COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Loperamide HCl Tenshi 2 mg, oral lyophilisate (loperamide)

NL/H/4900/001/DC

Date: 8 November 2021

This module reflects the scientific discussion for the approval of Loperamide HCl Tenshi 2 mg, oral lyophilisate. The procedure was finalised at 26 August 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
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 Tenshi 2 mg, oral lyophilisate, from Tenshi Kaizen B.V.

The product is indicated for symptomatic treatment of acute diarrhoea in adults and adolescents aged 12 years and over.

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 Instant smelttablet 2 mg, orodispersible tablets (NL RVG 33724) which has been registered in the Netherlands by Johnson & Johnson Consumer B.V since 10 April 2007.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Czech Republic, Germany, Denmark, Greece, Spain, Finland, Croatia, Ireland, Iceland, Luxembourg, Norway, Portugal and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Loperamide HCl Tenshi is an oral lyophilisate and is a white to off-white, round tablet, debossed with “T” on one side.

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

The oral lyophilisate is packed in a PVC/polyamide/aluminium/PVC blister with peel-off lidding of paper/PET/aluminium foil.

The excipients are: pullulan (E1204), mannitol (E421), sodium hydrogen carbonate (E500), aspartame (E951), polysorbate 80 (E433) and peppermint flavour (corn maltodextrin, flavouring ingredients and modified waxy maize starch, 1450).

II.2 Drug Substance

The active substance is loperamide, 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 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 and meets the requirements of the monograph in the Ph. Eur. for loperamide hydrochloride. Adequate in-house criteria are used for related substances, residual solvent, particle size and polymorphism. The produced crystalline form is form I. The applicant has justified omission of microbiological purity test. Batch analytical data demonstrating compliance with the specification have been provided for two exhibit batches and three production batches.

Stability of drug substance

The submitted CEP does not contain information about a retest period, therefore, stability data of the active substance have been provided by the active substance manufacturer for eight validation batches in accordance with applicable European guidelines. The batches were stored at 25°C/60% RH (60 months completed) and 40°C/75% RH (six months completed) and packed in a double polyethylene bag (outer black) placed in a polyethylene container. All results comply with the established specification; only one impurity has been detected, which is acceptable. Although no photostability studies are performed, the storage condition “Protect from light” has been proposed (as per recommendation of the respective Ph. Eur. monograph). Based on the data submitted, the claimed retest period of 60 months has been accepted, when stored in a double polyethylene bag (outer black) placed in a polyethylene container. The drug product manufacturer has assigned a re-test period of 12 months.

II.3 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 aim of the pharmaceutical development was to develop a product essentially similar to the innovator product. The drug product was developed using the quality by design approach. A detailed study of the reference product was carried out which resulted in a quality target product profile (QTPP); from the QTPP the drug product Critical Quality Attributes (CQAs) were identified. A risk assessment has been provided for the drug substance and formulation attributes, but no Design of Experiments (DoE) studies are presented and no design space is claimed. The development of the product has been presented in detail. General properties of the drug substance have been adequately described. Excipients have been chosen to resemble those of the innovator product, however, after formulation studies the MAH has changed one of the matrix agent excipients.

Comparative dissolution studies complementary to a bioequivalence study have been performed at three different media, in accordance with applicable guidelines.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The detailed description of the manufacturing process and in-process controls are satisfactory given. Due to manufacturing process techniques which includes quick freezing and freeze-drying, the process is considered as non-standard. Process validation data on the product have been presented for six production scale batches in accordance with the relevant European guidelines.

Control of excipients

Except for peppermint flavour, compliance with current versions of the respective Ph. Eur. monographs is confirmed. In-house specifications of the peppermint flavour have been provided. These specifications are acceptable.

Microbiological Attributes

The drug product is a non-sterile oral dosage form, and microbial limit test is incorporated in the finished product specification. Established specification complies with requirements for non-sterile pharmaceutical products described in the European Pharmacopoeia.

The container closure system comprising blister packs of satisfactorily described, and primary packaging of the product complies with the corresponding requirements of the legislation on foodstuffs and with the current requirements of the Ph. Eur. for primary packaging materials (Ph. Eur. 3.1.11 and EU Directive EU 10/2011).

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 appearance, water content, disintegration,

uniformity of dosage units (content uniformity), identification, dissolution, assay, related substances and microbiological purity. The release and shelf-life limits are identical, except for the limit for individual unknown impurities. 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 three commercial size batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data have been provided for six batches packed in the final packing material (aluminium blisters) stored at 25°C/60% RH (three batches; 24 months storage) and at 40°C/75% RH (three batches; six months storage) according to ICH guidelines. The proposed shelf-life of 24 months for the drug product is considered acceptable. A photostability study showed that the product is not sensitive to light. The results provided at both conditions meet the specification requirements for all the tested batches. No temperature restriction is necessary as the drug product is stable at accelerated conditions. No specific storage conditions need to be included in the SmPC or on the label.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Loperamide HCl Tenshi 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 Tenshi 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 Instant smelttablet, 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 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 under fasting conditions and one bioequivalence study under fed conditions, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Loperamide HCl Tenshi 2 mg, oral lyophilisate (Tenshi Kaizen B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Imodium Instant smelttablet 2 mg, orodispersible tablets (Johnson & Johnson Consumer B.V, The Netherlands).

