CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Imodium Instant smelttablet 2 mg, orodispersible tablets
Johnson & Johnson Consumer B.V., the Netherlands

loperamide (as hydrochloride)

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.
It reflects the scientific conclusion reached by the MEB 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.

Registration number in the Netherlands: RVG 33724

5 August 2010

Pharmacotherapeutic group:	antidiarrheals, intestinal antiinflammatory/antiinfective agents - antipropulsives
ATC code:	A07DA03
Route of administration:	oral
Therapeutic indication:	symptomatic treatment of acute and chronic diarrhea when causal treatment is not possible.
Prescription status:	non prescription
Date of authorisation in NL:	10 April 2007
Application type/legal basis:	Directive 2001/83/EC, Article 8(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.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Imodium Instant smelttablet 2 mg, orodispersible tablets from Johnson & Johnson Consumer B.V. The date of authorisation was on 10 April 2007 in the Netherlands.

The product is indicated for symptomatic treatment of acute and chronic diarrhea. Diarrhea should be treated causally whenever causal treatment is available.

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

Loperamide hydrochloride is a synthetic opioid which inhibits gut motility by binding to opiate receptors in the gut wall and may also reduce gastrointestinal secretions, resulting in improvement in diarrhoea symptoms. Loperamide also increases the tone of the anal sphincter.

This national procedure concerns a line extension to the registered product Imodium capsules 2 mg (NL License RVG 06945) which has been authorised in the Netherlands since 20 January 1976 by the same MAH. The product at issue concerns an orodispersible tablet, which differs from the original product with regard to pharmaceutical form. The indication sought is the same as for the Imodium capsules product.

The marketing authorisation is granted based on article 8(3) Directive 2001/83/EC.

For the purpose of registration in the Netherlands, a full dossier, dossier has been submitted, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data, in accordance with Directive 65/65/EEC, currently article 8(3) of Directive 2001/83/EC.
In addition for this application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the registered capsules. To this end the MAH has submitted a three-way bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the products Zydis 2 mg tablets and Zydis 2 mg capsules, registered in Belgium. This product is a legitimate line extension to the products already marketed.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for a line extension.

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 substance
The active substance is loperamide hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white to almost white powder, which is slightly soluble in water, and freely soluble in alcohol and methanol. Loperamide shows polymorphism; only polymorph I is manufactured.

The CEP procedure is used for both suppliers of the active substance. 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 new 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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and CEPs. Batch analytical data has been provided for three batches per manufacturing location.

Stability of drug substance
The product at issue is a line-extension of Imodium Capsules 2 mg and as the production sites of the active substance for both products are the same, the same retest period could be granted: 72 months with no special storage condition.

** 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
Imodium Instant smelttablet 2 mg contains as active substance 2 mg of loperamide hydrochloride, and is a white to off-white, round tablet.

The tablets are packed in Aluminium blister packs

The excipients are: gelatin (E485), mannitol (E421), aspartame (E951), flavouring agent (mint), sodium hydrogen carbonate.

Pharmaceutical development
The orodispersible tablets are formulated to consist of a matrix of soluble carrier materials containing a unit dose of loperamide hydrochloride. The choice of manufacturing process and excipients has been sufficiently explained. The antimicrobial properties of the suspension were investigated by performing challenge tests.

The formulation of this fast dissolving dosage form is designed to disintegrate in water or on the tongue within 10 seconds. This rapid disintegration is investigated using the Ph.Eur. test for disintegration of tablets. The results comply with the Ph.Eur. requirement of less than 3 minutes for orodispersible tablets.
The pharmaceutical development has been sufficiently described and explained.

Manufacturing process
The manufacture consists of suspension preparation, dispensing into the preformed blister pockets, freezing, freeze drying and sealing. The freeze drying procedure has been adequately described. Process validation data on the product have been presented for 3 production-scale batches in accordance with the relevant European guidelines.

Control of excipients
Except for the mint flavour all excipients comply with the Ph.Eur. For mint flavour a separate specification has been laid down. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for diameter, identification, assay, degradation compounds, dissolution, uniformity of mass, content uniformity, disintegration time, moisture content and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from 5 commercial-scale batches have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for 3 production-scale batches stored at 25°C/60% RH (48 months), 30°C/65% RH (48 months) and 40°C/75% RH (6 months), and 3 smaller batches stored under the same conditions for 56, 48 and 12 months, respectively. The stability results show that no trends are observed at the different stability conditions. Based on these results, the proposed shelf life of 5 years could be granted. No special storage condition is required.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

This active substance has been available on the Dutch market since 1976. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

Environmental risk assessment
The product is intended as a substitute for other comparable products on the market. The approval of this product will not result in an increase in the total quantity of loperamide 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 is a well-known active substance with established efficacy and tolerability.

