**IPAR**

**Public Assessment Report for a**
**Medicinal Product for Human Use**

Scientific Discussion

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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## I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Imodium LiquiRelief 2mg Soft Capsules from McNeil Healthcare (Ireland) Limited on 1st April 2011 for the symptomatic treatment of acute diarrhoea in adults and children aged 12 years and over.

This application is made in accordance with Article 8(3) of Directive 2001/83/EC. A marketing authorisation (MA) already exists in Ireland for the active constituent of the product. The product for which a marketing authorisation already exists is Arret 2mg Hard Capsule PA 823/53/1. The current application involves a new pharmaceutical form Imodium Soft Capsules 2mg.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at www.imb.ie.

| | |
|---|---|
| Name of the product | Imodium LiquiRelief 2mg Soft Capsules |
| Name(s) of the active substance(s) (INN) | Loperamide hydrochloride |
| Pharmacotherapeutic classification (ATC code) | A07DA03 |
| Pharmaceutical form and strength(s) | 2mg |
| Marketing Authorisation Number(s) in Ireland (PA) | PA23490/025/003 |
| Marketing Authorisation Holder | JNTL Consumer Health I (Ireland) Limited |

## II. QUALITY ASPECTS

### II.1. Introduction

This application is for Imodium LiquiRelief 2mg Soft Capsules.

### II.2 Drug substance

The active substance is loperamide hydrochloride Ph.Eur, an established active substance described in the Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

### II.3 Medicinal product

P.1 Composition

Each capsule contains 2mg loperamide hydrochloride as active substance.
The capsule also contains the following excipients: Capsule fill: propylene glycol monocaprylate, propylene glycol, purified water, Capsule shell: gelatin, glycerol, propylene glycol, FD&C Blue (E133), soya lecithin and triglycerides, medium chain.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for soft capsules, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as PVC/PVDC aluminium blisters which are placed in cardboard cartons containing 12 capsules.

Evidence has been provided that blister material complies with Ph. Eur. requirements and with the relevant EU legislation.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 2 years when stored at or below 30ºC in the original package in order to protect from moisture and light.

**II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects**

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Imodium LiquiRelief 2mg Soft Capsules.

## III. NON-CLINICAL ASPECTS

**III.1 Introduction**

This active substance has been available on the European/Irish market for over 30 years. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

## IV. CLINICAL ASPECTS

**IV.1 Introduction**

Loperamide hydrochloride is a well known active substance with established efficacy and tolerability. This medicinal product is a new pharmaceutical form, or line extension, of Arret 2mg Hard Capsule which is authorised on the Irish market.

The content of the SPC approved during the national / procedure is in accordance with that accepted for the reference product marketed by the marketing authorisation holder (MAH).

The applicant has submitted the results of a three-way bioequivalence test of Imodium Direct Soft Capsules, versus Imodium 2mg Quick Dissolve Tablets and Imodium 2mg capsules in fasting, normal, healthy, non-smoking male and female subjects. Bioequivalence was assessed by measuring and comparing the AUC 0-t and the Cmax between treatments. The results indicated that the test / reference geometric mean ratios of Cmax and the 90% confidence intervals of mean ratios for AUC 0-t of loperamide were within the 80-125% range.

The IMB has been assured that good clinical practice (GCP) standards were followed in an appropriate manner, in the studies conducted.

**IV.2 Pharmacokinetics**

The half-life of loperamide in man is 10.8 hours with a range of 9-14 hours. Studies on distribution in rats show high affinity for the gut wall with preference for binding to the receptors in the longitudinal muscle layer. Loperamide is well absorbed from the gut, but is almost completely extracted and metabolised by the liver where it is conjugated and excreted via the bile. Due to its high affinity for the gut wall and its high first pass metabolism, very little loperamide reaches the systemic circulation.

