LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Dimor Comp
dimeticone, loperamide, loperamide hydrochloride, simethicone

SE/H/2251/001/DC

This module reflects the scientific discussion for the approval of Dimor Comp. The Public Assessment Report was written in februari 2014 by the previous RMS NL after initial procedure NL/H/2730/001/DC and is attached at the end of this document. RMS transfer from NL/H/2730/001/DC to SE was completed 2022-01-25. For information on changes after this date please refer to the module 'Update'.

Active substance	dimeticone, loperamide, loperamide hydrochloride, simethicone
Pharmaceutical form	Tablets
Strength	2mg/125mg
Applicant	Nordic Drugs AB
EU-Procedure number (original)	NL/H/2730/001/DC

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Introduction

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Losibere 2 mg/125 mg, tablets
Disphar International B.V., the Netherlands

loperamide (as hydrochloride)/simeticone

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2730/001/DC
Registration number in the Netherlands: RVG 111976

11 February 2014

Pharmacotherapeutic group:	antipropulsive antidiarrheals
ATC code:	A07DA53
Route of administration:	oral
Therapeutic indication:	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.
Prescription status:	non-prescription
Date of authorisation in NL:	27 January 2014
Concerned Member States:	Decentralised procedure with SE
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

INTRODUCTION

I.

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Losibere 2 mg/125 mg, tablets from Disphar International B.V. The date of authorisation was on 27 January 2014 in the Netherlands.

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 SPC.

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 tablets 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 tablets. The tablets are a line-extension of the Imodium Plus 2 mg/125 mg chewable tablets, which has been registered in Ireland by McNeil Healthcare since 14 August 1998. In the Netherlands Imodium Duo 2 mg/125 mg tablets (NL License RVG 33869) has been authorized as non-prescription medicinal product since 12 April 2007 as part of the MRP UK/H/0241/002 with Johnson & Johnson Consumer B.V. as MAH.

The UK/H/0241/002/MR product concerns Loperamide HCl/Simeticone ‘caplets’ (capsule-shaped tablets), whereas the Irish product is a chewable tablet. With variation UK/H/0241/II/50 the MAH submitted, as a post-approval commitment, a study to investigate the therapeutic equivalence of the caplet and the chewable tablet. This variation was approved in 2011.

The product applied for is not regarded as a straightforward generic product. The MEB is of the opinion that this product is a locally applied product, where a bioequivalence study or biowaiver is used as a surrogate study and as such can be considered supportive.
Taking this into account, the legal basis under Article 10(3) of Directive 2001/83/EC (hybrid application) was designated for this application.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, *i.e.* including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product.
A supportive bioequivalence study has been performed and it was concluded that the fixed-dose combination loperamide hydrochloride/simeticone 2 mg/125 mg (Disphar International BV, Netherlands) is bioequivalent to reference Imodium® plus (fixed dose combination of loperamide HCl/simeticone 2 mg/125 mg, McNeil Products Limited, UK) for loperamide under fasting conditions. For simeticone, no specific requirements are necessary regarding proof of

bioavailability and bioequivalence, as simeticone is not absorbed. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety.
This hybrid product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

Scientific advice was given by the Dutch Medicines Evaluation Board on 15 June 2010, regarding the dossier requirements and legal basis for this application.

No paediatric development programme has been submitted, as this is not required for a hybrid application.

II. SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in

place for this product type at all sites responsible for the manufacturing of the active substance as well

as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substances
The active substances are loperamide HCl and simeticone, established active substances described in the European Pharmacopoeia (Ph.Eur.*). Loperamide HCl 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.
Simeticone is a viscous, greyish-white, opalescent liquid that is practically insoluble in water, very slightly soluble or practically insoluble in anhydrous ethanol, practically insoluble in methanol, partly miscible with ethyl acetate, with methylene chloride, with methyl ethyl ketone and with toluene.

The CEP procedure is used for both active substances. 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
CEPs have 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. and the additional requirements of the CEPs. Batch analytical data demonstrating compliance with the drug substances specifications have been provided for three batches of both drug substances. The MAH uses the analytical methods of the Ph.Eur.

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.
For simeticone stability studies were conducted on three full-scale batches stored at 25°C (36 months) and 40°C (36 months). The batches were stored in 500 ml HDPE bottles. Stability results showed no changes or trends in any of the parameters tested when stored under long-term and accelerated conditions for 36 months. Based on the above observations a re-tests period of 36 months can be granted. The claimed storage condition “No special storage conditions are required” is justified.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Losibere 2 mg/125 mg is a white to off white capsule-shaped tablet with “LO-SI” debossed on one side and ‘2’ & ‘125’ debossed on the opposite side at either side of a score line. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. Each tablet contains loperamide hydrochloride 2 mg and simeticone equivalent to 125 mg dimeticone.

