IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Buplex 200mg film-coated tablets
Ibuprofen
PA1986/116/001

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

This product was initially authorised under procedure number MT/H/0100/001-002 with the MT as RMS. The responsibility of RMS was transferred to Ireland on 07/07/2021] under procedure number IE/H/1195/001-002.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1986/116/001-002
Marketing Authorisation Holder: Teva B.V.

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

The MT public assessment report published at the time of the initial marketing authorisation is provided herein.

I. INTRODUCTION

This is an application for Ibuprofen 200mg and 400mg film-coated tablets (OTC), under the trade names Ibunin 200mg and Ibunin 400mg based on Article 10 (generics) of Directive 2001/83/EC as amended. The active substance, ibuprofen is not considered a new active substance.

The original medicinal product which has been authorised for not less than 6/10 years in the EEA is Brufen 400 mg film-coated tablets by Abbott Laboratories A/S, registered in Denmark since 1972. Since Brufen is not authorised in Malta, the applicant has chosen Brufen (Abbott Scandinavia AB) as the European Reference Medicinal Product.

With Malta as the Reference Member State in this Decentralised Procedure the applicant (Alchemia Limited, United Kingdom) is applying for Marketing Authorisations in the following Member States: AT, BE, BG, CZ, DE, DK, EE, FI, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SE and SK.

Ibunin 200mg and Ibunin 400mg was approved for the treatment of

- mild to moderate pain, such as headache including migraine headache, dental pain;
- primary dysmenorrhoea; and
- fever

II. QUALITY ASPECTS

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II.1 Introduction

Pharmaceutical form: Film-coated tablets

Formulation:

Active ingredient: Ibuprofen

Excipients:

Tablet core
Cellulose, microcrystalline
Silica, colloidal anhydrous
Hydroxypropylcellulose
Sodium laurylsulfate
Croscarmellose sodium
Talc

Film coating (Opadry (white) 06B28499)
Hypromellose
Macrogol 400
Titanium dioxide (E171)

Container system:

Opaque PVC/Aluminium blister packs.
Clear PVC/Aluminium blister packs.

Tablet containers (polyethylene) with polypropylene caps.

Pack sizes:

Blisters:
6, 10, 12, 20, 24, 30 and 50 film-coated tablets.

Tablet containers:
10, 20, 30 and 50 film-coated tablets.

II.2 Drug Substance

Pharmacological classification: Anti-inflammatory and anti-rheumatic products, non-steroids; propionic acid derivatives. ATC code: M01 AE01

Ibuprofen is a well known substance described in the European Pharmacopeia (Ph. Eur.) Version 6.1 Monograph 0721. It is practically insoluble in water. The manufacturer of the substance is Shasun Chemicals and Drugs Ltd, India who has been granted the certificate of suitability R1-CEP-1996-061-Rev 03, therefore the route of synthesis is covered by this CEP. Ibuprofen quality can be suitably controlled according to its Ph. Eur. monograph complemented by a control on residual solvents and particle size distribution. The drug substance specifications adopted by the applicant, are in line with the current Ph. Eur. monograph 6.1 and with the additional tests given in the CEP. Issues raised to the applicant regarding particle size have been adequately addressed and the applicant has also adopted all additional parameters of the CEP as his own set of specifications as requested. All batch analytical data complied with the limits set out in the CEP and with the new Ph.Eur. monograph 6.1 for ibuprofen. Stability studies have been performed with the drug substance and no significant changes in any parameters were observed.

II.3 Medicinal Product

The development of the product has been described. Excipients common to pharmaceutical manufacture have been selected and each is described in the Ph.Eur. All excipient functions are explained. Comparative dissolution of the different strengths of the tablets manufactured by Alchemia Limited and reference products sourced from several EU countries have been provided and indicate that Ibuprofen Alchemia tablets are comparable to the corresponding Brufen® (Abbott Laboratories Limited, Kent, United Kingdom) tablets used in the Bioequivalence study and to the European reference product in the RMS.

The product specifications cover appropriate parameters for this dosage form. Subdivision of tablets has also been included in the product specifications as requested since the purpose of the score line is for tablet division into equal halves as stated by the applicant. Tightened dissolution limits in line with the results obtained for the batches used in the Bioequivalence study have been adopted by the applicant. Validation results of the analytical methods have been presented. Batch analysis has been performed on two pilot scale size batches for each strength and one full scale production batch. The batch analysis results show that the finished products meet the specifications proposed.

Stability data has been provided for two pilot scale batches and one production scale batch. The conditions applied in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The data submitted (for all tablet strengths) support the proposed shelf-life of 24 months for the product as stored under no special

conditions.

III. NON-CLINICAL ASPECTS

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III.1 Introduction

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

III.2 Environmental Risk Assessment

No Environmental Risk Assessment Report has been submitted. This is acceptable since ibuprofen is a well-known active ingredient and ibuprofen drug products have been marketed worldwide for more than 30 years.