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

According to the *Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract* (CPMP/EWP/239/95 Rev. 1, Corr.1*) bioequivalence studies under both fasting and fed conditions are appropriate for this locally acting drug product in the gastrointestinal tract.

In both studies, a loperamide dose of 8 mg (2 mg x 4 tablets) was tested in order to maximise the systemic exposures and overcome the issues with quantification of the low levels of the drug detected in plasma. Loperamide acts locally on the gastrointestinal tract and only a small fraction of the drug reaches the systemic circulation. The provided rationale for using 4 x 2 mg tablets is acceptable.

IV.2.1 Bioequivalence studies

IV.2.1.1 Study under fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 78 healthy subjects, aged 19-44 years. Each subject received a single dose of 8 mg (2 mg x 4 tablets) of one of the two loperamide formulations. The tablet was orally administered after a fasting period of at least ten hours. The tablets were placed on the upper part of the tongue at scheduled dosing time under sodium vapor lamp at ambient temperature to dissolve quickly and then the entire resultant liquid was swallowed. Just prior to dosing 20 mL of water was provided to wet the mouth. Subjects were advised not to chew or crush or swallow the whole tablet. There were two dosing periods, separated by a washout period of 14 days. Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, 48, 72, 96 and 120 hours after administration of the products.

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.

Results

Out of 78 subjects, 73 subjects were eligible for pharmacokinetic analysis. Five subjects were withdrawn during the conduct of the study due to the following reasons: tablet fell from mouth (one subject), withdrew consent (one subject), adverse event (one subject) and not reporting to study facility (two subjects).

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

Treatment N=73	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	47.7 ± 17.2	50.5 ± 18.7	2.3 ± 0.9	2.0 (0.5-8.0)
Reference	47.0 ± 17.4	50.0 ± 19.3	2.4 ± 1.0	2.0 (0.5-8.0)
***Ratio (90% CI)**	1.024 (0.981-1.069)	--	0.992 (0.919-1.071)	--
CV (%)	15.68	--	28.24	--

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

**ln-transformed values*

IV.2.1.2 Study under fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 78 healthy subjects, aged 18-44 years. Each subject received a single dose of 8 mg (2 mg x 4 tablets) of one of the two loperamide formulations. After an overnight fasting period of at least ten hours, the tablets were placed on the upper part of the tongue at scheduled dosing time exactly 30 minutes after the start of a high-fat high calories breakfast (62.6 g fat; 987.1 kcal) under sodium vapor lamp at ambient temperature to dissolve quickly and then the entire resultant liquid was swallowed. Just prior to dosing 20 mL of water was provided to wet the mouth. Subjects were advised not to chew or crush or swallow the whole tablet. There were two dosing periods, separated by a washout period of 14 days. Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, 48, 72, 96 and 120 hours after administration of the products.

The design of the study is acceptable. The high-fat, high-calorie breakfast was in line with relevant guidelines.

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

Out of 78 subjects, 71 subjects were eligible for pharmacokinetic analysis. Seven subjects were withdrawn during the conduct of the study due to the following reasons: not completing high fat high calorie breakfast (one subject), withdrew consent (one subject), adverse event (three subjects) and not reporting to study facility (two subjects).

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of loperamide under fed conditions.

Treatment N=73	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	68.7 ± 21.7	72.6 ± 23.1	2.3 ± 0.9	6.0 (2.5-12)
Reference	67.1 ± 23.8	71.2 ± 26.1	2.2 ± 0.9	6.0 (0.8-24)

***Ratio (90% CI)**	1.023 (0.960-1.091)	--	1.013 (0.939-1.091)	--
CV (%)	23.07	--	27.28	--

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

**ln-transformed values*

IV.2.1.3 Conclusion on bioequivalence studies

For both bioequivalence studies 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 studies, Loperamide HCl Tenshi is considered bioequivalent with Imodium Instant smelttablet 2 mg, orodispersible tablets.

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 Tenshi.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Severe skin reactions, including Stevens Johnson syndrome, Toxic epidermal necrolysis and Erythema multiforme • Ileus (including paralytic ileus) • Megacolon
Important potential risks	• QT prolongation and/or serious ventricular arrhytmias, including Torsades de Pointes associated with abuse and misuse of loperamide • CNS toxicity due to relative overdose in patients with hepatic impairment • Prolonged use masking an underlying condition requiring medical attention
Missing information	• 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 Instant smelttablet 2 mg, orodispersible tablets. No new clinical studies were conducted. The MAH demonstrated two bioequivalence studies under fasting and fed conditions 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

The package leaflet (PL) 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 four participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Loperamide HCl Tenshi 2 mg, oral lyophilisate has a proven chemical-pharmaceutical quality and is a generic form of Imodium Instant smelttablet 2 mg, orodispersible tablets. Imodium Instant smelttablet 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 Tenshi with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 August 2021.

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