Public Assessment Report

Scientific discussion

Livoden
(flurbiprofen)

SK/H/0325/001/DC

Date of this report:	17/12/2025

This module reflects the scientific discussion for the approval of Livoden. The procedure was finalised at date of day 210. For information on changes after this date please refer to the module 'Update'.

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I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Livoden; oromucosal spray, solution; 8,75 mg/dose.
The product is indicated for the short-term symptomatic relief of acute sore throat in adults.
A comprehensive description of the indications and posology is given in the SmPC.

II EXECUTIVE SUMMARY

II.1 Rationale for the product

As this product is a local acting product, bioavailability studies cannot be used to demonstrate bioequivalence, therefore the legal basis chosen in compliance with Article 10(3) of Directive 2001/83/EC is hybrid.

II.2 About the product

Mode of action
Flurbiprofen is a NSAID/propionic acid derivative that exerts its efficacy by inhibiting prostaglandin synthesis. In humans, flurbiprofen has pronounced analgesic, antipyretic and anti-inflammatory properties. Flurbiprofen is a mixed COX-1/COX-2 inhibitor with some selectivity for COX-1, according to studies conducted with the "whole blood test". Flurbiprofen has been shown to be effective in reducing the discomfort of sore throat when given topically.

Pharmacological classification
Throat preparations, other throat preparations
ATC Code: R02AX01

Claimed indication and recommendation for use (including a possible risk management strategy) and posology

<Product name> is indicated for the short-term symptomatic relief of acute sore throat in adults.

Posology
Adults aged 18 years and over
One dose of 8.75 mg (3 actuations) administered to the back of the throat every 3-6 hours as required, up to a maximum of 5 doses in a 24-hour period.

Do not inhale whilst spraying.

It is recommended that this product should be used for a maximum of three days.

The lowest effective dose should be administered for the shortest duration necessary to control symptoms.

Paediatric population
The safety and efficacy of <Product name> in children or adolescents under 18 years has not been established.

Elderly patients
A general dose recommendation cannot be given, since to date clinical experience is limited. The elderly are at increased risk of the serious consequences of adverse reactions.

Renal and hepatic impairment

No dose adjustment is needed in patients with mild to moderate stages of renal or hepatic impairment. In severe stages medicinal product is contraindicated.

Method of administration
For oromucosal use and short-term administration only.

Before first use, shake the device and activate the pump by pointing the nozzle away from you and spraying a minimum of four times until a fine, consistent mist is produced. The pump is then primed and ready for use.

Between each dose point the nozzle away from you and spray a minimum of once ensuring a fine, consistent mist is produced. Always ensure a fine consistent mist is produced before dosing the product.

II.3 General comments on the submitted dossier

This concerns an application for a marketing authorisation of a Livoden; oromucosal spray, solution; 8,75 mg/dose according to Article 10(3) (hybrid application) of the European directive 2001/83/EC as amended.

As a reference medicinal product for providing the proof of data exclusivity expiry Strepfen Citroen & Honing 8,75 mg, zuigtabletten (NL/H/4456, ***lozenge)*** from Reckitt Benckiser was chosen. For the reference medicinal product authorised in the RMS and CMS product authorised under procedural No. NL/H/4455 from Reckitt Benckiser under several brand names (Strepfen/Strepsils, **oromucosal spray, solution)** was chosen.

Applicant did not generate new own clinical data. As this product is a local acting product, the applicant claims that bioavailability studies cannot be used to demonstrate bioequivalence, therefore the legal basis chosen in compliance with Article 10(3) of Directive 2001/83/EC was hybrid. Instead, the Applicant proposed to waive clinical study on the basis of essential similarity of the reference and tested product from the quality point of view. The results of in vitro experiments showed comparability with reference product in terms of single actuation content, droplet size distribution, spray pattern and plume geometry.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer of the proposed product and batch release site situated in the EU.

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The development of the product has adequately been performed and described.
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The control tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.“

III.2 Non clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of flurbiprofen are well known. As flurbiprofen is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

Environmental Risk Assessment (ERA)
The Applicant provided consumption data over the years 2018-2021 which showed that in Slovakia, consumption is decreasing. The Applicant also provided consumption data over the years 2018-2021 for Poland. They show that the consumption of flurbiprofen is not increasing significantly and is rather stable. Thus, the environmental exposure is not expected to increase.