For this line extension, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Imodium Instant smelttablet 2 mg is compared with the pharmacokinetic profile of Imodium 2 mg tablets and Imodium 2 mg capsules (Janssen Pharmaceutica, Belgium, part of the same

pharmaceutical company, the loperamide capsules are under the name of Imodium on the Dutch market). As no Imodium 2 mg tablet is registered in the Netherlands, results obtained with this formula are considered supportive. Only the Imodium 2 mg capsule is registered in the Netherlands

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, three-way crossover bioequivalence study was carried out under fasted conditions in 24 healthy subjects (12 males/12 females), aged 21-41 years. Each subject received a single dose of 4 mg (2 x 2 mg) of one of the 3 loperamide formulations. The orodispersible test tablet was taken without water - which is in line with the posology - whereas the tablet and capsule were administered with 200 ml of water after fasting overnight. There were 2 dosing periods, separated by a washout period of 2 weeks.
Blood samples were collected pre-dose and at at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 32 and 48 hours after administration of the products.

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.

Results
All 24 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of loperamide under fasted conditions.

Treatment N=24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	14.6 ± 6.4	16.4 ± 7.0	0.82 ± 0.35	5.0 (1.0-6.0)	14 ± 2
Capsules (C)	13.8 ± 4.3	14.9 ± 4.8	0.78 ± 0.29	5.0 (1.0-7.0)	13 ± 2
Tablets (T)	14.3 ± 4.9	15.1 ± 5.7	0.81 ± 0.34	5.0 (0.5-6.0)	13 ± 2
***Ratio (90% CI) Test/C**	1.05 (0.95-1.15)	-	1.03 (0.92-1.16)	-	-
CV (%) Test/C	24.49	-	24.49	-	-
***Ratio (90% CI) Test/T**	1.03 (0.94-1.14)	-	1.00 (0.89-1.13)	-	-
CV (%) Test/T	24.49	-	19.4	-	-

$AUC_{0-\infty}$ 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 Imodium Instant smelttablet 2 mg and Imodium 2 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. In addition, Imodium Instant smelt was shown to be bioequivalent with Zydis 2 mg tablets.

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).

Risk management plan

Loperamide was first approved in 1976, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of loperamide 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 registered medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The SPC is in line with that of Imodium 2 mg capsules, which is considered appropriate.

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 two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Imodium Instant smelttablet 2 mg, orodispersible tablets has a proven chemical-pharmaceutical quality and is a legitimate line extension of Imodium capsules 2 mg. Imodium capsules 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, package leaflet and labelling are in the agreed templates and are in agreement with those for Imodium capsules.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered the product a legitimate line extension to the existing Imodium authorisations, and has therefore granted a marketing authorisation. Imodium Instant smelttablet 2 mg, orodispersible tablets was authorised in the Netherlands on 10 April 2007.

Several post-approval commitments have been made during the procedure, which have been fulfilled.

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
Update of Quality Module.	--	II	31-5-2007	9-10-2007	Approval	N
Submission of a new or updated Ph.Eur Certificate of Suitability, from a manufacturer currently approved.	--	IA	13-12-2007	22-1-2008	Approval	N
Addition of postmarketing adverse drug reactions to product information.		II	12-6-2008	8-7-2009	Approval	N
Change in the specification of the finished product.	--	IA	22-4-2009	5-9-2009	Approval	N
Change in test procedure of the finished product.	--	IB	22-4-2009	5-9-2009	Approval	N
Change in the specification of the finished product.	--	IB	22-4-2009	5-9-2009	Approval	N
Change in the specification of the finished product.	--	IB	22-4-2009	5-9-2009	Approval	N
Change in test procedure of the finished product.	--	IB	22-4-2009	5-9-2009	Approval	N
Change in test procedure of the finished product.	--	IB	22-4-2009	5-9-2009	Approval	N
Change in the shelf life of the drug product as packaged for sale.	--	IB	22-4-2009	5-9-2009	Approval	N
Change in the storage conditions of the finished product.	--	IB	22-4-2009	5-9-2009	Approval	N
Change in the name and/or address of the marketing authorisation holder.	--	IA	18-6-2009	30-7-2009	Approval	N
Submission of a new European Pharmacopoeia Certificate of Suitability for an active substance from a currently approved manufacturer.	--	IA	4-8-2009	10-8-2009	Approval	N
Change in the qualitative and/or quantitative composition of the immediate packaging material.	--	IA	2-9-2009	7-9-2009	Approval	N
Variation regarding the change of a brand name in the Netherlands.	--	IB	3-11-2009	7-12-2009	Approval	N