IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Ryhogen 400 mg film-coated tablets
Ibuprofen lysine
PA1701/015/001

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.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Ryhogen 400 mg film-coated tablets from Zentiva k.s., on the for short-term symptomatic treatment of
- mild to moderate pain, such as headache, toothache and period pain
- fever

This application for a marketing authorisation was submitted in accordance with Article 10.1 of Directive 2001/83/EC and is referred to as a 'Generic" application. Ireland acted as the Reference Member State in this Decentralised with CMS Portugal.

The marketing authorisation for Ryhogen 400 mg film-coated tablets, was issued based on the acceptable demonstration of bioequivalence to the designated reference product. The reference product is a European reference product used in RMS, Nurofen Immedia 400 mg film-coated tablets, MAH Reckitt Benckiser Deutschland GmbH, MA: 43917.01.00. The reference product used in the pharmacokinetic was from the same global authorisation, Nurofenflash 400 mg film-coated tablets by Reckitt Benckiser Netherlands from the French market.

To support the article 10.1 generic applicant, the applicant has provided
- Bioequivalence study
- Product information from EU states where the product strength is registered.
- A systematic review of previously published studies on the pharmacology, safety and efficacy of ibuprofen lysinate.

This medicinal product is subject to medical prescription which may be renewed.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Ryhogen 400 mg film-coated tablets
Name(s) of the active substance(s) (INN)	Ibuprofen lysine
Pharmacotherapeutic classification (ATC code)	M01AE01,
Pharmaceutical form and strength(s)	400 milligram(s) Film-coated tablet
Marketing Authorisation Number(s) in Ireland	PA1701/015/001,
Marketing Authorisation Holder	Zentiva k.s.
MRP/DCP No.	IE/H/1315/001/DC
Reference Member State	IE
Concerned Member State	PT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Ryhogen 400 mg film-coated tablets.

II.2 Drug substance

The active substance is Ibuprofen lysinate, is an established active substance, 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

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

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 the dosage form, 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 approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

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 and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

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 Ryhogen 400 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Nurofen Immedia 400mg Film-coated tablet on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

The pharmacodynamic, pharmacokinetic and toxicological properties of Ibuprofen are well known.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Ibuprofen poses a risk to the aquatic environment. Since Ryhogen 400 mg film-coated tablets, are intended for generic substitution, this will not lead to an increased exposure to the environment. Additional studies on environmental risk assessment are therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of Ibuprofen are well known. As Ibuprofen is a widely used, well-known active substance, the applicant has not provided additional studies, and further studies are not required. A nonclinical overview based on literature review was provided and is acceptable. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ibuprofen lysine is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the European reference product Nurofen Immedia 400 mg film-coated tablets, marketed by MAH Reckitt Benckiser Deutschland, MA: 43917.01.00.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Ryhogen 400 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Nurofenflash 400 mg film-coated tablets.

An open label, balanced, randomized, two-treatment, two-sequence, two-period, single oral dose, crossover, bioequivalence study was carried out. Ryhogen 400 mg film-coated tablets by Zentiva k.s, was compared to the reference product Nurofenflash 400 mg film-coated tablets by Reckitt Benckiser Netherlands from the French market. Based on the pharmacokinetic parameters of active substance Ibuprofen lysinate and, the reference tablet Nurofenflash 400 mg film-coated tablets marketed by Reckitt Benckiser in the French market and test tablet Ryhogen 400 mg film-coated tablets are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

In support of this application, the applicant submitted the following bioequivalence study:

PMRI Study Number: 2023-5414:
A Single-Dose, Comparative Bioavailability Study of test product (*Lirepin (Ibuprofen lysinate), 400 mg film-coated tablets by Zentiva k.s*) **of Ibuprofen Lysinate, vs Reference product (***Nurofenflash 400 mg film-coated tabletsby RB, Netherlands from the French market*) **under Fasting Conditions.**

After an overnight fast of at least 10 hours, the subjects were administered orally 1 tablet (400 mg) of ibuprofen (as lysinate) with approximately 240 mls of water.

Blood samples were collected for plasma levels before dosing and up to and including 16hours after each administration.

The washout period between the treatment phases was 7 days, which was sufficient to eliminate any carryover effect of the drug between treatment periods.

Summary statistics for the pharmacokinetic parameters for zopiclone, between the test and reference medicinal products, are presented below

Table 1: Geometric mean and 90% CI for Ibuprofen

Treatment	**AUC_{0-t}** µg /ml/h	**C_{max}** µg/ml
Test	124.00±33.15	47.84 ±9.83
Reference	124.29 ±29.60	47.51 ±11.08
***Ratio (90% CI)**	99.11 (96.45 – 101.84)	101.29 (97.15 -105.60)

Cmax = maximum plasma concentration
AUC0-t = area under the plasma concentration-time curve from zero to t hours

The 90% confidence intervals of the test/reference ratio for AUC 0-t and C max values for Ibuprofen lie within the acceptable limits of 80.00 % to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's test product, Lirepin (Ibuprofen lysinate), 400 mg film-coated tablets by Zentiva k.s is bioequivalent to the Reference product Nurofenflash 400 mg film-coated tablets by RB, Netherlands from the French market.

IV.3 Pharmacodynamics

No new studies on pharmacodynamics have been submitted. As bioequivalence with the reference product has been demonstrated, additional pharmacodynamic data is not necessary.

IV.4 Clinical Efficacy

No additional efficacy clinical studies to demonstrate efficacy have been included in the application. This is appropriate for this type of application.

IV.5 Clinical Safety

The overall safety profile of ibuprofen lysinate is established and generally known. No additional safety clinical studies to demonstrate safety have been included in the application and none are required.

A Risk Management Plan version 1.0, signed 5th March 2025 has been submitted, 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 ibuprofen lysinate . It is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

Summary table of safety concerns as approved in RMP:

Important identified risks	None
Important potential risks	None
Missing information	None

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.

IV.6 Discussion on the clinical aspects

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required.

The applicant has submitted the results of suitable bioequivalence studies, which have demonstrated the similarity of the test products against the reference products, in accordance with the relevant guidance.

No additional tests are required for this application.

The applicant has also submitted a clinical overview and summary of the evidence demonstrating the efficacy and safety of this product in clinical practice.

Full Patient Leaflet testing was conducted.

V. OVERALL CONCLUSIONS

Ryhogen 400 mg film-coated tablets is a generic form of Nurofen Immedia Film-coated tablet. Nurofen Immedia Film-coated tablet is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

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 HPRA, on the basis of the data submitted considered that Ryhogen 400 mg film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

9th of May 2025