**IV.3 Pharmacodynamics**

Loperamide binds to the opiate receptor in the gut wall, reducing propulsive peristalsis and increasing intestinal transit time. Loperamide increases the tone of the anal sphincter.
In a double blind randomised clinical trial in 56 patients with acute diarrhoea receiving loperamide, onset of anti-diarrhoeal action was observed within one hour following a single 4 mg dose. Clinical comparisons with other antidiarrhoeal drugs confirmed this exceptionally rapid onset of action of loperamide.

**IV.5 Clinical Safety**

A risk minimisation plan (RMP) is not required with this marketing authorisation application as loperamide has well-established safety and for which no specific risk minimisation measures beyond the product information are necessary.

The periodic safety update report (PSUR) cycle is to be harmonised with the currently approved imodium product and should be submitted in a 3 year cycle in line with existing loperamide products, based on the international birth date (IBD) of 31$^{st}$ May 1973.
The next PSUR will cover the reporting period 01 June 2009 to 31 May 2012.

The marketing authorisation holder (MAH) submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

**IV.6 Discussion on the clinical aspects**

This application was made for a change to an existing marketing authorisation leading to a national line extension under Article 8(3) of Directive 2001/83, as referred to in Annex II of Regulation 1084/2003/EC.

This medicinal product is a new pharmaceutical form or line extension of Arret 2mg Hard Capsule which is authorised on the Irish market.

The new pharmaceutical form is Imodium LiquiRelief 2mg Soft Capsules.

The applicant submitted the results of a three-way bioequivalence test of Imodium Direct Soft Capsules, versus Imodium 2mg Quick Dissolve Tablets and Imodium 2mg capsules in fasting, normal, healthy, non-smoking male and female subjects.

This was a three way crossover, randomised, blinded, single-dose, fasting, bioequivalence study. The protocol was approved by the Quebec Institutional Review Board and the study was performed in compliance with GCP. The population consisted of normal, healthy, male and female subjects between the ages of 18 and 55 years.

There were 36 subjects dosed in period I, 34 of whom completed the study. One subject withdrew because of an adverse event (AE), and 1 subject was dismissed because of administrative reasons (positive nicotine result at check-in for period III). Pharmacokinetic and statistical analyses were performed on the 34 subjects who completed the study.
Bioequivalence was assessed by comparing the peak and total systemic exposure of loperamide using AUC 0-t, AUC 0-inf and Cmax.

The statistical results indicated that test / reference geometric mean ratios and the 90% confidence intervals for AUC 0-t, AUC 0-inf and Cmax of loperamide were within the 80.00%-125.00% range. Therefore, bioequivalence was established between a test formulation of Loperamide HCl 2 mg Direct Soft Capsules and the reference, Imodium™ 2 mg Capsules, under single-dose, fasting conditions.

## V. OVERALL CONCLUSIONS

BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Imodium LiquiRelief 2mg Soft Capsules from McNeill Healthcare (Ireland) Limited for the symptomatic treatment of acute diarrhoea in adults and children aged 12 years or over.

This application was made for a change to an existing marketing authorisation leading to a national line extension under Article 8(3) of Directive 2001/83, as referred to in Annex II of Regulation 1084/2003/EC.

The new pharmaceutical form is Imodium LiquiRelief 2mg Soft Capsules.

The applicant submitted the results of a three-way bioequivalence test of Imodium Direct Soft Capsules, versus Imodium 2mg Quick Dissolve Tablets and Imodium 2mg capsules in fasting, normal, healthy, non-smoking male and female subjects.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

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

The IMB, on the basis of the data submitted considered that Imodium LiquiRelief Soft Capsules demonstrated bioequivalence with the reference product, as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

## VI. REVISION DATE

March 2024

## VII. UPDATES

| SCOPE | PROCEDURE NUMBER | PRODUCT INFORMATION AFFECTED | DATE OF START OF PROCEDURE | DATE OF END OF PROCEDURE |
|---|---|---|---|---|
| MA transfer | CRN00F4T9 | SmPC section 7, 8, 10<br>Package Leaflet<br><br>New MA Holder:<br>JNTL Consumer Health I (Ireland) Limited,<br><br>New PA number:<br>PA23490/025/003 | N/A | 01/03/2024 |