IV. CLINICAL ASPECTS

IV. CLINICAL ASPECTS

IV.1 Introduction

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that possesses anti-inflammatory, analgesic and antipyretic activity. Animal models for pain and inflammation indicate that ibuprofen effectively inhibits the synthesis of prostaglandins. In humans, ibuprofen reduces pain possibly caused by inflammation or connected with it, swelling and fever. In addition ibuprofen has an inhibitory effect on adenosine diphosphate (ADP) or collagen-stimulated platelet aggregation.

IV.2 Pharmacokinetics

Racemic ibuprofen is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after ingestion. It is 90 – 99% bound to plasma proteins and has a plasma half-life of about 2 hours. It is rapidly excreted in the urine mainly as metabolites and their conjugates. About 1% is excreted in urine as unchanged ibuprofen and about 14% as conjugated ibuprofen. There appears to be little if any distribution in the breast milk. Ibuprofen's disposition is stereoselective and there is some metabolic conversion of the inactive R (-) enantiomer to the active S (+) enantiomer.

IV.3 Pharmacodynamics

Ibuprofen inhibits the prostaglandin synthesis in the uterus, thereby reducing intrauterine rest and active pressure, the periodic uterine contractions and the amount of prostaglandins released into the circulation. These changes are assumed to explain the alleviation of menstrual pain. Ibuprofen inhibits renal prostaglandin synthesis which can lead to renal insufficiency, fluid retention and heart failure in risk patients. Prostaglandins are connected with ovulation and the use of medicinal products inhibiting prostaglandin synthesis may therefore affect the fertility of women.

IV.4 Clinical efficacy

All issues concerning indications and posology which were raised by the RMS or the CMS(s) have been adequately resolved by the applicant.

IV.5 Clinical safety

All issues concerning clinical safety which were raised by the RMS or the CMS(s) have been adequately resolved by the applicant.

IV.6 Discussion on the clinical aspects

To support this application, the applicant has submitted one randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Ibuprofen 200 mg tablets of Actavis Group PTC ehf, Iceland and Brufen® (Ibuprofen) 200 mg tablets of Abbott Laboratories Limited, Kent, United Kingdom, in 30 healthy adult males, under fasting conditions, with a washout period of 10 days. The applicant requested a biowaver for the higher 400 mg strength.

The references supplied by the applicant indicate that at higher doses, ibuprofen exhibits nonlinear kinetics due to nonlinear plasma protein binding with a resulting less than proportionate increase in AUC with the given dose. Under these circumstances the largest sensitivity to detect differences between two products would be with a single-strength study conducted on the lowest dose (or a dose in the linear range).

Results of the study show that the 90% confidence intervals of the test/reference (T/R) ratio lie well within the prospectively defined 80 -125% acceptance for AUCt, AUC0-∞, and Cmax for both S (+) and R (-) enantiomers of ibuprofen.

The RMS considers that the request for a Biowiaver for the 400mg strength is justified. There were no safety issues identified during the BE study.

In conclusion bioequivalence between Ibuprofen 200 mg tablets of Actavis Group PTC ehf, Iceland and Brufen® (Ibuprofen) 200 mg tablets of Abbott Laboratories Limited, Kent, United Kingdom has been appropriately demonstrated in this study.

V. OVERALL CONCLUSIONS

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ibuprofen is a well established non-steroidal anti-inflammatory drug (NSAID) that possesses anti-inflammatory, analgesic and anti-pyretic activity. Its clinical efficacy and safety are well-documented.

This application deals with a generic version of the original product Brufen, which has been registered in Denmark since 1972.

Bioequivalence has been shown between Ibuprofen 200 mg tablets of Actavis Group PTC ehf, Iceland and Brufen® (Ibuprofen) 200 mg tablets of Abbott Laboratories Limited, Kent, United Kingdom in a well-designed and well-conducted Bioequivalence study.

The RMS considers that the request for a BW for the 400mg strength is justified.

The final SPC is acceptable to the RMS.

In conclusion the benefit/risk ratio for the product Ibunin 200 and Ibunin 400mg is positive. The application is approvable. The applicant committed to perform post-authorisation follow-up measures to be reported back to the RMS and CMSs as listed below.

Follow-up measures:

Area[1]	Description
Quality	The Applicant hereby commits to perform an in-use stability study for tablets packed in polyethylene containers, and to provide the results as soon as available.
Quality	
Quality	

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance

User consultation

The package leaflet 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 language used for the purpose of user testing the Patient Leaflet was English. The results show that the package leaflet 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. REVISION DATE

December 2022

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
RMS transfer	From MT/H/0100/001-002/DC to IE/H/1195/001-002			
MA transfer	CRN00CSXJ	SmPC section 7, 8, 10 Package Leaflet New MA Holder: Teva B.V. New PA number: PA1986/116/001-002	N/A	16/12/2022