IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Mybufen Max Rapid 400 mg soft capsules
Ibuprofen
PA1436/046/001

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Mybufen Max Rapid 400 mg soft capsules, from Bluefish Pharmaceuticals AB on 16th August 2024 for use as an anti-inflammatory, analgesic and antipyretic for short term management of mild to moderate pain, fever and inflammation such as is associated with headache, dental pain, period pain, muscular strain, neuralgia, rheumatic pain and migraine and for the management of the symptoms of head colds and influenza.

This application for a national marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a "generic" application.

The reference product is Nurofen Rapid Relief Maximum Strength 400mg Liquid Capsules, Reckitt Benckiser Ireland Ltd, PA0979/032/013 from Reckitt Benckiser Ireland Ltd authorised in Ireland since 24/07/2009.

Mybufen Max Rapid 400 mg soft capsule will be supplied as a non-prescription medicinal product available through pharmacies only, and promotion to the public subject to the following restrictions: maximum strength 400 mg, maximum pack size 24, maximum dose: 400 mg, maximum daily dose 1200 mg, limited indications. For use in adults and children over 12 years.

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	Mybufen Max Rapid 400 mg soft capsules
Name(s) of the active substance(s) (INN)	Ibuprofen
Pharmacotherapeutic classification (ATC code)	M01AE01
Pharmaceutical form and strength(s)	400 mg, soft capsule
Marketing Authorisation Number(s) in Ireland (PA)	PA1436/046/001
Marketing Authorisation Holder	Bluefish Pharmaceuticals AB

II. QUALITY ASPECTS

II.1. Introduction

This application is for Mybufen Max Rapid 400 mg soft capsules.

II.2 Drug substance

The active substance is ibuprofen, an established active substance described in the European 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 400 mg of ibuprofen.

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/*Ancillary Substances*)

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 a soft capsule, 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.

Adventitious Agent Safety

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by EDQM have been provided for gelatin and compliance with the Note For Guidance on Minimising the Risk if Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products has been satisfactorily demonstrated

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 Mybufen Max Rapid.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Nurofen Rapid Relief Maximum Strength 400mg Liquid Capsules on the Irish market, since 2009. 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.

III.5 Ecotoxicity/environmental risk assessment

Since Mybufen Max Rapid 400 mg is a generic product, it will not lead to an increased exposure to the environment. Further environmental risk assessment is therefore not deemed necessary.
As ibuprofen is known to pose a risk to the aquatic environment, appropriate wording has been included in Sections 5.3 and 6.6 of the SmPC.

III.6 Discussion on the non-clinical aspects

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. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction
Ibuprofenis a well-known active substance with established efficacy, safety and tolerability.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product (for product information) Nurofen Rapid Relief Maximum Strength 400mg Liquid Capsules, marketed by Reckitt Benckiser Ireland Ltd.

To support this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Mybufen Max Rapid 400 mg Soft Capsules is compared with the pharmacokinetic profile of the reference product Nurofen Rapid 400mg Soft Capsules, Reckitt Benckiser Healthcare, SA, Spain.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Mybufen Max Rapid 400 mg Soft Capsules, Bluefish Pharmaceuticals AB, was compared to the reference product Nurofen Rapid 400mg Soft Capsules, Reckitt Benckiser Healthcare, SA. Based on the pharmacokinetic parameters of active substance ibuprofen, the reference product Nurofen Rapid 400mg Soft Capsules, marketed by Reckitt Benckiser Healthcare, SA and test product Mybufen Max Rapid 400 mg Soft Capsules 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.

The bioanalytical analysis was conducted in accordance with the relevant guidelines in operation at the time of conduct of the clinical trial.

IV.2 Pharmacokinetics
The pharmacokinetics of Ibuprofen are well known.

Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. Ibuprofen diffuses into the synovial fluid.

Peak plasma concentration of ibuprofen occurs 1-2 hours after administration of ibuprofen acid. When taken with food, peak plasma levels may be delayed. These times may vary with different dosage forms.

Following hepatic metabolism (hydroxylation, carboxylation, conjugation), the pharmacologically inactive metabolites are completely eliminated, mainly renally (90%), but also with the bile. The elimination half-life in healthy individuals and those with liver and kidney diseases is 1.8 to 3.5 hours. Plasma-protein binding is about 99%.
Elimination half-life is approximately 2 hours. The excretion is rapid and complete via the kidneys.

IV.3 Pharmacodynamics
Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and antipyretic activity. The drug's therapeutic effects as a NSAID are thought to result from inhibitory activity on prostaglandin synthetase. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

IV.4 Clinical Efficacy
The efficacy of Ibuprofen is well known. No new efficacy data have been submitted and none are required for this type of application.

IV.5 Clinical Safety

With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted, and none are required for this type of application. No new or unexpected safety issues arose during the bioequivalence study. The safety of ibuprofen is described in the clinical overview and is well known.

Risk Management Plan

Risk Management Plan version 0.3, with date of final sign off 21 Feb 2024 is considered acceptable. The approved summary of safety concerns is outlined below:

Summary of Safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Routine pharmacovigilance and routine risk minimisation measures are proposed, and this is considered acceptable.

Periodic Safety Update Report (PSUR):

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

Sufficient clinical information has been submitted by the applicant to support authorisation of this medicinal product. The benefit/risk of the product is considered favourable from a clinical perspective and therefore granting a marketing authorisation for Mybufen Max Rapid 400 mg Soft Capsules is recommended.

V. OVERALL CONCLUSIONS

Mybufen Max Rapid 400 mg Soft Capsules is a generic form of Nurofen Rapid Relief Maximum Strength 400mg Liquid Capsules. Nurofen Rapid Relief Maximum Strength 400mg Liquid Capsules 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 Mybufen Max Rapid 400 mg 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

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New National	CRN00DJZV	SmPC, Product Leaflet, PAR	16th August 2024	15th August 2029