Public Assessment Report

Scientific discussion

Loperuma 2 mg/125 mg, chewable tablets

(loperamide hydrochloride/simeticone)

NL/H/3113/001/DC

Date: 22 October 2015

This module reflects the scientific discussion for the approval of Loperuma 2 mg/125 mg, chewable tablets. The procedure was finalised on 27 January 2015. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Loperuma 2 mg/125 mg, chewable tablets from Disphar International B.V.

The product is 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.

A comprehensive description of the indications and posology is given in the SmPC.

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 does not act centrally.

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

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Imodium Plus 2 mg/125 mg chewable tablets, registered in the EU by McNeil Healthcare via MRP UK/H/0241/001/MR since 14 August 1998 (Ireland). In the Netherlands the chewable tablets are not authorised. However, Imodium Duo 2 mg/125 mg tablets (NL License RVG 33869) are authorized since 12 April 2007 as part of the MRP UK/H/0241/002/MR (MAH Johnson & Johnson Consumer B.V.).

The concerned member states (CMS) involved in this procedure were Denmark and Finland.

In a scientific advice given by the MEB in 2010 about loperamide hydrochloride/simeticone tablets, the MAH was advised that this is not a straightforward generic product, as it is locally acting. Therefore the MEB considered that the legal basis for this type of medicine should be a hybrid application. The same rationale is considered applicable to the loperamide/simeticone chewable tablets. The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Loperuma 2 mg/125 mg is a white to off white round tablet with “LO-SI” debossed on one side. The tablets may show light brown spots. Each tablet contains loperamide hydrochloride 2 mg and simeticone equivalent to 125 mg dimeticone.

The chewable tablets are packed in push through blisters comprising transparent PVC/ACLAR or PVC/PVDC film, heat seal coating and aluminium foil.

The excipients are: microcrystalline cellulose (E460), hypromellose (E464), calcium phosphate (E341), mannitol (E421), carmellose sodium, sacralose (E955), ethyl vanillin, peppermint flavour, magnesium stearate (E572).

II.2 Drug Substances

Loperamide hydrochloride

Loperamide hydrochloride is an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white powder, slightly soluble in water, freely soluble in 96% ethanol and in methanol. The substance shows polymorphism. The polymorphic form of produced is form I.
The CEP procedure is used for loperamide HCl. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

**Manufacturing process**
A CEP has been submitted; therefore no details on the manufacturing process have been included.

**Quality control of drug substance**
The drug substance specification is in line with the Ph.Eur. with an additional requirement for particle size distribution. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for six batches of loperamide hydrochloride by the drug substance manufacturer and of two batches by the drug product manufacturer.

**Stability of drug substance**
The active substance loperamide HCl is stable for 60 months if stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

**Simeticone**
Simeticone is an established active substance described in the European Pharmacopoeia. It is a viscous, greyish-white, opalescent liquid that is practically insoluble in water. The CEP procedure is used for simeticone.

**Manufacturing process**
A CEP has been submitted; therefore no details on the manufacturing process have been included.

**Quality control of drug substance**
The drug substance specification is in line with the Ph.Eur. without any additional requirements. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches by the drug product manufacturer.

**Stability of drug substance**
For simeticone stability studies were conducted on full-scale batches stored at 25°C (36 months) and 40°C (36 months). No trends or changes were seen in any of the tested parameters at both storage conditions. The proposed retest period of 36 months without any special storage precautions is justified.

**II.3 Medicinal Product**

**Pharmaceutical development**
The development of the product has been described, the choice of excipients is justified and their functions explained. As part of the development the compatibility of the excipients with the drug substances was investigated, the reference product was characterised, the formulation was optimized to achieve the desired release properties and preliminary stability studies were performed. The excipients are well known. The choices of the packaging and manufacturing process are justified. A bioequivalence study was performed. The batch used in the bioequivalence study was manufactured according to the finalized composition and manufacturing process. Comparative dissolution profiles have been provided between the bioequivalence study test and reference batches in 0.1N HCl, pH 4.5 and pH 6.8 dissolution media. Similarity between the batches has been adequately demonstrated in 0.1 N HCl as well as in pH 4.5 medium. Similarity in pH 6.8 medium was not confirmed. However, the results of the *in vivo* bioequivalence study prevail. As simeticone is inert and not absorbed in the body, bioequivalence studies are not required. A comparison of the disintegration time between the test and reference product is not deemed relevant as the product is a chewable tablet, that disintegrates upon chewing, similar to the reference product.

