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HEALTH PRODUCTS REGULATORY AUTHORITY

PUBLIC ASSESSMENT REPORT FOR A
MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Brupro 200mg Film-coated tablets
Brupro Max 400mg Film-coated tablets
Brupro Rx 600mg Film-coated tablets
IBUPROFEN
PA0074/067/001-003

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.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Brupro 200mg, Brupro Max 400mg and Brupro Rx 600mg Film-coated tablets from Rowa pharmaceuticals on 13th March 2015 for:

Brupro Rx 600mg Film-coated tablets
Symptomatic management of various arthroses such as rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's disease) and osteoarthritis, fibrositis, ankylosing spondylitis and other muscular syndromes, such as low back pain, soft tissue trauma and various inflammations of tendon, joint capsules and ligaments.
Brupro is also used as an analgesic in the relief of mild to moderate pain.

Brupro Max 400mg Film-coated tablets.
For the management of muscular pain, backache, dental pain and dysmenorrhoea.

Brupro 200mg Film-coated tablets
For the short-term management of mild to moderate pain such as headache, dental pain, period pain, muscular strain and backache and for the management of feverishness and the symptoms of colds and influenza.

Brupro Rx 600mg tablets are prescription only category B for supply through pharmacy and promotion to healthcare professionals only.

Brupro 200mg and Brupro Max 400mg tablets will be supplied as non-prescription medicinal products available through pharmacy only.

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

Name of the product	Brupro 200mg, Brupro Max 400mg & Brupro Rx 600mg Film- coated tablets
Name(s) of the active substance(s) (INN)	IBUPROFEN
Pharmacotherapeutic classification (ATC code)	M01AE01
Pharmaceutical form and strength(s)	200mg, 400mg & 600mg Film-Coated Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA0074/067/001-003
Marketing Authorisation Holder	Rowa Pharmaceuticals Limited

II QUALITY ASPECTS

II.1. Introduction

This application is for Brupro 200mg Film-coated tablets, Brupro Max 400mg Film-coated tablets and Brupro Rx 600mg Film-coated tablets.

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 film-coated tablet contains 200mg, 400mg or 600mg 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 guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, 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 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 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

Compliance with the Note for Guidance on Minimising the Risk of 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 Brupro 200mg Film-coated tablets, Brupro Max 400mg Film-coated tablets and Brupro Rx 600mg Film-coated tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of Ibuprofen are well known and the active substance is the same as the reference product Brufen which has been marketed in the EU for a number of years no new preclinical studies were conducted which is acceptable given that this application is for a generic medicinal product of Brufen which has been licensed for over 10 years.

As this product is intended for generic substitution with similar products that are currently marketed, no increase in environmental burden is expected.

There are no objections to the approval of this product from a non-clinical viewpoint.

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

IV CLINICAL ASPECTS

Ibuprofen is 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 Brufen marketed by Abbott laboratories Ltd.

No new clinical efficacy or safety studies were conducted for this application, which is acceptable given that that this application is for a generic version of Ibuprofen was has been licensed for over 10 years.

For this application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Brupro Rx 600mg Film-coated tablets is compared with the pharmacokinetic profile of the reference product Brufen 600mg Film-coated tablets.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Based on the pharmacokinetic parameters of active substance, the reference tablet Brufen 600mg Film-coated tablets marketed by Abbott laboratories ltd and test tablet Brupro Rx 600mg 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.

Criteria for evaluation:
Safety parameters: The clinical safety was evaluated by recording clinical parameters ECG, vital signs, well being and adverse events. The laboratory safety was evaluated by recording routine laboratory tests including biochemistry, hematology and urine analysis before and after the study.

Primary Pharmacokinetic Parameters:
C_{max}, AUC_{0-t} and AUC_{0-inf} were evaluated for % Test / Reference Ration and 90 % CI was calculated for Log – transformed data.
Ration of AUC_{0-t} / AUC_{0-inf} was calculated for test and reference product.

Secondary Pharmacokinetic Parameters:
T_{max}, K_{el} and $t_{1/2}$ were comparatively evaluated by calculating test to reference % Ratio.

Criteria for Bioequivalence:
The 90% confidence intervals were constructed for the ratios (Test / Reference) of the means of log-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf}. Bioequivalence was concluded on the basis of confidence intervals within the range of 80% - 125% for C_{max}, AUC_{0-t} and AUC_{0-inf}.

Statistical Method: ANOVA, two one-sided tests for bioequivalence, 90% CI and ratio analysis for untransformed and log-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} were performed.

SUMMARY:

Pharmacokinetic Results
Primary Pharmacokinetic Parameters:

S-IBUPROFEN
% Test / Reference Ration of Untransformed Data

Pharmacokinetic Parameters	Test Product	Reference Product	% Ratio of Test to Reference Product
C_{max} (µg/ml)	23.074	25.026	92.10
AUC_{0-t} (µg x hr/ml)	94.279	95.755	98.46
AUC_{0-inf} (µg x hr/ml)	98.451	100.243	98.21

90% Confidence Interval from Log Transformed Data

Pharmacokinetic Parameters	Acceptance Criteria	Confidence Interval
LnC_{max}	80-125%	85.02 – 99.01
$LnAUC_{0-t}$	80-125%	88.30 – 103.74
$NnAUC_{0-inf}$	80-125%	88.54 – 103.77

The applicant has provided justification for a biowaiver of the lower strengths 400mg and 200mg film coated tablets which are in line with the CHMP bioequivalence guideline criteria for a biowaiver. Therefore the results of the bioequivalence study performed with the 600mg strength apply to the other strengths.

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 was well known.

Ibuprofen is rapidly absorbed after oral administration, is strongly plasma protein bound. In adults, ibuprofen administered orally is primarily metabolized in the liver by CYP2C9. Ibuprofen and its metabolites are further conjugated to acyl glucuronides.
Ibuprofen is mainly excreted in the urine as inactive metabolites.
The elimination half-life of IV ibuprofen 400mg and 800mg is 2.22 hours and 2.44 hours respectively. Ibuprofen is not dialyzable.

IV.3 Pharmacodynamics

Ibuprofen is a phenylpropionic acid derivative with analgesic, anti-inflammatory and antipyretic activity. The drug's therapeutic effects as a NSAID are thought to result from its inhibitory effect on the enzyme cyclo-oxygenase, which results in a marked reduction in prostaglandin synthesis.
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.

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 Brupro 200mg, Brupro Max 400mg & Brupro Rx 600mg Film-coated tablets.

Based on consideration of the identified risks, the potential risks and the need for additional information on the medicinal product, it is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

The applicant will submit PSURs in line with the agreed submission cycle.

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 Brupro 200mg, Brupro Max 400mg and Brupro Rx 600mg Film-coated tablets is recommended.

V OVERALL CONCLUSIONS

Brupro 200mg, Brupro Max 400mg and Brupro Rx 600mg Film-coated tablets are generic forms of Brufen film coated tablets. Ibuprofen 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 and similar products available on the market.

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 Brupro Rx 600mg film-coated tablets demonstrated bioequivalence with the reference product, provided adequate justification for a biowaiver for lower strengths as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.