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

The excipients are: microcrystalline cellulose (E460), sodium starch glycolate, hypromellose (E464), povidone (E2101), calcium phosphate (E341), mannitol (E421), magnesium stearate (E572).

Pharmaceutical development
The development of the product has been described, the choice of excipients justified and their functions explained. All excipients used are well known. The choices of the packaging and manufacturing process are justified. The dosage advice does not require halved tablets. In view of that, the tablets do not have to comply with the requirements for breakability of tablets of the Ph Eur Monograph ‘Tablets’.
The manufacture and composition of the biobatch used in bioequivalence study is identical to the final formulation. The reference product used in the study is similar to the Dutch reference product. Both products are approved in application procedure UK/H/0241/MR.
Comparative dissolution profiles at three different media have been provided. Differences in dissolution behaviour for the biobatch and the innovator product have been adequately discussed. The differences observed *in vitro* do not have an influence on *in vivo* performance, as shown in the bioequivalence clinical study.
As simeticone is inert and not absorbed in the body, bioequivalence studies are not required. The provided data showed that the disintegration of the tablets is fast and comparable for the test and the Dutch reference product. The pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process consists of dry mixing followed by wet granulation of loperamide HCl, simeticone absorption, blending, lubrication and compression. The manufacturing process can be considered a non-standard process.

The manufacturing process has been sufficiently described. Adequate process validation data on the product has been presented.

Control of excipients
The excipients comply with their respective Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, thickness, resistance to crushing, friability, identification, disintegration time, water content, dissolution of loperamide HCl, uniformity of dosage units, related substances, assay and microbiological limit test.
The release and shelf-life limits for all tests are the same except for the limits for water content, assay and related substances. All specifications are acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three production-scale batches, demonstrating compliance with the release specifications.

Stability of drug product
Stability data on the product has been provided for two pilot-scale batches stored at 30°C/60% RH (12 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//Alu blister or ACLAR/PVC//Alu blister.
Trends were observed, but all tested parameters remained within the specifications. A photostability study was performed in conformity with ICH topic Q1B. Photostability testing reveals no important degradation.
The proposed shelf-life of 24 months is justified. The proposed storage condition “No specific storage condition is required” 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.

II.2 Non-clinical aspects

This product is a hybrid formulation of Imodium Plus, which is available on the European market. 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.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of loperamide HCl or simeticone released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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.

For this hybrid application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Losibere 2 mg/125 mg (Disphar International B.V., NL) capsule-shaped tablets is compared with the pharmacokinetic profile of the reference product Imodium® plus 2 mg/125 mg capsule-shaped tablets (caplets) (McNeil Products Limited, UK).

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

Design
A two stage, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 16 healthy male subjects, aged 23-39 years. Each subject received a single dose (2 x 2 mg/125 mg) of one of the 2 loperamide HCl/simeticone formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 1.0, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 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.

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.

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.

The applied dose for loperamide is 2 x 2 mg, as 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 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of loperamide under fasted conditions.

Treatment N=16	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	28338 ± 8972	31551 ± 10284	1462 ± 457	5.2 ± 1.5	22.9 ± 3.8
Reference	30564 ± 9058	33701 ± 10088	1623 ± 482	5.6 ± 1.3	21.3 ± 4.0

***Ratio (90% CI)**	0.92 (0.85 – 1.01)	--	0.90 (0.83 – 0.96)	--	--
CV (%)	14	--	11.5	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of loperamide under fasted conditions, it can be concluded that Losibere 2 mg/125 mg and Imodium® plus 2 mg/125 mg caplets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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 CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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).

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 excipients and active substances similar to that of the reference product, it can also be assumed that this also accounts for simeticone.

Risk management plan

The combination of loperamide HCl and simeticone has been on the market for more than 10 years. The safety profile of the active substances can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The risk of serious adverse events, use in patients with hepatic impairment, and drug-drug interactions are minimized by adequate text in the SPC, in line with the SPC of the reference product.
The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. A Risk Management Plan was provided.

Status	Safety concern
Important identified risks	Hypersensitivity
	Ileus, megacolon and toxic megacolon
Important potential risks	Exposure during pregnancy and breast feeding
	Fertility
Important missing information	Exposure in children younger than 12 years old

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Imodium Plus 2 mg/125 mg.

Readability test
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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Overall, each and every question meets criterion of 81% correct answers. No PIL revisions were suggested in the testing rounds based on results.
The readability test has been sufficiently performed.

III. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Losibere 2 mg/125 mg, 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.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 Losibere 2 mg/125 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 13 June 2013. Losibere 2 mg/125 mg, tablets was authorised in the Netherlands on 27 January 2014.

The date for the first renewal will be: 13 June 2018.

The following post-approval commitments have been made during the procedure:

<u>Quality - medicinal product</u>

- The MAH committed to place the first three production-scale batches on stability as per protocol given for the formal stability study.
- The MAH committed to test the first 3 consecutive industrial batches on microbial purity before switching to non-routine control testing.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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