The pharmaceutical development of the product has been adequately performed.
Manufacturing process
The manufacturing process consists of the preparation of loperamide granules by wet granulation, preparation of the simeticone phase by adsorption, blending and lubrication of the loperamide granules with the simeticone adsorbate, lubrication and compression. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches.

Control of excipients
The excipients comply with Ph.Eur. or in-house requirements. Additional in-house requirements to the Ph.Eur. monographs were set for some of the relevant functionality related characteristics. The specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, thickness, resistance to crushing, friability, identity, dissolution of loperamide, uniformity of dosage units, assay, related substances and microbial quality. Except for assay of simeticone and related substances, the release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data have been provided on three full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on three full-scale batches stored at 25°C/60% RH (18 months), 30°C/75% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVdC-PVC/Al-blisters and ACLAR-PVC/Al-blisters. During storage light brown spots were observed at all three storage conditions, with no impact on the drug product quality, safety or taste. Results of a photostability study showed that the product is light sensitive.

The proposed shelf-life of 24 months with storage conditions ‘Store below 25°C’ and ‘Keep the blister in the outer carton in order to protect from light’ is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. The magnesium stearate used is of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects
Based on the submitted dossier, the member states consider that Loperuma 2 mg/125 mg, chewable tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)
Since Loperuma 2 mg/125 mg is intended as a substitute for other identical products on the market, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects
This product is a hybrid formulation of Imodium Plus, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate
additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Loperamide HCl and simeticone are well-known active substance 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. Therefore, the member states agreed that no further clinical studies are required.

According to the Note for Guidance on the Clinical requirements for locally applied, locally acting products containing known constituents (CPMP/EWP/239/95) none of these products can be considered essentially similar, but rather therapeutic equivalence should be shown. Additionally it mentions that for locally applied products bio-equivalence is generally not a suitable way to show therapeutic equivalence since plasma levels are not relevant for local efficacy.

For this hybrid application, the MAH has submitted a bioequivalence study, which is discussed below. As this product is a locally acting product, the bioequivalence study is used as a surrogate study and as such can be considered supportive.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Loperuma 2 mg/125 mg (Disphar International B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Imodium Plus 2 mg/125 mg chewable tablets (Mc Neil Healthcare Ltd., Ireland).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A two-stage, randomized, open-label, single dose, balanced, two-treatment, two-sequence, two-period, crossover bioequivalence study was carried out under fasted conditions. In Stage I, 16 healthy male subjects, aged 21 - 39 years, were included, and in Stage II 34 healthy male subjects, aged 18 – 40 years, were included. Subjects received a single dose (4 mg loperamide and 250 mg simeticone; 2 x 2 mg/125 mg chewable tablet) of the test and reference loperamide/simeticone formulation.

The chewable tablet had to be chewed by the subjects. This activity was followed by oral examination to assess compliance to dosing. The tablets were administered after an overnight fast. Fasting was continued for 4 hours after dosing.

Blood samples were collected pre-dose and at 1.0, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 9.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of the products. The wash-out period was 7 days.

A single dose, crossover study to assess bioequivalence is considered adequate. Fasting conditions has been applied. This is acceptable, as the SmPC does not state specific food conditions for administration. Furthermore the tablets were chewed without water before intake, in accordance with the SmPC. Loperamide is analysed and was used to prove bioequivalence. As simeticone is a chemically inert compound which is not absorbed, the lack of bioequivalence data is acceptable.
Analytical/statistical methods
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. Two tablets were taken, to obtain sufficient high loperamide plasma concentrations, to overcome the possibly too low sensitivity of the analytical method.

After Stage I, an interim analysis was conducted to estimate the intra-subject coefficient of variation (CVintra) for the primary endpoints and the point estimate (PE) of the ratio of the geometric means of test and reference for the primary endpoints. These results were used for the estimation of the total sample size.

