR SUPPLY

GSL

15. INSTRUCTIONS ON USE

To treat sudden short-lived (acute) attacks of diarrhea and calm additional abdominal discomfort such as cramps, wind and bloating.

Adults over 18 years: Swallow two tablets initially, followed by one tablet after each loose bowel movement.

Children and young adults (12 to 18 years): Swallow one tablet initially, followed by one tablet after each loose bowel movement.

Not recommended for children under 12 years.

Do not take more than 4 tablets in any 24 hour period.

Do not take for more than 48 hours. If symptoms persist for more than 48 hours talk to your doctor.

Please read the package leaflet carefully before use. Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.

16. INFORMATION IN BRAILLE.

Loperamide Hydrochloride and Simeticone 2 mg / 125 mg Tablets
<table>
<thead>
<tr>
<th><strong>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLISTER FOIL</strong></td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

   Loperamide Hydrochloride and Simeticone 2 mg / 125 mg Tablets
   Loperamide Hydrochloride / Simeticone

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

   Wraifon Laboratories Limited.

3. **EXPIRY DATE**

   <To be embossed in the format MM/YYYY>

4. **BATCH NUMBER**

   <To be embossed>

5. **OTHER**

   Loperamide hydrochloride 2 mg and simeticone (equivalent to 125 mg dimeticone)
   Press tablets through from other side
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON</th>
</tr>
</thead>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Loperamide Hydrochloride and Simeticone 2 mg / 125 mg Tablets
Loperamide Hydrochloride / Simeticone

2. **STATEMENT OF ACTIVE SUBSTANCES**

Each tablet contains 2 mg loperamide hydrochloride and simeticone equivalent to 125 mg dimeticone.

3. **LIST OF EXCIPIENTS**

N/A

4. **PHARMACEUTICAL FORM AND CONTENTS**

Tablet

<table>
<thead>
<tr>
<th>Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Tablets</td>
</tr>
<tr>
<td>8 Tablets</td>
</tr>
<tr>
<td>10 Tablets</td>
</tr>
<tr>
<td>12 Tablets</td>
</tr>
<tr>
<td>15 Tablets</td>
</tr>
<tr>
<td>16 Tablets</td>
</tr>
<tr>
<td>18 Tablets</td>
</tr>
<tr>
<td>20 Tablets</td>
</tr>
</tbody>
</table>

5. **METHOD AND ROUTES OF ADMINISTRATION**

Read the package leaflet before use.
For oral use.
Swallow the tablets with water.
6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Talk to a doctor at once if you take too much of this medicine, even if you feel well.
Immediate medical advice should be sought in the event of an overdose, even if you feel well.
Do not exceed 4 tablets in 24 hours.
Do not take for more than 2 days unless instructed by your doctor.
Not recommended for children under 12 years.

8. EXPIRY DATE

<To be overprinted in the format MM/YYYY>

9. SPECIAL STORAGE CONDITIONS

Not applicable

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

Not applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Wrafton Laboratories Limited, Wrafton, Braunton, Devon, EX33 2DL, UK.

12. MARKETING AUTHORISATION NUMBER(S)

PL 12063/0139

13. BATCH NUMBER

<To be overprinted>
14. GENERAL CLASSIFICATION FOR SUPPLY

p

15. INSTRUCTIONS ON USE

To treat sudden short-lived (acute) attacks of diarrhoea and calm additional abdominal discomfort such as cramps, wind and bloating.

Adults over 18 years: Swallow two tablets initially, followed by one tablet after each loose bowel movement.

Children and young adults (12 to 18 years): Swallow one tablet initially, followed by one tablet after each loose bowel movement.

Not recommended for children under 12 years.

Do not take more than 4 tablets in any 24 hour period.

Do not take for more than 48 hours. If symptoms persist for more than 48 hours talk to your doctor.

Please read the package leaflet carefully before use.
Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.

16. INFORMATION IN BRAILLE.

Loperamide Hydrochloride and Simeticone 2 mg / 125 mg Tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Loperamide Hydrochloride and Simeticone 2 mg / 125 mg Tablets
Loperamide Hydrochloride / Simeticone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Wafco Laboratories Limited.

3. EXPIRY DATE

<To be embossed in the format MM/YYYY>

4. BATCH NUMBER

<To be embossed>

5. OTHER

Loperamide hydrochloride 2 mg and simeticone (equivalent to 125 mg dimeticone)
Press tablets through from other side
Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<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 Y/N (version)</th>
</tr>
</thead>
</table>