III.3 Clinical aspects

Flurbiprofen is a propionic acid derivative NSAID which acts through inhibition of prostaglandin synthesis.

Flurbiprofen is indicated for the short-term symptomatic relief of acute sore throat in adults. One dose of 8.75 mg (3 actuations) administered to the back of the throat every 3-6 hours as required, up to a maximum of 5 doses in a 24-hour period. It is recommended that this product should be used for a maximum of three days.

A single dose of flurbiprofen 8.75 mg is delivered directly to the throat as three sprays and the flurbiprofen is readily absorbed, with detection in the blood between 2 and 5 minutes and plasma concentrations peaking at 30 minutes after administration, but remaining at a mean low level of 1.6 µg/ml which is approximately 4 times lower than a 50 mg tablet dose. Flurbiprofen oromucosal spray formulation has demonstrated to be bioequivalent to flurbiprofen 8.75 mg lozenges. Absorption of flurbiprofen can occur from the buccal cavity by passive diffusion. Rate of absorption is dependent on pharmaceutical form with peak concentrations

achieved more rapidly than, but of similar magnitude to, those achieved after an equivalent swallowed dose.

Flurbiprofen is rapidly distributed throughout the body and is extensively bound to plasma proteins. Flurbiprofen is excreted via the kidneys. It has an elimination half-life of 3 to 6 hours. Flurbiprofen is excreted in very small amounts in human milk (less than 0.05 µg/ml). Approximately 20-25% of a flurbiprofen oral dose is excreted unchanged.

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

No clinical study has been submitted. The Applicant proposed to waive clinical study on the basis of essential similarity of the reference and tested product from the quality point of view.

The applicant followed draft of US guideline "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action". The results of *in vitro* experiments showed comparability with reference product in terms of single actuation content, droplet size distribution, spray pattern and plume geometry. Amount of drug in small particles was outside of BE CI, however, the draft guidance considers this as acceptable as it was lower than for reference product which suggests lower delivery into airways which supports better safety. The results altogether shows absence of clinically relevant differences between test and reference product.

According to EU guidelines found in Equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract, in recommendations for products acting locally in the mouth and/or throat state that if product is a solution what the case of both test and reference product is, clinical studies can be waived if excipients are sufficiently similar.

The Applicant provided a discussion of excipients. Excipients except preservatives are qualitatively similar and that the Applicant conducted number of *in vitro* tests which showed similarity of test and reference products in terms of single actuation content, droplet size distribution, spray pattern and plume geometry.

Considering that the formulations contain flavouring, no local residence time issues are expected. This is same for viscosity and surface tension as physical properties were shown to be similar with the reference product. Also, identical dissolution enhancers are used.

To conclude, no clinically relevant impact is expected.

Summary Pharmacovigilance system

The Applicant has submitted a signed Summary of the Proposed Pharmacovigilance System version 02. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

The applicant has also submitted a signed Summary of the Pharmacovigilance System for the MAH Pharmalab Poland Sp. z o.o., which is accepted.

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 Livoden.

Safety specification

Table: Summary of safety concerns proposed by the applicant in RMP version 0.1

Summary of safety concerns	
Important identified risks	- None
Important potential risks	- None
Missing information	- None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
The safety information in the proposed product information is aligned to the reference medicinal product.

Summary of the RMP

The submitted Risk Management Plan, version 0.1 signed 21.03.2024 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:
- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The applicant proposed renewal date 5 years after the end of procedure.

IV BENEFIT RISK ASSESSMENT

This application concerns a hybrid medicinal product referencing Strepfen Sprej 8,75 mg orálna roztoková aerodisperzia.
Bioequivalence with the reference medicinal product has been not demonstrated.
Overall, from the quality, non-clinical and clinical point of view the application is of sufficient quality in view of the present European regulatory requirements.

V RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

NA

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

NA

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

Assessment of the User Testing is attached in the 'QRD Guidance and Checklist for the Review of User Testing Results.

V.5 Labelling

The approved Labelling is available in the MRI Product Index.

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
-	-	-	-	-	-