Results
In Stage I, one subject was withdrawn because of an adverse event in period II, and 15 subjects were analysed. In Stage II, one subject was withdrawn due to non-compliance with protocol specifications, and 33 more subjects were included in the analysis. Therefore a total of 48 subjects completed the study and were included in the final analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of loperamide under fasted conditions at Stage I.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=15</th>
<th>AUC₀–₄</th>
<th>AUC₀–∞</th>
<th>Cmax</th>
<th>tmax</th>
<th>1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td>23006 ± 7557</td>
<td>25554 ± 9056</td>
<td>1150 ± 429</td>
<td>5.5 (4.0 – 8.0)</td>
<td>21.1 ± 3.3</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td>20366 ± 6057</td>
<td>22432 ± 6508</td>
<td>1067 ± 455</td>
<td>5.0 (3.0 – 9.0)</td>
<td>21.1 ± 3.8</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td></td>
<td>1.12 (0.89 - 1.41)</td>
<td>--</td>
<td>1.09 (0.78 - 1.54)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>CV (%)</td>
<td></td>
<td>16.6</td>
<td>--</td>
<td>24.5</td>
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<td></td>
</tr>
</tbody>
</table>

AUC₀–₄ area under the plasma concentration-time curve from time zero to t hours
AUC₀–∞ area under the plasma concentration-time curve from time zero to infinity
Cmax maximum plasma concentration
tmax time for maximum concentration
t₁/₂ half-life
CV coefficient of variation

*ln-transformed values

As can be seen in table 1, the 90% confidence intervals for Cmax and AUC(0-t) were not within the bioequivalence range of 0.80 – 1.25. The calculated in intra-individual coefficients of variation (CVs) for Cmax and AUC(0-t) were 24.5% and 16.6%, respectively. These CVs obtained in the interim analysis were used to determine the sample size for the second stage of the study.

The MAH calculated that the sample size for Stage II should be 34 subjects. Thirty-three of them completed the second stage. The final pharmacokinetic and statistical analysis, based on all 48 subjects completing the study, is presented in table 2.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of loperamide under fasted conditions after Stage II.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=48</th>
<th>AUC₀–₄</th>
<th>AUC₀–∞</th>
<th>Cmax</th>
<th>tmax</th>
<th>1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td>26514 ± 7487</td>
<td>29279 ± 8354</td>
<td>1355 ± 481</td>
<td>5.0 (2.0 – 8.0)</td>
<td>21.4 ± 4.8</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td>26094 ± 8915</td>
<td>29532 ± 10738</td>
<td>1360 ± 563</td>
<td>5.0 (2.0 – 9.0)</td>
<td>24.1 ± 12.9</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td></td>
<td>1.04 (0.99 - 1.09)</td>
<td>--</td>
<td>1.02 (0.95 - 1.10)</td>
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</tr>
</tbody>
</table>
The data on all subjects (n=48; 15 in Stage I and 33 in Stage II) show that the 90% confidence intervals calculated for AUC_{0-t} and C_{max} of loperamide are within the bioequivalence acceptance range of 0.80–1.25.

**Conclusion on bioequivalence study**

Based on the submitted two-stage bioequivalence study Loperuma 2 mg/125 is considered bioequivalent with Imodium Plus 2 mg/125 mg chewable tablets. As simeticone is not absorbed from the gastrointestinal tract, there are no specific requirements regarding proof of bioavailability and bioequivalence. For this component essential similarity with the reference product is sufficiently confirmed by having the same amount of this drug substance.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

**IV.3 Risk Management Plan**

The MAH has submitted a risk management plan, 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 Loperuma.

- **Summary table of safety concerns as approved in RMP**

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Central nervous system (CNS) toxicity in patients with hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypersensitivity</td>
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<tr>
<td></td>
<td>Ileus, megacolon and toxic megacolon</td>
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<tr>
<td></td>
<td>Masking of bacterial enterocolitis or amoebiasis caused by invasive organisms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important potential risks</th>
<th>Acute pancreatitis with loperamide use and elevated pancreatic enzyme levels in the setting of an overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposure during pregnancy and breast feeding</td>
</tr>
<tr>
<td></td>
<td>Fertility</td>
</tr>
</tbody>
</table>

| Missing information       | Exposure in children younger than 12 years old                                                                   |

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

**IV.4 Discussion on the clinical aspects**

For this authorisation, reference is made to the clinical studies and experience with the innovator product Imodium Plus. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study on the active substance loperamide that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.
V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. The MAH submitted a bridging report referring to the successfully user tested PL for Loperamide HCl/Simeticone tablets approved in previous procedures. The minor changes in pharmaceutical form and information that the tablets may be chewed on do not result in decreased readability. The MAH confirmed that the PLs have the same house style. The bridging report has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Loperuma 2 mg/125 mg, chewable tablets has a proven chemical-pharmaceutical quality and is a hybrid form of Imodium Plus 2 mg/125 mg chewable tablets. Imodium Plus is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. For the inert active substance simeticone no bioequivalence study was required.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Loperuma 2 mg/125 mg, chewable with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 January 2015.
<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
</table>

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY