COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Loperamide HCl Sanias 2 mg, hard capsules

(loperamide hydrochloride)

NL/H/4046/001/DC

Date: 8 November 2018

This module reflects the scientific discussion for the approval of Loperamide HCl Sanias 2 mg, hard capsules. The procedure was finalised at 6 June 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Loperamide HCl Sanias 2 mg, hard capsules from Aurobindo Pharma B.V.

The product is indicated for the symptomatic treatment of acute diarrhoea in adults and children aged 12 years and older.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Imodium 2 mg capsules (NL Licence RVG 6945) which has been registered in the Netherlands by Johnson & Johnson Consumer Health Netherlands since 20 January 1976.

The concerned member states (CMS) involved in this procedure were Belgium, Czech Republic, Germany, Poland and Romania.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Loperamide HCl Sanias is a white opaque cap/white opaque body, hard gelatin capsule shell, imprinted with '2'on cap and 'L' on body with black ink filled with white to off-white power.

The product contains as active substance 2 mg of loperamide hydrochloride.

The hard capsule is packed in clear PVC/aluminium blisters pack.

The excipients are:
Capsules content - lactose monohydrate, maize starch, talc (E553b) and magnesium stearate (E470b)
Capsules shell - titanium dioxide (E171) and gelatin (E441)
Printing Ink - shellac (E904) and black iron oxide (E172)

II.2 Drug Substance

The active substance is loperamide hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white powder and is slightly soluble in water. The drug substance exhibits polymorphism, control of polymorphic form I has been demonstrated.

The CEP procedure is used for 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 general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has 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. The specification is in line with the CEP, and includes additional requirements for particle size and microbial contamination. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for eight full batches stored at 25°C/60% RH (up to 60 months) and 40°C/75% RH (6 months). No changes are observed for any of the tested parameters during the accelerated and long-term stability studies. Based on the data submitted, a retest period could be granted of 60 months when protected from light.

II.1 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. Polymorphic stability of the drug substance in the drug product has been demonstrated.

The manufacture and composition of the bioequivalence batch is identical to those of the validation and commercial batches. Comparative dissolution profiles at three pHs have been provided. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The capsules are manufactured by a direct filling process. This consists of blending the sifted components after which they are blended with the lubricant and then filled into the capsules. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph.Eur. 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 description, identification, dissolution, related substances, content uniformity, assay, water content, lock length, average fill mass, identification of titanium dioxide and microbial contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life acceptance limits are identical, except wider limits for related substances and water content. Acceptable acceptance limits for dissolution and total impurities are included.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for three full scaled batches stored at 25°C/60% RH (12 months), 30°C/65% 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 the proposed packaging. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

Additional stability data concerning dissolution determined at 30 minutes have been provided and support the claimed shelf-life and storage conditions.

On basis of the data submitted, a shelf life was granted of two years. The labelled storage condition is ‘store below 30°C’. An additional storage precaution “store in the original container in order to protect from moisture” is included.

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 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Loperamide HCl Sanias 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 Loperamide HCl Sanias is 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Imodium 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 hydrochloride is a 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 generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Loperamide HCl Sanias 2 mg hard capsules (Aurobindo Pharma B.V., The

Netherlands) is compared with the pharmacokinetic profile of the reference product Imodium 2 mg hard capsules (Janssen-Cilag, France).

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 studies

Design

A open-label, randomised, two-treatment, two-sequence, two-period, cross-over, single dose bioequivalence study was carried out under fasted conditions in 42 healthy male/female subjects, aged 21-43 years. Each subject received a single dose (2x 2 mg) of one of the two loperamide hydrochloride formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected at 0.33, 0.67, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

The design of the study is acceptable. The sampling times and the wash-out period are considered sufficiently long considering the range of T_{max} between 2 and 4 hours and the elimination half life of 11 hours.

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

One subject was withdrawn from the study due to vomiting in period I and one subject was absent for period II check-in. The plasma samples of one subject were analysed and presented but not considered for pharmacokinetic analysis and statistical analysis as per the protocol section 13.2 “Pharmacokinetic Parameters and Analysis” as the pre-dose value is greater than 5% of C_{max} in period-II for this subject. Therefore, 39 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=39	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	33190.0 ± 11383	37975.0 ± 13825	1546.9 ± 549	4.50 (1.50 - 8.00)

Reference	34969.6 ± 11908	39858.2 ± 14387	1690.9 ± 527	4.50 (1.00 - 6.00)
***Ratio (90% CI)**	0.95 (0.90 – 1.00)	--	0.90 (0.85 – 0.97)	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Loperamide HCl Sanias 2 mg hard capsules is considered bioequivalent with Imodium 2 mg hard capsules.

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 Loperamide HCl Sanias.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Ileus (including paralytic ileus) • Megacolon (including toxic megacolon) • Severe skin reactions, including Stevens Johnson syndrome, toxic epidermal necrolysis and erythema multiforme
Important potential risks	• Prolonged use masking an underlying condition requiring medical attention • CNS toxicity due to relative overdose in patients with hepatic impairment • QT prolongation and/or serious ventricular arrhythmia, including Torsades de Pointes associated with abuse and misuse of loperamide
Missing information	• Use in children under two years of age • Use in pregnant or breastfeeding women

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. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Loperamide Galpharm 2 mg hard capsules (UK/H/4344/001/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content of the leaflet. Additionally for the design and lay-out the Loperamide HCL Aurobindo is similar to Metoprolol Aurobindo PL.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Loperamide HCl Sanias 2 mg, hard capsules has a proven chemical-pharmaceutical quality and is a generic form of Imodium 2 mg hard capsules. Imodium 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 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 Loperamide HCl Sanias with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 June 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse